Insulin Sensitivity, Glucose Effectiveness, and β-Cell Function in Obese Males With Essential Hypertension: Investigation of the Effects of Treatment With a Calcium Channel Blocker (diltiazem) or an Angiotensin-Converting Enzyme Inhibitor (quinapril)

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It has been suggested that hyperinsulinemia secondary to insulin resistance may be a pathogenetic factor common to obesity, non–insulin-dependent diabetes mellitus (NIDDM), and hypertension. Furthermore, β-blockers and thiazide diuretics have been shown to be capable of increasing insulin resistance and thus of inducing NIDDM in predisposed individuals. We used the minimal model approach (MMA) to glucose metabolism and insulin kinetics to compare peripheral insulin sensitivity and β-cell function in hypertensive and normotensive obese men. The hypertensive group consisted of 37 obese men with mild to moderate hypertension; following a drug-free period of 4 weeks, 20 of these subjects received diltiazem and 17 quinapril over the 12-week study period. The normotensive (control) group contained 17 obese men without microalbuminuria, dyslipidemia, or a family history of essential hypertension or NIDDM. Before and at the end of the 12-week study period, subjects underwent frequently sampled intravenous glucose tolerance (FSIGT) tests. The results were used to estimate an insulin sensitivity index (S_I), a glucose effectiveness index (S_G), and β-cell sensitivity to glucose indices during first- and second-phase insulin secretion (Φ_1 and Φ_2) using the minimal models of glucose metabolism and insulin kinetics. No significant differences in S_I or S_G were detected between the hypertensive and control groups. Twelve weeks' treatment with diltiazem led to a slight but significant increase in Φ_1; however, neither diltiazem nor quinapril had significant effects on S_I or S_G. We conclude that men with obesity and hypertension have no greater insulin resistance than those with obesity alone, suggesting that hypertension is not generally associated with any significant increase in insulin resistance. Treatment with diltiazem or quinapril does not have undesirable effects on glucose metabolism. However, treatment with diltiazem led to a significant increase in β-cell sensitivity to glucose; this is of particular interest, given the importance of Φ_1 for peripheral glucose uptake.

THE ASSOCIATION OF non–insulin-dependent diabetes mellitus (NIDDM), obesity, and essential hypertension is common in industrial societies, particularly in older people. Both NIDDM and obesity are generally accompanied by hyperinsulinemia unless β-cell function is impaired. In both disorders, hyperinsulinemia has been reported to be secondary to increased insulin resistance.[1-3] More recently, insulin resistance has been reported to be abnormally high in subjects with essential arterial hypertension,[4] and Modan et al[5] have suggested that hyperinsulinemia may constitute the pathogenetic link between the three conditions.

In subjects with NIDDM or obesity, insulin resistance is due to a reduced sensitivity of both muscle and hepatic tissue.[1] On the other hand, the insulin resistance putatively associated with essential hypertension has been reported to be exclusively due to reduced sensitivity of muscle,[6,7] and it has thus been suggested that insulin resistance is induced in essential-hypertensive subjects by a different mechanism than in subjects with NIDDM or obesity.

On the other hand, despite the proven efficacy of modern drugs in the treatment of essential arterial hypertension and the prevention of its principal complications, epidemiological studies have shown a much less marked decline than expected in the incidence of ischemic atherosclerotic cardiopathy.[8] This apparent inconsistency may be due, in part, to the effects of certain antihypertensive drugs on glucose metabolism. Specifically, β-blockers[9] and thiazide diuretics[10] may induce insulin resistance and consequent compensatory hyperinsulinemia, or, conversely, may inhibit the secretion of insulin by β cells; such effects may lead to NIDDM in predisposed individuals. By contrast, angiotensin-converting enzyme (ACE) inhibitors appear to have no significant effects on insulin-related glucose metabolism,[10] whereas prazosin causes only a slight increase in sensitivity to insulin.[11] The possible effects of calcium channel blockers on insulin-related metabolism are not well understood. On the basis of experiments in vitro, such drugs have been reported to cause an increase in the insulin sensitivity of adipocytes,[12] although in other in vitro studies, numerous adverse metabolic effects were detected in rat skeletal muscle.[13] In euglycemic-hyperinsulinemic clamp studies of human subjects, diltiazem had no effect on insulin sensitivity,[14] whereas case-control studies have indicated that long-term diltiazem treatment of subjects with insulin-dependent diabetes mellitus only rarely leads to insulin resistance.[15]

The aims of the study reported herein were (1) to quantify sensitivity to insulin and glucose-induced insulin secretion in men with mild or moderate essential-hypertension and obesity, and (2) to investigate the effects on these parameters of treatment with a calcium channel blocker (diltiazem) or an ACE inhibitor (quinapril).

