

Relationship Between Insulin Resistance and Nonmodulating Hypertension

Linkage of Metabolic Abnormalities and Cardiovascular Risk

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Insulin resistance is a feature common to patients with diabetes and to some with hypertension. It is assumed that this feature confers the increased metabolic risk in hypertension. However, the state of the renin-angiotensin system might contribute to cardiovascular risk, although there is no clear mechanistic explanation. Our recent observation that insulin levels are increased in a specific subset of patients with normal/high-renin hypertension, the nonmodulators, provided the background for the current hypothesis: to ascertain whether abnormalities in lipid and carbohydrate metabolism are observed in the same patients in whom alterations in sodium transport, sodium homeostasis, and the renin-angiotensin system response have been identified. Exploration of a family history of cardiovascular risk was a secondary goal. Insulin sensitivity (assessed by a 75-g oral glucose load), lipid levels, and two defects in the renin-angiotensin system were assessed in 62 hypertensive and 14 normotensive subjects placed on a high (210 mmol/l) and a low (10 mmol/l) sodium intake for 2 weeks, to classify them as low-renin, nonmodulator, or modulating hypertensive subjects. Only in nonmodulators were the following cardiovascular risk factors significantly increased: fasting insulin ($P < 0.01$); increment in post-glucose load insulin ($P < 0.01$); total, LDL, and VLDL cholesterol and triglyceride levels ($P < 0.05$); and erythrocyte Na^+/Li^+ countertransport activity ($P < 0.001$). Both nonmodulators and low-renin hypertensive subjects had a significantly ($P < 0.01$) increased frequency of a family history of hypertension by questionnaire compared with subjects with intact modulation. However, only nonmodulators had a significantly ($P < 0.02$) higher frequency of a family history of myocardial infarction. Thus, there is a clustering of metabolic abnormalities in a discrete subset of the essential hypertensive population with a spe-

cific dysregulation of the renin-angiotensin system—nonmodulation. The absence of this cluster in low-renin hypertensive subjects may explain their relatively diminished cardiovascular risk. Its presence in nonmodulators likely contributes to the increased cardiovascular risk observed in normal/high-renin hypertension. *Diabetes* 48:1623–1630, 1999

Diabetes and hypertension are both associated with insulin resistance. It is this condition that presumably confers an increased cardiovascular risk to these diseases. Recent studies have suggested that the state of the renin-angiotensin system should also be added to the list of factors that might influence cardiovascular risk (1,3). The mechanisms underlying that influence have been the subject of substantial speculation, but are as yet undefined. Among the approaches that have been used to classify renin status in hypertension, the most long-standing and widely recognized relates plasma renin activity (PRA) levels to the state of sodium balance, thereby identifying PRA that is low, high, or in the normal range (4). An alternative, more recent attempt to categorize anomalies includes identification of the low-renin hypertensive subject, and divides the normal and high-renin groups into two subsets, based on angiotensin (ANG)-mediated control of the two tissues that are most sensitive to ANG II, i.e., aldosterone release and renal perfusion (5). Both tissues are far more sensitive to ANG II than is blood pressure, both tissues have a crucial influence on sodium homeostasis, and both normally show a very large shift in sensitivity to ANG II with shifts in salt intake (5,6). This normal modulation process is lost in a subset, who are called for that reason “nonmodulators” (6). Multiple lines of evidence have suggested that this abnormality is familial with a strong genetic component (7–10), and one genetic polymorphism specifically associated with nonmodulation has been identified: nonmodulators are homozygous for threonine at codon 235 in the angiotensinogen gene (11).

Two observations made during attempts to characterize these patients suggest that nonmodulators might carry an especially heavy burden of cardiovascular risk. They have an increase in erythrocyte Na^+/Li^+ countertransport (12), and they have an increase in plasma insulin concentration and evidence of insulin resistance (13,14). Both are strongly associated with an increase in cardiovascular risk (15–17). Our goal in this

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ANG, angiotensin; ANOVA, analysis of variance; AUC, area under the curve; dBp, diastolic blood pressure; OGTT, oral glucose tolerance test; PAH, *p*-aminohippuric acid; PRA, plasma renin activity; RIA, radioimmunoassay; sBP, systolic blood pressure.

study was to examine widely recognized cardiovascular risk factors in patients with essential hypertension classified according to the state of their renin system, and relate these abnormalities to family history of cardiovascular events.

RESEARCH DESIGN AND METHODS

Subjects. Informed witnessed consent to participate in this study was obtained from 103 consecutive Caucasian hypertensive patients; 62% (42 men, 20 women) finished all phases of the study and were therefore available for analysis. The protocol was approved by the human subjects committee of the Andrea Cesalpino Foundation, University of Rome "La Sapienza." Patients who remained in the study had to have supine diastolic blood pressures (dBPs) between 95 and 110 mmHg at four consecutive weekly visits after withdrawal from antihypertensive medications (Fig. 1). Thus, subjects were off all medications for 4–5 weeks before the initial measurements were made. No women were taking estrogens. All had a BMI between 18 and 30 kg/m², serum creatinine <100 μmol/l, normal ^{99m}Tc-diethylene-triamine pentacetic acid and/or [¹³¹I]o-iodohippurate scintirenoigrams, no proteinuria and/or glycosuria in any of three consecutive 24-h urine samples, and no concomitant diseases. None had a personal history of ischemic cerebral, cardiac, and/or leg disease, alcohol abuse, diabetes, smoking, or a family history of diabetes. Secondary forms of hypertension were screened out by clinical and laboratory assessments. A group of 14 healthy volunteers (blood pressure levels <135/85 mmHg) served as control subjects. None had a history of hypertension in a first-degree relative. Both the inclusion criteria and the study conditions were identical to those used for the hypertensive subjects.

