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See REVIEWER COMMENTARY page 9

Prevalence of Insulin Resistance and Related Risk Factors for Cardiovascular Disease in Patients With Essential Hypertension

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BACKGROUND
There is evidence that the subgroup of patients with essential hypertension who are also insulin resistant is at increased risk of cardiovascular disease (CVD). We are unaware of the frequency of insulin resistance in patients with essential hypertension as well as the CVD risk in this subgroup of patients. This analysis was aimed at providing the prevalence of insulin resistance and associated CVD risk factors in treated and untreated patients with essential hypertension.

METHODS
The study population consisted of 126 patients with hypertension: 56 untreated and 70 in a stable treatment program. Body mass index (BMI), blood pressure, plasma glucose and insulin responses to an oral glucose challenge, lipid and lipoprotein concentrations, and steady-state plasma glucose (SSPG) concentration during the insulin suppression test were measured. Insulin resistance was defined operationally as a SSPG concentration >180 mg/dl.

RESULTS
Demographic characteristics and metabolic CVD risk factors were comparable in both groups, with 30–50% of both treated and untreated patients having abnormalities of all risk factors measured. Approximately 50% of patients met the criteria for insulin resistance in both groups, and the prevalence of abnormal CVD risk factors in this group was increased two to threefold as compared to the other half of the subjects.

CONCLUSIONS
Approximately 50% of patients with essential hypertension, both treated and untreated, appear to be insulin resistant, and CVD risk factors are greatly accentuated in this subset of patients.

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There is a general agreement that cardiovascular disease (CVD) is increased in patients with essential hypertension, and as pointed out by Kannel, "hypertension clusters with dyslipidemia, insulin resistance, glucose intolerance and obesity."[1] In this context, electrocardiographic evidence of ischemic heart disease in asymptomatic patients with hypertension is increased in individuals who are insulin resistant, and CVD risk factors are also significantly increased in this subgroup of patients.[2] Consistent with this observation is evidence from the Copenhagen Male Study that patients with hypertension with the lowest triglyceride (TG) and highest high-density lipoprotein cholesterol (HDL-C) concentrations were not at increased risk of CVD as compared to subjects with normal blood pressure with similar lipid concentrations.[3] In view of these observations, it seems important to know (i) the proportion of patients with essential hypertension that are insulin resistant and (ii) what effect this has on CVD risk factors.

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In this context, we are only aware of three studies that have attempted to address this issue. In one study, it was estimated that ~50% of newly diagnosed patients with essential hypertension were hyperinsulinemic, and presumably, insulin resistant.[4] Two other studies have provided estimates of prevalence of insulin resistance in patients with pharmacologically treated hypertension of ~20% in nondiabetic subjects[5] and ~9% in those without evidence of glucose intolerance.[6] However, surrogate estimates of insulin sensitivity were used in all three of these studies, and the classification of insulin resistance was based on arbitrary definitions of this abnormality. This study was initiated to evaluate the effect of insulin resistance on CVD risk in patients with essential hypertension and avoid some of the confounding issues present in previous reports by (i) quantifying insulin sensitivity with a specific measure of insulin-mediated glucose uptake (IMGU) and (ii) determining the prevalence of CVD risk factors in 126 patients with hypertension, divided into insulin-resistant and insulin-sensitive subgroups based on knowledge of clinical outcome gained from previous prospective studies.[7,8]

METHODS

The current analysis is based on experimental measurements made in individuals who had previously participated in our

research studies related to insulin resistance and related clinical syndromes approved by the Institutional Review Board at Stanford University. All of the participants responded to newspaper advertisements asking for individuals to volunteer for our studies of the role of insulin resistance in human disease. Volunteers had all provided informed consent and were included in this analysis if they were nondiabetic,[9] with body mass index (BMI) between 19 and 35 kg/m^2, and other than being hypertensive, in good general health with no history of coronary artery, kidney, or liver disease. There was no clinical evidence of secondary hypertension. The volunteers were primarily white (80%), with 17 and 3% being of Asian or African American ancestry, respectively. Variables measured were BMI; systolic and diastolic blood pressures; plasma glucose and insulin concentrations before and at frequent intervals, following a 75-g oral glucose challenge; lipid and lipoprotein concentrations; and insulin sensitivity as determined by the insulin suppression test, a quantitative evaluation of IMGU described below.