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SUBJECTS AND METHODS

Subjects

Thirty-seven obese hypertensive men aged 18 to 55 years were selected for inclusion in the drug-treated group (Table 1). This age range was chosen because some degree of insulin resistance exists at puberty and in those older than 55.[16] Diastolic blood pressure (DBP) was between 95 and 115 mm Hg. Both supine and standing blood pressure were determined 2 weeks and 1 week before the start of the study, and in no case did these values differ by more than 10 mm Hg for DBP. Glucose intolerance (World Health Organization criteria), microalbuminuria, dyslipidemia, and a family history of NIDDM were ruled out (Table 1).

The control group contained 17 obese but otherwise healthy normotensive men (Table 1). The possibility of a family history of essential hypertension or NIDDM was ruled out for all control group subjects, since the prevalence of insulin resistance has been reported to be high in subjects with essential-hypertensive or NIDDM parents[17-22] and since NIDDM is characteristically associated with β-cell dysfunction.[1] A family history of NIDDM and hypertension was ruled out by a personal interview with the parent and siblings of the subjects and by measuring blood pressure twice and with a routine glycemic control. The subjects were not taking any medication that could alter glucose tolerance or lipid metabolism.

All subjects were fully informed of the characteristics of the study and provided written consent. The project was approved by the Research Ethics Committee of our hospital.

Experimental Design

The study was an open-label trial. Drug treatment of hypertensive subjects was discontinued at least 4 weeks before the start of the study as a washout period, and then resumed over the 12-week study period. In the course of recruitment, hypertensive patients were randomly assigned to one or the other therapeutic protocol. Diltiazem-treated subjects received 120 mg of the drug twice daily (at breakfast and dinner) over the first 4 weeks, and 120 mg three times daily (at breakfast, lunch, and dinner) over the subsequent 8 weeks. Quinapril-treated subjects received a single 20-mg dose daily throughout the study period. In all cases, the first dose was administered in the Outpatient Department, with monitoring of systolic and diastolic arterial blood pressure (SBP and DBP) over the subsequent 3 hours.

Before week 1 and at the end of week 12 of the study period, peripheral glucose metabolism and glucose-induced insulin secretion were investigated on the basis of frequently sampled intravenous glucose tolerance (FSIGT) tests, as follows. A cannula was inserted into an antecubital vein in each arm, after which the subject rested for 15 minutes in a chair with armrests. Basal blood samples were then taken 20, 15, 10, 5, and 1 minute before administration (over a period not longer than 2 minutes) of 0.33 g/kg 40% dextrose. Blood samples (4 mL) were then taken 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 100, 120, 140, 160, and 180 minutes after administration of dextrose (Fig 1). In all cases, FSIGT testing was performed between 8 and 9 AM to avoid the afternoon reduction in glucose tolerance that has been reported for normal subjects,[23,24] although no such reduction has been detected in obese subjects.[25] Blood samples were collected on ice in glass tubes containing 10 IU heparin (sodium salt) to prevent coagulation and 4 mg sodium fluoride to prevent glycolysis. After centrifugation (2,500 rpm at 4°C for 20 minutes), the plasma fraction was stored at −20°C until analysis. Glucose was determined by the glucose oxidase technique. Insulin was determined by radioimmunoassay with kits from Corning Medical Scientific (Corning Hazelton, North Yorkshire, UK). All assays were performed in triplicate, and all were previously validated in our laboratory (glucose, intraassay coefficient of variation [CV] 2.5% and interassay CV 3.2%; insulin, intraassay CV 6.0% and interassay CV 7.9%).

FSIGT test data were used to evaluate sensitivity to insulin, glucose effectiveness, and β-cell sensitivity to glucose, using the minimal model

Table 1. Basic Statistics for the Obese Normotensive and Hypertensive Subjects

Variable	OBC	OBH	*P*
No.	17	37	
Age (yr)	28 ± 10	44 ± 6	<.01
BMI (kg/m²)	36 ± 6	31 ± 3	<.05
WHR	0.90 ± 0.02	0.92 ± 0.03	NS
SBP (mm Hg)	135 ± 8	151 ± 13	<.001
DBP (mm Hg)	81 ± 4	101 ± 16	<.001
Basal glucose (mmol/L)	5.1 ± 0.4	5.3 ± 0.5	NS
2-hour glucose*	6.8 ± 0.9	6.6 ± 1.0	NS
Triglycerides (mmol/L)	1.58 ± 0.39	1.55 ± 0.42	NS
Total cholesterol (mmol/L)	5.68 ± 0.65	5.53 ± 0.78	NS
HDL cholesterol (mmol/L)	1.30 ± 0.11	1.35 ± 0.28	NS
LDL cholesterol (mmol/L)	3.95 ± 0.69	3.82 ± 0.71	NS
LDL/HDL cholesterol	3.02 ± 1.28	2.82 ± 1.01	NS

Abbreviations: OBC, obese normotensive subjects; OBH, obese hypertensive subjects; WHR, waist to hip ratio.