Assessment of glucose tolerance. To avoid the influence of changes in caloric intake (18), diet composition (19), and sodium intake (20) on glucose tolerance, at the first visit each patient was given a weight-maintaining diet. The composition of the diet was 60% complex carbohydrates, 25% protein, and 15% lipids. Fiber intake was maintained at ~25 g per day. The diet was controlled for sodium (120 mmol/day), potassium (60 mmol/day), calcium (20 mmol/day), and magnesium (20 mmol/day). In each patient, daily intake of sodium was kept constant by adding to a 10 mmol/day sodium diet a daily supplement of four capsules (each capsule contained 27.5 mmol NaCl). To simulate as close as possible local (Italian) eating customs, the capsules were administered twice daily during lunch and supper. Patients were advised to drink 1.5 L of tap water per day. Adherence to the assigned sodium intake was assessed by measuring the 24-h urine creatinine, sodium, and chloride excretion on the last 3 days of each week. Patients were considered compliant when sodium excretion was >80 mmol/day but <130 mmol/day.

After 4 weeks on this diet (and an overnight fast), at 8:00 A.M., blood was drawn for plasma insulin and glucose assays at baseline, a 75-g oral glucose load was given, and blood was obtained at 30-min intervals over a period of 3 h. Before the oral glucose tolerance test (OGTT) in patients wearing light clothing and without

shoes, triceps, subscapular, and iliac skinfold thicknesses were measured with the Harpenden skinfold caliper (British Indicators, Luton, Bedfordshire, U.K.). Each measurement was repeated four times and the average of the last three recorded. Abdominal and gluteal circumferences were assessed with patients in the standing position to calculate waist-to-hip ratios.

Blood samples were also obtained to assess fasting total serum cholesterol, LDL, HDL, and VLDL cholesterol levels, and erythrocyte Na⁺/Li⁺ countertransport activity.

Family histories. From each patient, a family history of hypertension, coronary heart disease, or stroke was obtained using a previously described questionnaire (21). The same questionnaire was administered to the normotensive volunteers. Validation was performed in all cases by contacting the primary care physician of each first-degree relative.

Identification of the nonmodulating and low-renin subgroups. After the assessment of glucose tolerance, hypertensive and normotensive subjects were assigned to receive first a low-sodium (10 mmol) and then a high-sodium (200 mmol) intake for 2 weeks each in a double-blind fashion (Fig. 1). Both the low- and the high-sodium diets were achieved by continuing the previous regimen but substituting the daily supplement of four capsules containing 27.5 mmol NaCl each with four identical capsules containing either placebo or 50 mmol NaCl each. Compliance to the diet was verified by measuring creatinine, sodium, and chloride excretion on the last 3 days of each week. Patients with a 24-h urine sodium >20 mmol/day during the low-salt intake and/or <150 mmol/day during the high-sodium intake were considered noncompliant and excluded from the study. In a similar fashion, patients manifesting gastric intolerance after beginning the salt-containing tablets were excluded. Low-renin subjects were identified as previously described (14,21). In hypertensive patients having a normal to high level of PRA, the nonmodulating phenotype was defined as the presence of the following characteristics: 1) an aldosterone increase of <420 pmol/l in response to a 3-ng ANG II infusion while on a low-sodium intake (5–7,14,21); and 2) a *p*-aminohippuric acid (PAH) clearance decrement <120 ml · min⁻¹ · 1.73 m⁻² in response to a 3-ng ANG II infusion while on a high-sodium intake (5–7,14,21,22). Importantly, no subject's classification was known until completion of the study and data entry.

ANG II infusion. Before starting the ANG II infusion, patients were asked to void at 8:30 A.M., to complete the previous 24-h urine collection. ANG II amide (Hypertensin; Ciba-Geigy, Pharmaceutical Division, Summit, NJ) was infused at successive doses of 1 and 3 ng · kg⁻¹ · min⁻¹ for 30 min each using a peristaltic pump (Life Care Pump; Abbott Shaw, Chicago). During the ANG II infusion, blood samples for aldosterone were drawn at 0, 30, and 60 min by using a heparin lock catheter system installed in an antecubital vein of the left forearm. Blood pressure was constantly measured every 5 min by a standard Riva-Rocci sphygmomanometer with a cuff position over the brachial artery of the arm containing the heparin lock catheter. After evaluation of the aldosterone response to ANG II, subjects began the high-sodium diet. After 2 weeks on that diet, renal plasma flow was assessed using the method described by Shoback et al. (5). Briefly, at 9:30 A.M. after 1 h in the supine position, an intravenous catheter was installed in the right arm. A controlled blood sample was obtained, and a bolus injection of PAH (8 mg/kg) was infused. A constant infusion of PAH (12 mg/min) was then started, the infusion rate being controlled by the above-mentioned peristaltic pump. PAH clearance was calculated from the plasma concentrations and the infusion rate and corrected for body surface area. After basal PAH clearance was measured, ANG II amide was infused at successive doses of 1 and 3 ng · kg⁻¹ · min⁻¹ for 45 min each, using the above-mentioned peristaltic pump without discontinuing the PAH infusion. To maintain complete blindness, all infusions were made by a separate staff of researchers who did not participate in the evaluation of the data.