The study population consisted of 126 patients with essential hypertension, defined by systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg (n = 56) or being treated with blood pressure lowering pharmacological agent(s) on a regimen that had been unchanged for at least 2 months before measurements were made (n = 76). Individual treatment programs varied considerably, with 42% of the subjects treated with one agent, 46% with two drugs, and 12% with three or more agents. More than half of the subjects were receiving diuretics (53%), with 59% treated with either an angiotensin-converting enzyme inhibitor (43%) or an angiotensin II receptor blocker (16%), while 46% were receiving either a β-blocker (25%) or a calcium channel blocker (21%). In light of the multiple drugs and drug combinations being used in 76 subjects, we were unable to create enough reasonable-sized groups to evaluate the possible differential impact of treatment program on CVD risk factors.

Blood pressure was measured using Dinamap automatic blood pressure recorder. Prior to the blood pressure measurements, patients were seated quietly for 5 min in a chair with feet on the floor and arm supported at heart level. Using an appropriately sized cuff, three blood pressure readings were taken at 1-min intervals. The data presented here are based on the mean of the three blood pressure readings.

All metabolic tests were performed at the General Clinical Research Center after an overnight fast. Plasma glucose and insulin concentrations were measured before (fasting) and 30, 60, 120, and 180 min after oral ingestion of 75 g of glucose.[9] In addition to comparing differences in fasting glucose and insulin concentrations, the total integrated glucose (glucose area under the curve (AUC)) and insulin (insulin AUC) responses were also determined as described previously.[10] Fasting lipid and lipoprotein concentrations were assayed in the core laboratory at Stanford University Medical Center by standardized methods approved by the Centers for Disease Control.

IMGU was quantified by a modified version[11] of the insulin suppression test as introduced and validated by our research group.[12,13] The values for IMGU obtained with this approach are highly correlated (r > 0.9) with the hyperinsulinemic, euglycemic clamp technique.[13] Briefly, after an overnight fast, an intravenous catheter is placed in each arm of the subjects. One arm is used for the administration of a 180-min infusion of octreotide (0.27 μg/m^2/min), insulin (32 mU/m^2/min) and glucose (267 mg/m^2/min); the other arm is used to collect blood samples. Blood is drawn at 10-min intervals from 150 to 180 min of the infusion to determine the steady-state plasma glucose (SSPG) and insulin concentrations. Because steady-state plasma insulin concentrations are similar in all subjects, the SSPG concentration provides a direct measure of the ability of insulin to mediate disposal of an infused glucose load; therefore, the higher the SSPG concentration, the more insulin resistant the individual.

There is no purely objective way to define insulin resistance, and for the purpose of this analysis, we operationally classified an individual as being insulin resistant if they had a SSPG concentration >180 mg/dl and insulin sensitive if the value was <96 mg/dl. These SSPG values place them in the upper and in the lower tertiles of 490 apparently healthy individuals described previously,[10] and we have shown in prospective studies that the third of an apparently healthy population that is most insulin resistant (the highest SSPG concentrations) have a significant increase in the development of clinical syndromes associated with insulin resistance,[7,8] whereas these events are absent in the most insulin-sensitive third (i.e., lowest SSPG concentrations).

Data are presented as mean ± s.d. The statistical significance of differences between groups was compared by Student's two-tailed, unpaired t test. In addition, Pearson correlation and standardized regression coefficients were calculated between SSPG concentration and the other experimental variables measured. χ^2 test was used to evaluate frequency distributions. Statistics were performed using the software SPSS 15.0 for Windows, 2006. A P value ≤0.05 was considered statistically significant.