*Plasma glucose at 120 minutes after 75-g oral glucose tolerance test.

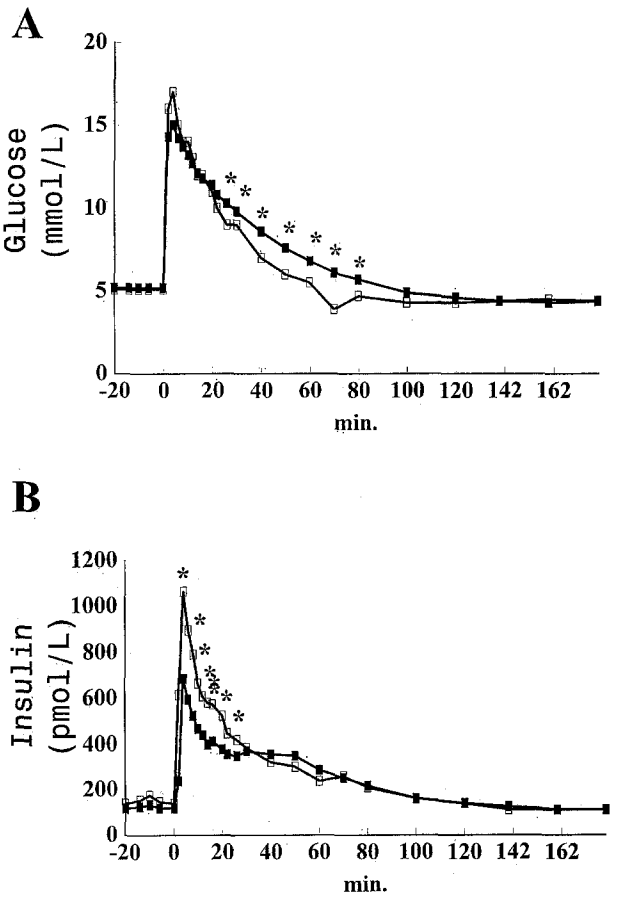

Fig 1. Glucose (A) and insulin (B) responses during a FSIGT test in 17 obese normotensive subjects (□) and 37 obese hypertensive subjects (■) before adjusting for age and BMI. Statistically significant differences are presented for each time point: *$P < .05$. Values are the mean ± SD.

approach (MMA)[26,27] with Fortran 77 software developed in our laboratory.[28] For least-squares minimization, these programs use the ZXSSQ subroutine[29] based on a modification of the Levenberg-Marquardt algorithm.[30] Table 2 lists definitions of the parameters estimated by MMA and other variables. The trapezoid method was used to calculate the area under the curve of insulin.

Statistical Analysis

Student's *t* test was used for between-group comparisons of mean basal parameter values, following verification of normality and subsequent logarithmic or square-root transformation when necessary. To avoid the influence of both age and body mass index (BMI) on the parameters studied and to discard any effect stemming from these variables, analysis of covariance was used, with age and BMI as covariates, including equality of slopes, zero slopes, and equality of adjusted means tests, thereby investigating the effects of hypertension on parameter values. For paired comparisons, the nonparametric Wilcoxon test was used. Results are expressed as the mean ± SD. For the accuracy of minimal model indices, the fractional standard deviation (FSD) was calculated[31]; when the FSD of the insulin sensitivity index (S_I) was higher than 6% or the FSD of the glucose effectiveness index (S_G) was higher than 15%, the CV of these indices was calculated using a Monte Carlo technique and only CVs less than 34% were accepted as valid.[32] *P* less than .05 was taken to indicate statistical significance. Statistical analysis was performed with the software package BMDP.

RESULTS

Analysis of covariance indicated that none of the MMA parameters differed significantly between the hypertensive obese group and the control obese group (Table 3). Most importantly, neither glucose uptake (whether total uptake as reflected by K_G, insulin-dependent uptake as reflected by S_I, or insulin-independent uptake as reflected by S_G) nor glucose-induced insulin secretion (Φ_1 and Φ_2) differed significantly between hypertensive and normotensive groups. These results indicate that neither insulin resistance nor β-cell sensitivity differ between hypertensive and normotensive obese subjects.