Blood and urine samples, blood pressure measurements, and laboratory procedures. PRA and aldosterone were assessed by radioimmunoassay (RIA) (Sorin Biomedica, Vercelli, Italy). These assays were performed no later than 1 week after blood collection (mean 6 days). In all cases, plasma samples were frozen at -80°C immediately after blood drawing. Na⁺/Li⁺ countertransport activity was assessed according to the method of Canessa and colleagues (12). Briefly, peripheral blood was collected in heparin-containing vacutainers. Erythrocytes were separated within 3 h by centrifugation for 10 min at 300g. The plasma and buffy coats were separated by suction. Erythrocytes were then washed three times in a non-sodium-containing washing solution (in mmol/l): magnesium chloride 75, sucrose 85, glucose 10, and Tris 10, MOPS 10, pH 7.4 at 4°C, 300–320 mOsm. V_{max} of the Na⁺/Li⁺ countertransport was assessed from the external sodium-stimulated lithium efflux after lithium loading.

Sodium, potassium, and other routine laboratory measurements were made on fresh samples of blood or urine. Plasma insulin levels were assessed by a commercially available RIA kit (Ares Sero, Milan, Italy). HDL cholesterol was assessed by an enzymatic method after precipitation of apoprotein B-containing lipoproteins by means of phosphotungstate and magnesium. LDL and VLDL cholesterol levels were assessed by the Friedewald method (23).

Blood pressure was taken weekly at 8:00 A.M. by personnel blinded to the diet and/or blood pressure status of the subject. Blood pressure was measured after

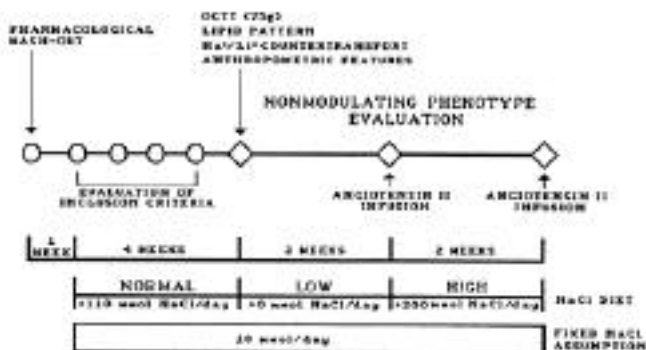


FIG. 1. Study protocol schema. In the week after recruitment, all medications were stopped, and subjects were given a calculated diet containing 120 mmol sodium per day for 4 weeks. During this period, clinical, biochemical, and blood pressure assessments were performed to ensure the subject met the inclusion criteria. Next, basal studies were obtained, and an oral glucose (75-g) load was performed. Subjects were then placed on a low-sodium (10 mmol) diet for 2 weeks, and an upright posture study and ANG II infusion were performed. Subjects were switched to a high-sodium (210 mmol) daily intake for 2 weeks, and the ANG II infusion was repeated. A similar calculated diet was used throughout the entire 8 weeks of the study, with the level of salt intake varied by means of capsules containing either NaCl or placebo. Compliance to the diet was assessed by measuring 24-h urine sodium excretion on the last 3 days of each week before any acute study.

TABLE 1

Descriptive characteristics of the study population at the completion of the normal salt phase of the study

	Hypertensive subgroups			Normotensive group
	Low-renin	Nonmodulating	Modulating	
<i>n</i>	18	23	21	14
Age (years)	55.2 ± 9.3*	45.6 ± 11.4	45.3 ± 10.2	43.3 ± 14.6
Sex (males)	12	18	12	10
Previous treatment	14	17	10	—
sBP (mmHg)	145.8 ± 12.4	140.5 ± 11.3	144.5 ± 9.5	122.5 ± 5.1†
dBp (mmHg)	91.5 ± 6.2	91.6 ± 5.4	96.8 ± 7.3	82.4 ± 4.2‡
Heart rate (bpm)	73.1 ± 5.7	73.6 ± 4.5	72.8 ± 6.1	71.8 ± 5.2
Serum total cholesterol (mmol/l)	4.85 ± 0.92	6.40 ± 1.49‡	4.90 ± 0.98	4.59 ± 0.75
HDL cholesterol (mmol/l)	1.34 ± 0.43	1.24 ± 0.46	1.47 ± 0.35	1.21 ± 0.26
LDL cholesterol (mmol/l)	3.26 ± 0.75	4.84 ± 1.21‡	3.12 ± 0.90	3.13 ± 0.78
VLDL cholesterol (mmol/l)	0.28 ± 0.08	0.46 ± 0.26‡	0.29 ± 0.11	0.25 ± 0.10
HDL:LDL ratio	0.41 ± 0.16	0.26 ± 0.11‡	0.42 ± 0.16	0.50 ± 0.18
Serum triglycerides (mmol/l)	1.33 ± 0.33	1.73 ± 0.54§	1.52 ± 0.47	1.29 ± 0.41
Fasting insulin (pmol/l)	65.3 ± 20.9	104.1 ± 12.9‡	81.7 ± 18.6	68.5 ± 41.7
Fasting glucose (mmol/l)	4.34 ± 0.25	4.67 ± 0.29	4.63 ± 0.35	4.64 ± 1.0
Plasma potassium (mmol/l)	3.85 ± 0.32	3.97 ± 0.31	3.91 ± 0.27	3.82 ± 0.18
Serum creatinine (μmol/l)	87.3 ± 5.1	88.7 ± 5.3	86.1 ± 4.8	86.6 ± 8.8
Na ⁺ /Li ⁺ countertransport (μmol · l cell ⁻¹ · h ⁻¹)	344.8 ± 135.1	577.1 ± 264.1‡	385.5 ± 147.6	360.1 ± 92.9
Low sodium supine				
Plasma aldosterone (pmol/l)	419 ± 292*	493 ± 329*	641 ± 270	518 ± 110
PRA (ng · l ⁻¹ · s ⁻¹)	0.17 ± 0.06‡	1.29 ± 1.36	1.38 ± 0.95	1.68 ± 0.35

Data are means ± SD. See Fig. 1. **P* < 0.05 vs. modulating hypertensive subjects and control subjects, †*P* < 0.05 vs. low-renin and modulating hypertensive subjects, ‡*P* < 0.001 vs. other groups, §*P* < 0.05 vs. low-renin hypertensive subjects and control subjects.