RESULTS

Table 1 compares the demographic characteristics of the two groups of patients. It can be seen that there were no significant differences in the age, gender distribution, and BMI. Not

Table 1 | Anthropometric characteristics of untreated and treated patients with hypertension (mean ± s.d.)

Variable	Untreated (n = 56)	Treated (n = 70)	P value
Age (years)	54 ± 11	57 ± 7	0.08
Male (%)	53	46	0.38
BMI (kg/m^2)	29.4 ± 3.2	29.0 ± 3.1	0.43
SBP (mm Hg)	149 ± 13	137 ± 19	<0.001
DBP (mm Hg)	88 ± 10	79 ± 11	<0.001
Statins (%)	13	24	0.09
Diuretics (%)	0	53	<0.001

BMI, body mass index; DBP and SBP, diastolic and systolic blood pressure.

surprisingly, both systolic blood pressure and diastolic blood pressure were significantly lower in the treated patients. It should be noted that although statin use was somewhat more common ($P = 0.09$) in the treated group, >75% of the study population were not receiving these agents. Also, there was a dramatic difference in the use of diuretics in the groups.

The CVD risk factors of the two groups are presented in Table 2. In addition to comparing mean concentrations of these variables, we have also calculated the percent of individuals in each subgroup whose values are considered to be abnormal by current guidelines.[14,15] At the simplest level, these data indicate that the values of most variables measured did not seem to vary as a function of whether the patients were treated or untreated. More importantly, it can be seen that the mean SSPG concentrations in both groups were equal to the cutoff point used to classify an individual as being insulin resistant. The prevalence of abnormal metabolic CVD risk factors varied from ~30 to 50%, and with the exception of treated men with low HDL-C concentrations, was not significantly different when comparing treated to untreated patients. It should also be noted that the abnormalities in lipid metabolism were seen despite the fact that ~25% of the treated patients were also receiving agents aimed at improving lipid metabolism.

Table 3 presents the relationship between degree of insulin resistance (SSPG concentration) and various CVD risk factors in the two groups. The relationships are presented as univariate correlations, as well as when adjusted for differences in age, gender, and BMI in multiple regression models. It can be seen that age was not correlated with SSPG concentrations, whereas BMI was, in both groups. Diastolic blood pressure and SSPG concentration were significantly correlated in the untreated group, and this relationship persisted when adjusted for differences in age, gender, and BMI. Although both fasting and AUC glucose were correlated with SSPG in the untreated group, these relationships disappeared when the adjustments were made, and there was no relationship seen in the treated patients. Fasting insulin and insulin AUC were significantly related to SSPG concentration in the untreated group, whereas only the insulin AUC and SSPG concentration relationship was significant in treated subjects. There was no relationship between SSPG concentration and total or LDL-C concentrations, and an increase in SSPG concentration and decrease

Table 2 | Clinical characteristics of untreated and treated patients with hypertension (mean ± s.d.)

Variable	Untreated ($n = 56$)	Treated ($n = 70$)	P value
SSPG (mg/dl)	180 ± 74	180 ± 70	0.90
Fasting glucose (mg/dl)	95 ± 11	99 ± 16	0.20
Percent glucose ≥100 mg/dl	30%	43%	0.12
Glucose AUC (mg/dl, 3 h)	367 ± 67	365 ± 79	0.89
Fasting insulin (μU/ml)	14 ± 7	11 ± 4	0.22
Insulin AUC (μU/ml, 3 h)	182 ± 104	132 ± 66	0.047
Total cholesterol (mg/dl)	205 ± 39	193 ± 39	0.15
Percent chol ≥200 mg/dl	51%	47%	0.73
LDL-C (mg/dl)	128 ± 35	116 ± 31	0.10
Percent LDL-C ≥130 mg/dl	38%	36%	0.78
HDL-C (mg/dl)	46 ± 12	46 ± 16	0.41
Percent HDL-C <40 mg/dl (men)	29%	63%	0.01
Percent HDL-C <50 mg/dl (women)	46%	45%	0.94
Triglycerides (mg/dl)	142 ± 71	151 ± 115	0.52
Percent TG ≥150 mg/dl	38%	43%	0.59

AUC, area under the curve; BMI, body mass index; chol, cholesterol; LDL-C and HDL-C, low-density and high-density lipoprotein cholesterol; SBP and DBP, systolic and diastolic blood pressure; SSPG, steady-state plasma glucose; TG, triglyceride.