Comparison of the data for diltiazem-treated hypertensive subjects at the start and end of the study period showed no significant differences in glucose uptake; however, β-cell sensitivity during Φ_1 was slightly but significantly higher after 3 months' treatment (Table 4).

Comparison of the data for quinapril-treated hypertensive subjects at the start and end of the study period showed no significant differences in glucose metabolism or β-cell sensitivity (Table 5).

It is important to emphasize that the apparent lack of effects of diltiazem and quinapril on glucose metabolism and insulin secretion (except for Φ_1 in the case of diltiazem) contrasts with the clearly significant effects of both drugs on blood pressure (Tables 4 and 5).

Table 2. Definitions for the Output Parameters of the Minimal Models of Glucose Metabolism and Insulin Secretion Kinetics and Other Variables Used in the Study

Variable	Definition
K_G	Glucose disappearance rate (min^{-1}), estimated as the slope of the regression of the natural logarithm of plasma glucose concentration on time over 10 to 40 minutes from the start of the FSIGT
S_I	Insulin sensitivity index ($\times 10^{-5} \cdot min^{-1} \cdot pmol/L^{-1}$)
S_G	Glucose effectiveness index (glucose-induced glucose uptake) ($\times 10^{-1} \cdot min^{-1}$)
Φ_1	β-cell sensitivity to glucose during the first phase of insulin secretion ($pmol/L \cdot min \cdot mmol/L^{-1}$)
Φ_2	β-cell sensitivity to glucose during the second phase of insulin secretion ($pmol/L \cdot min^{-1} \cdot mmol/L^{-1}$)
AUC_I	Area under the curve of insulin; first phase of insulin secretion, minute 0 to 10 of the FSIGT test ($pmol/L \cdot min$)
AUC_T	Area under the curve of insulin; insulin secretion over the full 180 minutes of the FSIGT ($pmol/L \cdot min$)

Table 3. Results of Analysis of Covariance to Compare MMA Values Obtained for Obese Hypertensives Before Drug Treatment (n = 37) and Obese Normotensives (n = 17)

Parameter	OBC	OBH	*P*
Fasting insulin (pmol/L)	126 ± 78 (114)	102 ± 24 (90)	.05 (NS)
Fasting glucose (mmol/L)	5.1 ± 0.4 (5.11)	5.3 ± 0.5 (5.05)	NS (NS)
K_G (min^{-1})	1.96 ± 0.7 (1.59)	1.42 ± 0.5 (1.68)	.01 (NS)
S_G ($\times 10^{-1} \cdot min^{-1}$)	0.203 ± 0.09 (0.19)	0.208 ± 0.08 (0.22)	NS (NS)
S_I ($\times 10^{-5} \cdot min^{-1} \cdot pmol/L^{-1}$)	5.8 ± 4.0 (6.78)	5.43 ± 3.0 (3.53)	NS (NS)
AUC_I ($pmol/L \cdot min$)	8,704 ± 5,076 (4,146)	4,890 ± 4,266 (4,614)	.001 (NS)
AUC_T ($pmol/L \cdot min$)	60,242 ± 37,764 (35,136)	42,669 ± 23,561 (35,220)	.05 (NS)
Φ_1 ($pmol/L \cdot min \cdot mmol/L^{-1}$)	1,035 ± 864 (592)	657 ± 572 (468)	.05 (NS)
Φ_2 ($pmol/L \cdot min^{-2} \cdot mmol/L^{-1}$)	4,644 ± 5,292 (1,674)	1,836 ± 1,512 (2,257)	.05 (NS)

NOTE. Values in parentheses are means adjusted for the covariates (BMI and age) and the corresponding *P* value. Each variable shown equals the slope not different from zero.

Abbreviations: OBC, obese normotensive subjects; OBH, obese hypertensive subjects.

DISCUSSION

In this study, the association between upper-body obesity and essential hypertension in normolipidemic men did not increase the insulin resistance already present in obesity. No change was

Table 4. MMA Values (mean ± SD) for Obese Hypertensives (n = 20) Before Treatment With Diltiazem and After 12 Weeks at a Daily Dose of 240 to 360 mg

Parameter	Before Treatment	After Treatment
K_G (min^{-1})	1.32 ± 0.51	1.44 ± 0.50
S_G ($\times 10^{-1} \cdot min^{-1}$)	0.19 ± 0.08	0.18 ± 0.08
S_I ($\times 10^{-5} \cdot min^{-1} \cdot mmol/L^{-1}$)	4.92 ± 2.98	4.96 ± 3.1
AUC_I ($pmol/L \cdot min$)	3,906 ± 3,570	3,936 ± 2,862
AUC_T ($pmol/L \cdot min$)	35,706 ± 19,710	34,188 ± 19,914
Φ_1 ($pmol/L \cdot min \cdot mmol/L^{-1}$)	659 ± 572	950 ± 745*
Φ_2 ($pmol/L \cdot min^{-2} \cdot mmol/L^{-1}$)	1,825 ± 1,512	2,473 ± 1,825
SBP (mm Hg)	153 ± 10	139 ± 9†
DBP (mm Hg)	99 ± 5	91 ± 6†

*$P < .05$.