15 min in the supine position by a standard mercury sphygmomanometer. The first reading was not considered, and the average of the next three readings taken at 3-min intervals was used as the blood pressure. Blood pressure was also measured at 6-min intervals with an automated device during the PAH clearance studies before and during ANG II infusion. All measurements were made with the subjects recumbent and after 60 min of rest. Because these studies were performed in subjects on both a high- and a low-salt intake, it was possible to assess the sensitivity of blood pressure to salt intake.

Statistical analyses. All data were collected using the database SuperCalc-3 (Computer Associates, San Jose, CA). Statistical evaluations were made with software for biomedical statistics (Primer of Biostatistics; MacGraw-Hill, New York) and SPSS packages and with the use of a PC Olivetti M380 (Ivrea, Italy). Data are presented as means ± SD. Statistical significance was considered as *P* < 0.05. Differences among the examined groups were tested for significance by one-way analysis of variance (ANOVA) followed by the Newman-Keuls test for pairwise comparisons. For multiple comparisons, ANOVA followed by a modified Student's *t* test and Bonferroni's test for adjusting the significance level were used. The area under the curve (AUC) was calculated for glucose and insulin response during an OGTT by the trapezoidal rule. χ^2 analysis was used for comparison of descriptive parameters. Pearson's correlation coefficients were used to examine relations among variables.

RESULTS

Hypertensive subgroup classification. In the hypertensive subjects, 18 had low renin levels; 44 had normal or high PRA levels. These 44 patients were further divided into nonmodulators (*n* = 23) or modulating hypertensive patients (*n* = 21) according to their plasma aldosterone and PAH clearance response to ANG II (see METHODS). The three subgroups were comparable with respect to BMI, blood pressure, duration of hypertension, serum creatinine, and a number of anthropometric measurements, except for subscapular skinfold thickness (Tables 1 and 2). Subscapular skinfold was greater (*P* < 0.05) in nonmodulators than in modulating and low-renin hypertensive subjects. All of the normotensive subjects had normal renin levels with intact modulation and had substantially lower blood pressures (19–23/10–14 mmHg).

Metabolic abnormalities

Glucose tolerance. The time course of the glucose and insulin responses during OGTTs is shown in Fig. 2 for the entire group of hypertensive subjects and the 14 normotensive subjects. Glucose levels were significantly higher in the hypertensive subjects than in the control subjects at 90 (*P* < 0.01) and 120 (*P* < 0.001) min. Plasma insulin levels were significantly higher in hypertensive subjects at baseline (*P* < 0.04) and at 90 (*P* < 0.002), 120 (*P* < 0.001), and 180 (*P* < 0.004) min after the glucose load (Fig. 2). When the hypertensive patients were subdivided into the three subgroups, the nonmodulators manifested significantly (*P* < 0.001) higher post-load insulin concentrations than did the modulators and low-renin hypertensive patients at 90, 120, and 180 min. No differences were found between the two other hypertensive

TABLE 2

Anthropometric features of the study population

	Hypertensive subgroups			Normotensive group
	Low-renin	Nonmodulating	Modulating	
<i>n</i>	18	23	21	14
BMI (kg/m ²)	25.8 ± 2.3	26.1 ± 2.9	25.8 ± 3.6	23.4 ± 2.4
Waist-to-hip ratio	0.95 ± 0.06	0.92 ± 0.06	0.92 ± 0.12	0.88 ± 0.11
Skinfold thickness (mm)				
Triceps	14.1 ± 6.7	11.2 ± 3.6	15.2 ± 9.1	11.1 ± 3.1
Subscapular	17.3 ± 9.2	28.9 ± 8.5*	22.7 ± 10.2	16.9 ± 6.1
Iliac	17.7 ± 10.8	15.2 ± 7.3	19.3 ± 9.4	11.4 ± 4.5

Data are means ± SD. **P* < 0.05 vs. low-renin hypertensive subjects and normotensive subjects.

subgroups and normotensive subjects at any time point (Fig. 3). Similarly, the AUC for insulin was significantly greater ($P < 0.001$) in nonmodulators (89 ± 34 [SD] $\text{mmol} \cdot \text{min}^{-1} \cdot \text{l}^{-1}$) than in modulators (56 ± 35 $\text{mmol} \cdot \text{min}^{-1} \cdot \text{l}^{-1}$), low-renin hypertensive subjects (52 ± 24 $\text{mmol} \cdot \text{min}^{-1} \cdot \text{l}^{-1}$), and

normotensive subjects (44 ± 30 $\text{mmol} \cdot \text{min}^{-1} \cdot \text{l}^{-1}$). There were no significant differences among the latter three groups. Glucose levels showed similar trends. In nonmodulators, the glucose AUC ($1,160 \pm 275$ [SD] $\text{mmol} \cdot \text{min}^{-1} \cdot \text{l}^{-1}$) was significantly ($P < 0.02$) greater than that in modulators ($920 \pm$