Table 3 | Correlation coefficient (r) and standardized regression coefficient (β) between SSPG and cardiovascular disease risk factors in untreated and treated patients with hypertension

	Untreated				Treated			
Variable	r	P	β	P	r	P	β	P
Age (years)	0.05	0.71	0.10	0.38[a]	−0.005	0.97	0.04	0.72[a]
BMI (kg/m^2)	0.60	<0.001	0.61	<0.001[b]	0.40	0.001	0.40	0.001[b]
SBP (mm Hg)	−0.03	0.84	−0.05	0.67[c]	0.12	0.36	0.08	0.48[c]
DBP (mm Hg)	0.51	<0.001	0.39	0.002[c]	−0.20	0.91	0.01	0.93[c]
Fasting glucose (mg/dl)	0.27	0.049	0.02	0.90[c]	0.23	0.06	0.20	0.09[c]
Glucose AUC (mg/dl, 3 h)	0.37	0.02	0.11	0.44[c]	0.31	0.23	0.26	0.29[c]
Fasting insulin (μU/ml)	0.70	<0.001	0.46	0.001[c]	0.30	0.27	−0.14	0.66[c]
Insulin AUC (μU/ml)	0.79	<0.001	0.64	<0.001[c]	0.67	0.006	0.54	0.02[c]
Total cholesterol (mg/dl)	0.05	0.71	0.02	0.88[c]	−0.10	0.45	−0.10	0.48[c]
LDL-C (mg/dl)	−0.06	0.70	−0.02	0.87[c]	−0.22	0.12	−0.28	0.04[c]
HDL-C (mg/dl)	−0.24	0.09	−0.09	0.50[c]	−0.34	0.01	−0.26	0.08[c]
Triglycerides (mg/dl)	0.51	<0.001	0.34	0.006[c]	0.41	0.002	0.36	0.004[c]

AUC, area under the curve; BMI, body mass index; LDL-C and HDL-C, low-density and high-density lipoprotein cholesterol; SBP and DBP, systolic and diastolic blood pressure; SSPG, steady-state plasma glucose.
[a]Adjusted for gender and BMI; [b]adjusted for gender and age; [c]adjusted for age, gender and BMI.

in HDL-C were only significant in the unadjusted analysis in the treated subjects. Finally, SSPG and TG concentrations were significantly correlated, and this was true of both patient groups, and the relationship persisted when adjusted for differences in age, gender, and BMI.

Figure 1 displays the percent of the treated and untreated groups who were classified as being insulin resistant, insulin sensitive, or intermediate using the cutoff points outlined in the Methods section. These data indicate that individuals in the two experimental populations were distributed in a comparable manner in all three categories of insulin action (P = 0.83). Most notably, ~50% of patients could be considered to be sufficiently insulin resistant to be at increased risk of adverse clinical outcomes, irrespective of treatment status. It is also of interest, that only 14% of either group could be considered to actually be insulin sensitive.

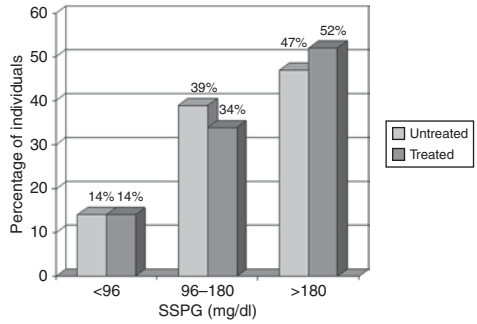

Figure 1 | Comparison of the percent of untreated and treated patients with hypertension in the three steady-state plasma glucose (SSPG) categories: <96 mg/dl = most insulin sensitive; 96–180 mg/dl = intermediate; >180 mg/dl = most insulin resistant (P = 0.83).