†$P < .001$.

Table 5. MMA Values (mean ± SD) for Obese Hypertensives (n = 17) Before Treatment With Quinapril and After 12 Weeks at a Daily Dose of 20 mg

Parameter	Before Treatment	After Treatment
K_G (min^{-1})	1.57 ± 0.47	1.54 ± 0.42
SG ($10^{-1} \cdot min^{-1}$)	0.21 ± 0.08	0.21 ± 0.08
S_I ($10^{-5} \cdot min^{-1} \cdot pmol/L^{-1}$)	6.48 ± 4.9	5.5 ± 3.21
AUC_I (pmol/L · min)	3,534 ± 1,998	4,110 ± 2,484
AUC_T (pmol/L · min)	29,256 ± 12,156	29,712 ± 13,584
Φ_1 (pmol/L · min · $mmol/L^{-1}$)	464 ± 400	529 ± 335
Φ_2 (pmol/L · min^{-2} · $mmol/L^{-1}$)	1,750 ± 1,145	2,862 ± 3,629
SBP (mm Hg)	162 ± 15	148 ± 14†
DBP (mm Hg)	104 ± 6	97 ± 7*

*$P < .05$.
†$P < .001$.

found in glucose effectiveness or in β-cell responsiveness to glucose. Moreover, hypertension did not increase obesity-associated hyperinsulinemia. On the other hand, antihypertensive therapy with an immediate-acting calcium channel antagonist (diltiazem) or with an ACE inhibitor (quinapril) does not seem to have any influence on insulin-related glucose metabolism, with the possible exception of a slight but significant increment in β-cell responsiveness to glucose during the first phase induced by the former.

Although the results of this study suggesting that the presence of mild to moderate hypertension does not significantly exacerbate insulin resistance in obese subjects agree with several previous reports,[33-35] they are discordant with studies that observed differences in insulin sensitivity between normotensive and hypertensive obese subjects.[36,37] A possible explanation for such a difference might be the different methodology used to calculate insulin sensitivity. Although it is well known that modified FSIGT tests with tolbutamide or insulin improve the accuracy of minimal model indices,[32,38] we did not use such modified protocols, because we wanted to use the insulin kinetics minimal model. However, it does not seem that these differences in the FSIGT protocol can account for the discrepancy with the other studies,[36,37] for several reasons. First, because the CVs for S_I and S_G indices of all subjects studied were within the criteria previously selected, which is a guarantee of accuracy.[32] Second, because we[39] and others,[40] using the standard FSGIT test, have found significant differences in insulin sensitivity of approximately 40% when comparing nonhypertensive lean and obese subjects, a decrement in insulin sensitivity similar to that found by Istfan et al[36] in comparing nonhypertensive and hypertensive obese subjects (43%). And finally, because others[33-35] using the euglycemic-hyperinsulinemic clamp for measuring insulin sensitivity did not find that hypertension exacerbates the defect in glucose disposal present in obesity.

There are probably other reasons that could explain the discrepancy with the above-mentioned studies.[36,37] In a recent study, Lind et al[41] demonstrated that the prevalence of insulin resistance in the lean hypertensive population is 16%. These data question the concept that essential hypertension is a generalized state of insulin resistance such as obesity or NIDDM.[4] Most importantly, their study[41] clearly indicates that there is an important degree of clustering of metabolic impairments (high waist to hip ratio, hypertriglyceridemia, and low high-density lipoprotein [HDL] cholesterol) in hypertensive subjects with insulin resistance. In our study, we excluded people with dyslipidemias and all subjects had normal HDL cholesterol, low-density lipoprotein (LDL), and triglycerides, which, in light of their study,[41] reduces the probability of finding higher insulin resistance in our hypertensive obese subjects. Moreover, these results agree with those of Bonora et al,[34] wherein the lipid profiles of obese subjects were normal. Since Istfan et al[36] and Maheux et al[37] did not indicate the lipid levels of their subjects, it is not possible to know if this fact could affect their results. Another important point is the gender difference between our study and their study.[36] We studied only men; however, 70% of the nonhypertensive obese group in their study[36] were women and the mean waist to hip ratio was 0.82. This ratio is less than the minimum value of 0.85 used to define abdominal obesity in women, and consequently, lower insulin resistance would be expected in this group.