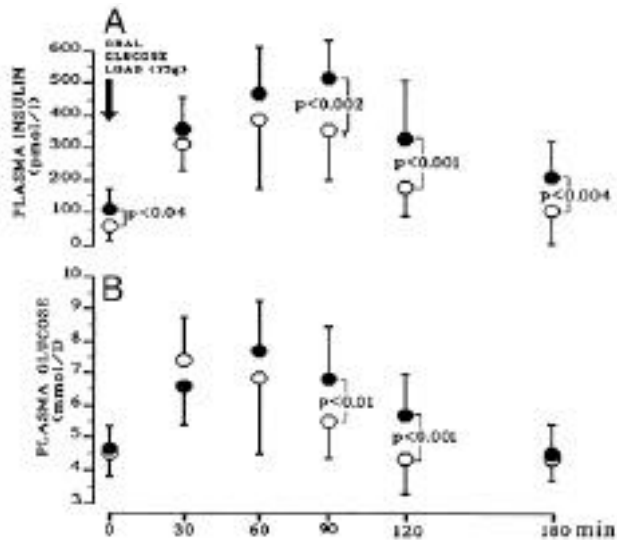


FIG. 2. Mean (\pm SD) plasma insulin (A) and glucose (B) concentrations before and after a 4-week period on a 120-mmol sodium intake in essential hypertensive subjects ($n = 62$) (●) and normotensive control subjects ($n = 14$) (○). Fasting insulin and glucose levels were significantly different ($P < 0.05$ by ANOVA followed by Bonferroni test) from all other levels except for the 180-min glucose level in the hypertensive subjects and the 120- and 180-min glucose and insulin levels in the normotensive subjects. Differences between the two groups are shown.

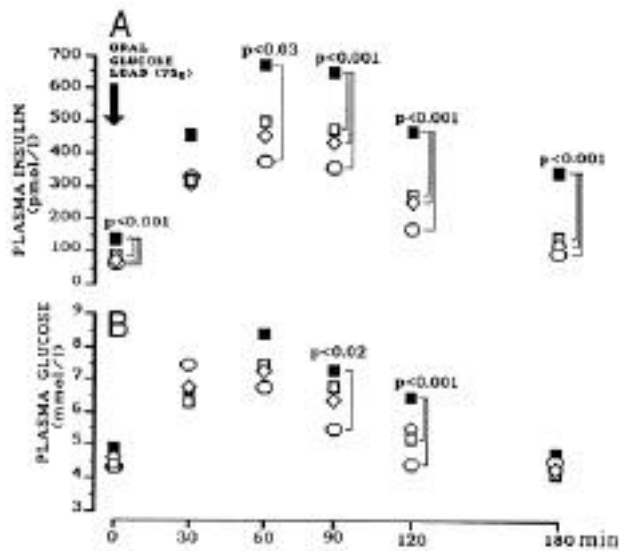


FIG. 3. Mean plasma insulin (A) and glucose (B) concentrations before and after a 75-g oral glucose load are depicted in the same hypertensive patients studied in Fig. 2, but this time, they are divided into three subgroups: nonmodulators ($n = 23$) (■), modulators ($n = 21$) (□) and low-renin subjects ($n = 18$) (◇). Normotensive subjects ($n = 14$) (○) are again shown. SDs have been omitted for clarity; differences between the groups are given by brackets. Overall, both the insulin ($P < 0.001$) and glucose ($P < 0.02$) responses were significantly higher in nonmodulators than in the other three groups, which were not different from each other.

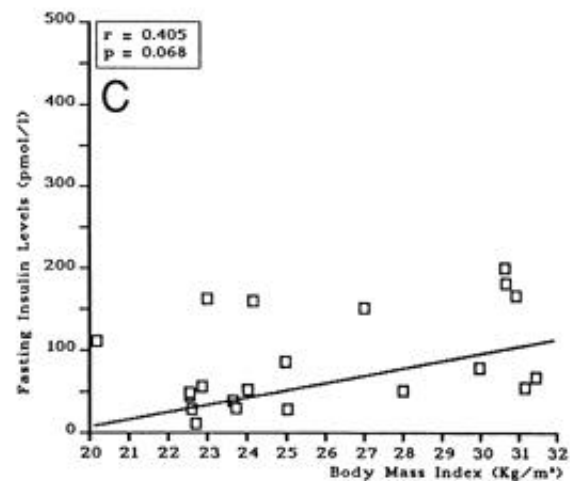
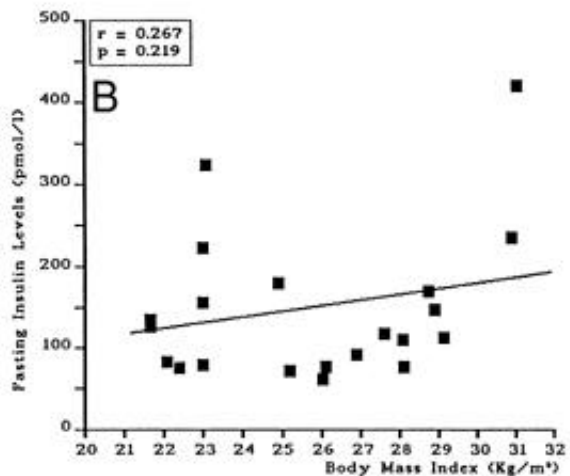
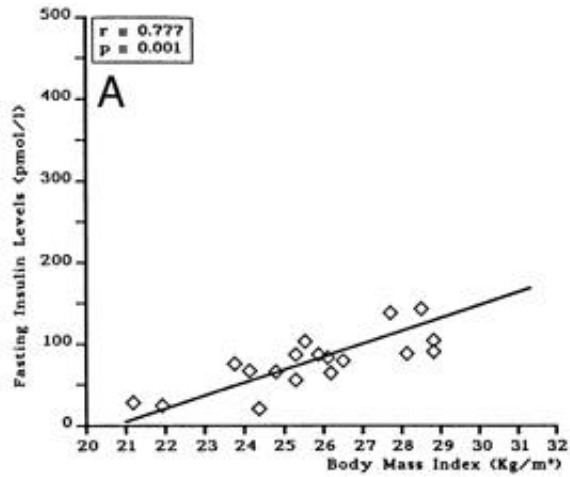


FIG. 4. Relationship between fasting insulin levels and BMI. The expected positive correlation was highly significant in the low-renin subjects (A) and of borderline significance in the modulators (C). However, in the nonmodulators (B), they were not correlated.