Table 4 | Comparison of cardiovascular disease risk factors (mean ± s.d.) in "noninsulin resistant" (non-IR) (SSPG ≤ 180 mg/dl) and "insulin resistant" (IR) (SSPG > 180 mg/dl) patients with hypertension

Variable	Non-IR (n = 64)	IR (n = 62)	P value
SSPG (mg/dl)	119 ± 36	245 ± 32	<0.001
BMI (kg/m^2)	27.9 ± 3.1	30.5 ± 2.6	<0.001
SBP (mm Hg)	142 ± 17	143 ± 18	0.60
DBP (mm Hg)	81 ± 9	85 ± 13	0.11
Fasting glucose (mg/dl)	95 ± 11	101 ± 16	0.02
Percent glucose ≥100 mg/dl	28%	47%	0.03
Glucose AUC (mg/dl, 3 h)	347 ± 65	387 ± 68	0.04
Fasting insulin (μU/ml)	9 ± 4	17 ± 6	<0.001
Insulin AUC (μU/ml, 3 h)	109 ± 53	231 ± 94	<0.001
Cholesterol (mg/dl)	197 ± 43	197 ± 35	0.95
Percent chol ≥ 200mg/dl	48%	50%	0.86
LDL-C (mg/dl)	124 ± 35	120 ± 31	0.52
Percent LDL-C ≥130 mg/dl	43%	31%	0.20
HDL-C (mg/dl)	50 ± 16	43 ± 12	0.002
Percent HDL-C <40 mg/dl (men)	39%	52%	0.35
Percent HDL-C <50 mg/dl (women)	31%	63%	0.02
Triglycerides (mg/dl)	115 ± 71	186 ± 97	<0.001
Percent TG ≥150 mg/dl	19%	65%	<0.001

AUC, area under the curve; BMI, body mass index; chol, cholesterol; LDL-C and HDL-C, low-density and high-density lipoprotein cholesterol; SBP and DBP, systolic and diastolic blood pressure; SSPG, steady-state plasma glucose; TG, triglyceride.

In order to evaluate the CVD risk profile of patients who were both insulin resistant and hypertensive, we compared variables in those classified as being insulin resistant, whether they were treated or untreated, with the combined insulin-sensitive and intermediate groups. These data appear in Table 4 and indicate that the two groups did not differ significantly in terms of blood pressure or total or LDL-C concentrations. By selection, SSPG concentrations were significantly greater in the IR subset. In addition to being more insulin resistant, the insulin-resistant group was heavier, with significantly higher fasting and post-glucose challenge glucose and insulin concentrations, as well as higher TG and lower HDL-C concentrations. Further, using conventional cutoff points for defining abnormalities,[14,15] the insulin-resistant group had values for fasting glucose, HDL-C, and TG concentrations that were two to threefold different than the ~50% of the study group that did not merit this designation.

DISCUSSION

In the most general sense, the results presented have demonstrated that (i) ~50% of patients with essential hypertension are insulin resistant, and this is true of whether they were untreated, or in a stable program of treatment with a variety of pharmacological agents; and (ii) risk factors for CVD are significantly accentuated in the insulin-resistant subset of patients with essential hypertension. To the best of our knowledge, this is the first study to address questions as to the prevalence of insulin resistance, and its associated metabolic abnormalities, in patients with hypertension, both treated and untreated, in which a specific method has been used to quantify insulin sensitivity, and a definition of insulin resistance has been used that was not arbitrary, but based upon prospective outcome data. Thus, a direct comparison of these results with the findings of previous publications is not possible, but it seems worthwhile to comment upon both the similarities and differences with previous studies. Concerning patients with untreated hypertension, the current results and the earlier findings of Zavaroni *et al.*[4] are very similar, and both studies concluded that ~50% of untreated patients with essential hypertension can be considered to be insulin resistant.