The existence of identical mechanisms for essential hypertension, obesity, and NIDDM-associated insulin resistance would impede any additional hypertension-induced increase in insulin resistance in obese subjects and obese NIDDM subjects; however, this did not appear to be the case, as pointed out earlier. It is also possible that when insulin resistance reaches a particular level as a result of obesity, it is not possible to increase it due to another factor (such as essential hypertension). However, this is not the case for obesity and NIDDM, since the former is capable of increasing the insulin resistance of the latter.[1] We suggest as an alternative hypothesis that essential hypertension is not associated with insulin resistance or that insulin resistance, if it exists, is negligible. So, we have also studied[42] insulin sensitivity and β-cell sensitivity in young non-obese subjects with one hypertensive parent but no family history of NIDDM and in mildly or moderately hypertensive non-obese subjects with no microalbuminuria, dyslipidemia, or family history of NIDDM, and in neither study did we detect abnormal insulin resistance.

Another point of controversy among the different studies of obesity and hypertension[34,36,43-45] is the different insulin responses found in these subjects. Manicardi et al[43] and Istfan et al[36] found higher hyperinsulinemia in obese hypertensive subjects, but Grugni et al,[44] Sechi et al,[45] Bonora et al,[34] and our group did not. However, this contradiction is only apparent if we take into account the hyperbolic relationship that exists between insulin sensitivity and insulin secretion.[46] Thus, it is not surprising that studies that found obese hypertensive subjects to be more insulin-resistant than nonhypertensive obese subjects also found these subjects to have a higher insulinemic response,[36] whereas both the study by Bonora et al[34] and the present study found no differences in insulin secretion, given that there was no decrease in insulin sensitivity. Factors such as the lipidemic profile, fat distribution, or degree of obesity could explain the differences found in the above-mentioned studies.

On the other hand, in the present study, the immediate-acting calcium channel antagonist, diltiazem, significantly reduced SBP and DBP, both in the supine and standing position.

However, this drug had no significant effect on insulin resistance, indicating that diltiazem does not generally induce glucose intolerance. Diltiazem did cause a slight but significant increase in β-cell sensitivity to glucose during Φ_1. Our results thus confirm that diltiazem is an effective antihypertensive drug and has no significant effects on insulin sensitivity, and these latter findings are in accordance with some previous reports[12-14] but not with others.[15] Furthermore, our results demonstrate for the first time that diltiazem causes a significant increase in Φ_1; this is an interesting finding, given the importance of insulin secretion kinetics for glucose metabolism during phase Φ_1.[47] Our results also confirm that quinapril is an effective antihypertensive drug with no effects on insulin sensitivity, β-cell sensitivity to glucose, or any of the other parameters studied, although other studies using AEC inhibitors have shown that these drugs slightly improve[10] or do not modify[48,49] insulin sensitivity.

In summary, our results do not provide evidence of any significant difference between obese hypertensive and obese normotensive men in terms of insulin sensitivity, fasting insulinemia, or insulin secretion rate, suggesting that hypertension does not cause any additional insulin resistance in normolipidemic normoalbuminuric obese subjects. However, it should be stressed that essential hypertension is a heterogeneous condition with a high prevalence (25% in Spain[50]); thus, the possibility that certain subsets of hypertensive patients may have decreased insulin sensitivity cannot be ruled out. For example, it has been reported that hypertensives with microalbuminuria[51] and salt-sensitive hypertensives[52-54] tend to have increased insulin resistance, although it should be kept in mind that the latter subgroup is itself highly heterogeneous.[54] Finally, our results demonstrate that antihypertensive treatment with diltiazem or quinapril has no undesirable effects on glucose metabolism.

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REFERENCES

1. DeFronzo RA: The triumvirate: β-Cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 37:667-687, 1987

2. Rabinowitz TZ, Zierler KL: Forearm metabolism in obesity and its responses to intra-arterial insulin. Characteristics of insulin resistance and evidence for adaptative hyperinsulinism. J Clin Invest 41:2163-2171, 1962

3. Ginsberg H, Kimmerling G, Olefsky JM, et al: Demonstration of insulin resistance in untreated adult onset diabetic subjects with fasting hyperglycemia. J Clin Invest 55:454-461, 1975

4. Ferrannini E, Buzzigoli G, Bonadonna R, et al: Insulin resistance in essential hypertension. N Engl J Med 317:350-357, 1987

5. Modan M, Halkin H, Almog S, et al: Hyperinsulinemia: A link between hypertension, obesity and glucose intolerance. J Clin Invest 75:809-817, 1985