240 mmol · min⁻¹ · l⁻¹), low-renin hypertensive subjects (1,035 ± 170 mmol · min⁻¹ · l⁻¹), and normotensive subjects (995 ± 240 mmol · min⁻¹ · l⁻¹). Finally, although fasting glucose levels were not different among any of the groups, fasting insulin levels were significantly higher ($P < 0.001$) in the nonmodulators than in the other three groups (Fig. 3, Table 1). As anticipated, there was an overall significant ($P < 0.02$) positive correlation between BMI and fasting insulin levels. However, when analyzed by subgroups, this correlation was not present in the nonmodulators, but only in the other two hypertensive subgroups (Fig. 4). These results suggest that some factor(s) associated with nonmodulation is(are) overriding the usual impact of weight on fasting insulin levels. There was neither protein nor glucose present in any of the three 24-h urine tests in any subject.

Fasting metabolic levels. Nonmodulators had significantly higher ($P < 0.001$) fasting insulin, LDL cholesterol, VLDL cholesterol, and triglyceride levels than the other hypertensive subgroups or normotensive subjects (Table 1). Similarly, erythrocyte Na⁺/Li⁺ countertransport was significantly higher ($P < 0.001$) in nonmodulating hypertensive subjects than in modulating and low-renin hypertensive subjects or normotensive subjects, whose levels were statistically indistinguishable.

Family history of cardiac risk factors. Of the 62 subjects who completed the study, 35 had at least one first-degree relative who experienced a myocardial infarction, stroke, or had hypertension before the age of 50. As anticipated, there was an increase in the frequency of family history of hypertension (19 of 23, 82.6%) in the nonmodulators in comparison to hypertensive subjects with intact modulation ($P < 0.001$). In addition, there was a striking increase in the frequency of vascular events (16 of 23, 69.6%) in the nonmodulators in comparison to both the low-renin hypertensive subjects (4 of 18, 22.2%) and in patients in whom modulation was intact (5 of 21, 23.8%; $P < 0.002$) (Table 3). This increase in vascular events reflected primarily myocardial infarction, where the increase in frequency was significantly different ($P < 0.02$). The frequency of a family history of stroke did not differ significantly among the three clinical hypertensive subsets, but the number of events was small. None of the normotensive subjects reported a family history of stroke or hypertension. Two had a family history of myocardial infarction.

Erythrocyte Na⁺/Li⁺ countertransport. Modulators, but not the other subgroups, showed a correlation between fasting insulin and Na⁺/Li⁺ countertransport ($r = 0.412$, $P = 0.05$). Na⁺/Li⁺ countertransport and LDL cholesterol levels were

also correlated in modulators ($r = 0.512$, $P = 0.018$) but not in low-renin hypertensive subjects ($r = 0.149$, $P = 0.5$) or in nonmodulators ($r = 0.403$, $P = 0.057$). Interestingly, when male nonmodulating hypertensive subjects ($n = 18$) were considered separately from females ($n = 5$), a significant correlation between Na⁺/Li⁺ countertransport and LDL cholesterol was observed ($r = 0.518$, $P = 0.03$). Most striking was the impact of hypertension status and the relationship between Na⁺/Li⁺ countertransport and HDL:LDL cholesterol ratios. Whereas as a group this correlation was significant ($P < 0.01$) in the hypertensive subjects, it was almost exclusively determined by the nonmodulators. In this subgroup the correlation was highly significant ($P = 0.0001$). The relationship was not significant in the other two groups.

Blood pressure sensitivity to salt intake. Our data confirmed the well-known salt sensitivity of blood pressure in subjects with low-renin essential hypertension. Furthermore, the data support a similar degree of blood pressure salt sensitivity in nonmodulating, but not modulating, hypertensive subjects (24). At the end of the 2 weeks on a high-sodium intake, both systolic blood pressure (sBP) and dBP were significantly higher than at the end of the 2 weeks on a low-sodium intake in both the low-renin subgroup (sBP: from 161 ± 11 to 151 ± 7 mmHg, $P < 0.005$; dBP: from 104 ± 10 to 90 ± 8 mmHg, $P < 0.0005$) and the nonmodulators (sBP: from 151 ± 11 to 140 ± 13 mmHg, $P < 0.005$; dBP from 104 ± 9 to 90 ± 9 mmHg, $P < 0.0005$) (Fig. 5). Accordingly, the percentage of subjects having a dBP > 10 mmHg fall after the low-salt diet was higher ($P < 0.05$) in the low-renin and nonmodulating hypertensive subgroups (67 and 74%, respectively) than in the modulators (24%).