However, our results are quite different from studies of patients with treated hypertension.[5,6] Thus, Mohteshamzadeh *et al.*[5] suggested that ~20% of treated patients with essential hypertension were insulin resistant, whereas Garcia-Puig *et al.*[6] concluded that the prevalence of insulin resistance in treated patients with essential hypertension, in the absence of states of glucose intolerance—what they designated as "isolated insulin resistance"—was 9.3%. Obviously, these results are quite different from our findings, and there are several explanations to account for this disparity. The two most obvious differences

are that (i) neither study quantified insulin action, but used homeostasis model assessment–insulin resistance as a surrogate estimate of insulin resistance; and (ii) both utilized an arbitrary definition of insulin resistance: a homeostasis model assessment–insulin resistance >3.8 in the case of Garcia-Puig *et al.*[6] and a homeostasis model assessment–insulin resistance >3.0 in the study by Mohteshamzadeh *et al.*[5] The correlation between homeostasis model assessment–insulin resistance and a direct measure of IMGU is significant, but only accounts for ~36% of the variability in direct measures of IMGU (r^2 = 0.36 in nondiabetic individuals).[10,16] Thus, we would argue that the prevalence of insulin resistance in both treated and untreated patients with essential hypertension is closer to 50% than <20% as suggested by the findings of the two earlier studies cited above.[5,6]

Turning now to a more clinically relevant point, the results presented demonstrate that the insulin-resistant subset of patients with essential hypertension, treated or untreated, have a two to threefold increase in glycemia, insulinemia, and a high TG and low HDL-C concentration. As there is evidence that insulin resistance and these associated metabolic changes increase risk of CVD,[3,7,8,17–23] it can be concluded that it is the subset of patients with essential hypertension, who are also insulin resistant, that are at greatest CVD risk. In direct support of this conclusion are the results of the Copenhagen Male Study,[3] showing that patients with essential hypertension in the study population, whose TG and HDL-C concentrations were in the lower third and upper third, respectively, were not at increased risk of CVD, whereas the greatest incidence of CVD was seen in the hypertensive patients with the highest TG and lowest HDL-C concentrations.

In conclusion, we have presented evidence that ~50% of patients with essential hypertension can be considered to be insulin resistant. However, this estimate must be viewed with caution for at least two important reasons. In the first place, we did not analyze an unselected population, but rather individuals who had volunteered for studies advertised to be focused on the role of insulin resistance in disease. Second, the diagnosis of untreated hypertension was based upon three readings at only one clinic visit. The impact of these potential confounders can only be speculated upon; in the first case, we run the risk of overestimating the importance of insulin resistance, whereas by recruiting individuals who may not have essential hypertension we may have diluted the importance of insulin resistance. Thus, an unequivocal estimate of the prevalence of insulin resistance in either treated and untreated patients with essential hypertension will require a proper prospective study.

Although our findings do not permit a firm estimate of the prevalence of insulin resistance in patients with essential hypertension, they do provide evidence that it is this subset of the patient population that is at greatest risk of CVD. There did not appear to be substantial differences in the CVD risk factors in those patients in a stable treatment program as compared to the untreated group. The variability of the pharmacological regimens in the treated group varied so much that we did not feel it justified to perform any subanalysis looking for differences in the metabolic impact of the drug(s) being used to lower blood pressure. Thus, the fact that there did not appear to be any substantial differences between the treated and untreated groups does not rule out the possibility that some agents may have beneficial and others adverse effects on the CVD risk factors we evaluated. Last, and perhaps most important, the obvious clinical corollary to our findings is to emphasize how common insulin resistance is in patients with essential hypertension and to reemphasize the need to initiate intensive efforts aimed at treating all of the CVD risk factors in patients with essential hypertension, not just the blood pressure.

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