6. Capaldo B, Lembo G, Napoli R, et al: Skeletal muscle is a primary site of insulin resistance in essential hypertension. Metabolism 40:1320-1322, 1991

7. Natali A, Santoro D, Palombo C, et al: Impaired insulin action on skeletal muscle metabolism in essential hypertension. Hypertension 17:170-178, 1991

8. The Working Group on Hypertension in Diabetes: Statement on hypertension in diabetes mellitus. Arch Intern Med 147:830-842, 1987

9. Pollare T, Lithel H, Selinus I, et al: Sensitivity to insulin during treatment with atenolol and metoprolol: A randomized, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. Br Med J 298:1152-1157, 1989

10. Pollare T, Lithell H, Berne C: A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. N Engl J Med 321:868-873, 1989

11. Pollare T, Lithel H, Selinus I, et al: Application of prazosin is associated with increase of insulin sensitivity in obese patients with hypertension. Diabetologia 31:415-420, 1988

12. Draznin B, Sussman KE, Eckel RH, et al: Possible role of cytosolic free calcium concentration in mediating insulin resistance of obesity and hyperinsulinemia. J Clin Invest 82:1848-1852, 1988

13. Foot EA, Leighton B: Effects of calcium antagonists on insulin-mediated glucose metabolism in skeletal muscle. Diabetes 43:73-79, 1994

14. Pollare T, Lithell H, Morlin C, et al: Metabolic effects of diltiazem and atenolol: Results from a randomized, double blind study with parallel groups. J Hypertens 7:551-559, 1989

15. Pershadsingh HA, Grant N: Association of diltiazem therapy with increased insulin resistance in patients with type I diabetes mellitus. JAMA 257:931-932, 1987

16. Moller DE, Flier JS: Insulin resistance: Mechanism, syndromes, and implications. N Engl J Med 26:938-948, 1991

17. Eriksson J, Franssila-Kallunki A, Ekstrand A, et al: Early metabolic defects in persons at increased risk for non–insulin-dependent diabetes mellitus. N Engl J Med 321:337-343, 1989

18. Warran JH, Martic BC, Krolewski AS, et al: Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic patients. Ann Intern Med 113:909-915, 1990

19. Ho LT, Chang ZY, Wang JT, et al: Insulin insensitivity in offspring of parents with type 2 diabetes mellitus. Diabet Med 7:31-34, 1990

20. Cabezas-Cerrato J, Araúxo D, García-Estévez DA, et al: Endocrine/metabolic markers in NIDDM. Diabetologia 36:A178, 1993 (suppl 1, abstr)

21. Ferrari P, Weidmann P, Shaw S, et al: Altered insulin sensitivity, hyperinsulinemia, and dyslipemia in individuals with a hypertensive parent. Am J Med 91:589-596, 1991

22. Widgren BR, Urbanavicius V, Attvall S, et al: Insulin sensitivity is more related to fat distribution than to heredity for hypertension in normotensive men. Metabolism 43:883-886, 1994

23. Jarret RJ, Baken IA, Keen H, et al: Diurnal variation in oral glucose tolerance, blood sugar and plasma insulin levels in the morning, afternoon and evening. Br Med J 1:199-201, 1972

24. Carroll KF, Nestel PL: Diurnal variation in glucose tolerance and insulin secretion in man. Diabetes 22:333-348, 1973

25. Lee A, Ader M, Bray GA, et al: Diurnal variation in glucose tolerance. Cyclic suppression in insulin action and insulin secretion in normal-weight, but not obese subjects. Diabetes 41:750-759, 1992

26. Bergman RN, Ider YZ, Bowden CR, et al: Quantitative estimation of insulin sensitivity. Am J Physiol 236:E667-E677, 1979

27. Bergman RN: Toward physiological understanding of glucose tolerance. Minimal model approach. Diabetes 38:1512-1527, 1989

28. Araúxo D, Camarero E, Iglesias M, et al: Insulin sensitivity in

non insulin dependent diabetes mellitus and obesity using the minimal model approach. Importance of early insulin secretion on carbohydrate tolerance, in Crepaldi G, Tiengo A, Enzy G (eds): Diabetes, Obesity and Hyperlipemias, vol 4. Amsterdam, The Netherlands, Elsevier Science, 1990, pp 211-213

29. ZXSSO. Houston, TX, International Mathematical Subroutine Library, 1982

30. Brown KM, Dennis JE: Derivative free analogues of the Levenberg-Marquardt and Gauss algorithms for non linear least squares approximations. Numerische Mathematik 18:289-297, 1992

31. Pacini G, Bergman RN: MINMOD: A computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. Comput Methods Programs Biomed 23:113-122, 1986