Data were also analyzed for confounders. The effects of age, sex, and BMI on the primary variables were determined using a general linear model's procedure with repeat measurement's ANOVA and an SAS program (Cary, NC). Using aldosterone basally and in response to ANG II as dependent variables, none of these potential confounders had a significant effect ($F < 1$; $P > 0.5$ whether using multiple ANOVA test criteria with repeat measures, univariate test, or ANOVA of contrast variables). In contrast, the clinical group (i.e., low-renin, nonmodulator, modulator) had a substantial impact on the change in the aldosterone levels ($P = 0.0001$). Similar

TABLE 3
Familial occurrence of hypertension, myocardial infarction, and stroke in the three hypertensive subgroups

	Hypertensive subgroups		
	Low-renin	Nonmodulating	Modulating
<i>n</i>	18	23	21
Hypertension	14	19*	7
Myocardial infarction	2	11†	3
Stroke	2	5	2

Data are *n*. * $P < 0.001$ vs. modulating hypertensive subjects, † $P < 0.02$ vs. low-renin and modulating hypertensive subjects.

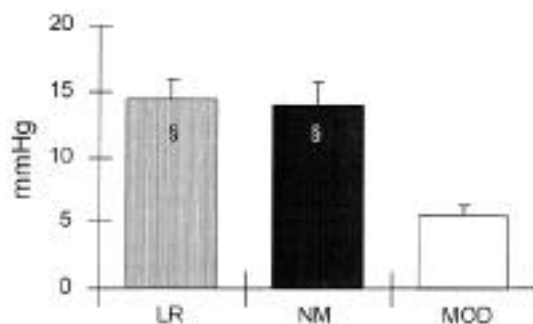


FIG. 5. dBP response to changes in dietary sodium intake. Mean ± SE dBP changed when subjects went from a low-sodium (10 mmol) to a high-sodium (210 mmol) intake. Blood pressures were measured at the end of 2 weeks on each diet. Hypertensive patients were divided into nonmodulators (NM, $n = 23$), modulators (MOD, $n = 21$), and low-renin (LR, $n = 18$) subgroups. Both the NM and LR patients had significant increases in dBP in response to salt loading, in contrast to the MOD group. There was no significant difference between the LR and NM groups. § $P < 0.03$ significantly different from the MOD group.

analyses were performed using weight and blood pressure as the dependent variables measured at the three diet stages of the protocol—at the end of the 120, 210, and 10 mmol sodium intake phases. There was minimal to no effect of age and sex, but a modest effect (P varying from 0.05 to 0.01) of group and BMI on weight changes. However, only the hypertensive subgroups influenced dBp changes with salt intake (P varying between 0.02 and 0.01).

DISCUSSION

The primary purpose of the present investigation was to determine whether there is an association between abnormalities in the renin-ANG system and insulin, glucose, and lipid metabolism that could explain both the decreased risk of myocardial disease in low-renin patients and the increased risk in the normal/high-renin hypertensive subjects. The results were striking, consistent, and persuasive in both the nonmodulator subgroup of the normal/high-renin hypertensive subjects and the low-renin hypertensive subjects. This study documented a triad of metabolic abnormalities associated with nonmodulation: insulin resistance, as defined by fasting hyperinsulinemia and an increased insulin response to a glucose load; hyperlipidemia; and an increase in family history of myocardial infarction. This triad is not present in low-renin essential hypertensive subjects, perhaps contributing to the differential effect of renin status on risk of myocardial disease.

The two commonly cited pathophysiological mechanisms associated with essential hypertension are insulin resistance (1,2,26,27) and abnormalities in the renin-ANG system (low-renin hypertension [4] and nonmodulation [5,7]). Characterization of individuals as low-renin hypertensive patients has been reported for more than 25 years (4). Among the features associated with this subgroup is a decreased risk of coronary events compared with other hypertensive subjects (3). A more recently described abnormality in the renin-ANG system is nonmodulation (5–7). The nonmodulating trait is characterized by abnormal aldosterone, renin, and renal blood flow responses to ANG II, with correction of these defects after administration of a converting enzyme inhibitor (6,25). These subjects have normal/high renin levels.

In this report, lipid abnormalities and an increased risk of cardiovascular morbidity and mortality in hypertension paralleled the insulin-resistant state. Fasting LDL cholesterol, VLDL cholesterol, and triglycerides were significantly higher in the nonmodulating subgroup than in the other hypertensive subgroups or normotensive subjects, which were indistinguishable from each other. Similarly, two factors associated with an increased risk of cardiovascular mortality—family history of myocardial infarction and increased erythrocyte Na^+/Li^+ countertransport—were also significantly more likely to be present in the nonmodulating than in the other hypertensive subgroups; the latter is in agreement with previous reports (12,28). Also confirmed was a direct correlation between Na^+/Li^+ countertransport activity and both LDL cholesterol and postload insulin levels (29–33). Na^+/Li^+ countertransport activity has also been reported to be increased in hypertensive patients having a family history of cardiovascular events (17) and insulin resistance (32), which has led to the hypothesis that it is a genetic marker of familial dyslipidemia and hypertension (30). The results of the present study provide additional evidence in support of this hypothesis, and per-

haps have identified the specific patient subset involved. Whether nonmodulators are insulin resistant could be debated, since a euglycemic-hyperinsulinemic clamp was not used. Whereas this represents the standard for assessing insulin sensitivity (34), fasting hyperinsulinemia and, in particular, a hyperinsulinemic response to an oral glucose load are generally recognized as excellent indicators of peripheral tissue resistance to insulin-mediated glucose uptake, at least in hypertensive patients. This may not be true for all hyperinsulinemic states (35,36). For example, individuals with the highest insulin levels in response to glucose loads were the same as those with the greatest insulin resistance as defined by the euglycemic clamp and vice versa (37). Therefore, it does not seem arbitrary to suggest that the subjects defined as nonmodulators in our study are insulin-resistant and that low-renin hypertensive subjects and those hypertensive subjects with intact modulation are not.