32. Prigeon RL, Kahn SE, Porte D Jr: Reliability of error estimates from minimal model: Implications for measurements in physiological studies. Am J Physiol 266:E279-E286, 1994

33. Bonora E, Bonadonna RC, Del Prato S, et al: In vivo glucose metabolism in obese and type II diabetic subjects with or without hypertension. Diabetes 42:764-772, 1993

34. Bonora E, Moghetti P, Zenere M, et al: B cell secretion and insulin sensitivity in hypertensive and normotensive obese subjects. Int J Obes 14:735-742, 1990

35. O'Shaughnessy IM, Myers TJ, Stepniakowski K, et al: Glucose metabolism in abdominally obese hypertensive and normotensive subjects. Hypertension 26:186-192, 1995

36. Istfan NW, Plaisted CS, Bistrian BR, et al: Insulin resistance versus insulin secretion in the hypertension of obesity. Hypertension 19:385-392, 1992

37. Maheux P, Jeppesen J, Sheu WHH, et al: Additive effects of obesity, hypertension and type 2 diabetes on insulin resistance. Hypertension 24:695-698, 1994

38. Welch S, Gebhart SSP, Bergman RN, et al: Minimal model analysis of intravenous glucose tolerance test–derived insulin sensitivity in diabetic subjects. J Clin Endocrinol Metab 71:1508-1518, 1990

39. Araújo D, García-Estévez DA, Cabezas-Cerrato J: Importance of glucose effectiveness on glucose tolerance in obese people. Int J Obes 20:87A, 1996 (suppl 4, abstr)

40. Bergman RN, Phillips L, Cobelli C: Physiologic evaluation of factors controlling glucose tolerance in man. Measurement of insulin sensitivity and β-cell glucose sensitivity from the response to intravenous glucose. J Clin Invest 68:1456-1467, 1981

41. Lind L, Berne C, Lithell H: Prevalence of insulin resistance in essential hypertension. J Hypertens 13:1457-1462, 1995

42. Cabezas-Cerrato J, García-Estévez DA, Araújo D, et al: Beta cell glucose sensitivity and peripheral insulin resistance in essential hypertension. Diabetologia 37:554A, 1994 (suppl 1, abstr)

43. Manicardi V, Camellini L, Bellodi G, et al: Evidence for an association of high blood pressure and hyperinsulinemia in obese man. J Clin Endocrinol Metab 62:1302-1304, 1986

44. Grugni G, Ardizzi A, Dubini A, et al: No correlation between insulin levels and high blood pressure in obese subjects. Horm Metab Res 22:124-125, 1990

45. Sechi LA, Tedde R, Marigliano A, et al: Insulin resistance and β-cell hypersecretion in essential hypertension. J Hypertens 8:S87-S89, 1990 (suppl 4)

46. Kahn SE, Pringeon RL, McCulloch DK, et al: Quantification of the relationship between insulin sensitivity and β-cell function in human subjects. Evidence for a hyperbolic function. Diabetes 42:1663-1672, 1993

47. Lerner RL, Porte D: Acute and steady state insulin responses to glucose in nonobese diabetic subjects. J Clin Invest 51:1624-1631, 1972

48. Santoro D, Natali A, Palombo C, et al: Effects of chronic angiotensin converting enzyme inhibition on glucose tolerance and insulin sensitivity in essential hypertension. Hypertension 20:181-191, 1992

49. Giordano M, Matsuda M, Sanders L, et al: Effects of angiotensin-converting enzyme inhibitors, Ca^{+2} channel antagonists, and alfa-adrenergic blockers on glucose and lipid metabolism in NIDDM patients with hypertension. Diabetes 44:665-671, 1995

50. Pardell H: Blood Hypertension as a Problem of a Community in Spain (ed 2). Madrid, Spain, Liga Española para la Lucha contra la Hipertension Arterial, 1986, pp 1-15

51. Bianchi S, Bigazzi R, Quiñones Galván A, et al: Insulin resistance in microalbuminuric hypertension. Sites and mechanisms. Hypertension 26:789-795, 1995

52. Sharma AM, Ruland K, Spies KP, et al: Salt sensitivity in young normotensive subjects associated with a hyperinsulinemic response to oral glucose. J Hypertens 9:329-335, 1991

53. Sharma AM, Schorr U, Distler A: Insulin resistance in young salt-sensitive normotensive subjects. Hypertension 21:273-279, 1993

54. Egan BM, Stepniakowski K, Nazzaro P: Insulin levels are similar in obese salt-sensitive and salt-resistant hypertensive subjects. Hypertension 23:I1-I7, 1994 (suppl 1)