Blood pressure sensitivity to salt intake is present in ~60% of the essential hypertensive population. Individuals with low-renin hypertension comprise half of this group (6). The present study confirms previous reports (5,7,38,39) that nonmodulators comprise the other half, whether the salt sensitivity is assessed with acute or chronic salt loading or depletion.

Is there a relationship between the two new features of nonmodulation documented in the present study and the original features, i.e., increased tissue ANG II production? The answer is unclear. In animal models, an inadequate modulation of the renin-ANG system is associated with increased cardiovascular damage (40,41). In humans, a potential role for renin and ANG II in the induction of vascular lesions is supported by a large number of experimental data (4). Furthermore, a high-renin/sodium profile has been proposed as an independent risk factor for myocardial infarction (42) but not for stroke (3) in essential hypertensive subjects. More recently, both impaired insulin sensitivity (42) and hyperdyslipidemia (43) have been described in healthy volunteers with a normal/high-renin profile compared with those with a low-renin profile. Thus, if one examines cardiovascular risk from renin profiling studies, a lowered risk is associated with low PRA levels. Yet, if one examines cardiovascular risk from the perspective of salt sensitivity of blood pressure, an increased risk is found in hypertensive patients whose blood pressure is sensitive to the level of salt intake. A hyperinsulinemic response to an oral glucose load (44) and a significant degree of insulin resistance (45) have been described in salt-sensitive but not salt-resistant normotensive subjects. Thus, salt sensitivity and normal/high renin levels—both features of nonmodulators—are associated with lipid and glucose metabolic abnormalities and increased cardiovascular risk. Low-renin hypertensive patients, who also have salt-sensitive blood pressures, have little evidence of metabolic abnormalities: they had normal fasting insulin levels, normal insulin responses to a glucose load, and normal LDL cholesterol and triglyceride levels.

How generalizable are these results? The answer is uncertain. It would be unlikely, if not impossible, to obtain evidence for or against the hypothesis proposed herein from any epidemiological data because of the variably modifying effects on the biochemical features assessed by diet, therapeutic agents (e.g., antihypertensive agents, nonsteroidal anti-inflammatory agents, and estrogens), and race. Yet, there are limited data that do suggest these results may be generalizable

beyond a relatively lean Italian population. For example, Alderman et al. (3) have reported an increased risk of myocardial infarction with an increased renin level in a New York City population. It is likely their higher renin group was enriched with nonmodulators. No data related to the state of insulin resistance in these subjects have been reported, however.

A final question arises. Does hyperinsulinemia produce the hormonal and renal abnormalities displayed by nonmodulators? Increased insulin concentrations can induce sodium and fluid retention (46). Furthermore, insulin may enhance sympathetic nervous system activity (47) that, in turn, could induce sodium retention by increasing renal nerve activity (48) and stimulating the renin axis (49). Thus, an association between hyperinsulinemia and blood pressure sensitivity to salt has been described in black normotensive and hypertensive subjects (50), obese adolescents (51), and adult hypertensive subjects (52). On the other hand, there is no consistent evidence that insulin resistance, per se, influences the adrenal responses to ANG II, the critical parameters defining the nonmodulating state (53). Also, a recent study did not confirm a relationship between pressor sensitivity to salt intake and hyperinsulinemia, at least in obese people (54). However, insulin resistance has been reported to be associated with an increased pressor response to ANG II (55,56). Thus, like the converse question, there is insufficient data to establish or exclude a cause-and-effect relationship between insulin resistance and nonmodulation.

Our results are unlikely to be related to an incorrect definition of nonmodulation, since we required every nonmodulator to meet both adrenal and renal criteria. Although age, body weight, and duration of hypertension could influence our results, these were identical in the three hypertensive subgroups and, where appropriate, were similar to our normotensive control subjects. The critical comparisons, however, are not with the normotensive subjects, but among the three groups of hypertensive subjects. In them, blood pressure, BMI, renal excretion of protein, age, and family history of diabetes were identical. Yet nonmodulators stand out from other hypertensive subjects. The fact that the other two groups were indistinguishable from normal in lipid and insulin levels despite being heavier, somewhat older, and hypertensive reinforces the uniqueness of the association of the insulin-resistant state with nonmodulation. However, even though the nonmodulators have a lower BMI, they have an increased subscapular skinfold thickness, suggesting they may have a selective increase in adiposity. Computed axial tomography or dual X-ray absorptiometry (DEXA) scans may be needed to resolve this issue. Finally, the reliability of family history data could be questioned because they were obtained from a questionnaire. However, the questionnaire answers were verified by contacting the primary care physicians. Furthermore, blinding of the questionnaire results and the metabolic results make observer bias an unlikely interpretation.

In conclusion, nonmodulators are a distinct subgroup of the essential hypertensive population, with normal/high renin levels, salt sensitivity of blood pressure, metabolic abnormalities associated with insulin resistance, and a familial predisposition to both hypertension and myocardial infarction. Nonmodulation is likely an inherited defect (8–11). Based on the present data, nonmodulators appear to be the major subgroup of relatively lean hypertensive patients with insulin resistance. Mechanisms linking nonmodulation with

some of the typical features of syndrome X—insulin resistance, lipid abnormalities, and hypertension—(15,36,57) are unclear. Whether insulin resistance and abnormalities in the renin-ANG system are separate or interdependent cardiovascular risk factors is yet to be determined. Yet, the fact that the adrenal, renal, and Na^+/Li^+ countertransport activity abnormalities of nonmodulators can be reversed by ANG-converting enzyme inhibitors (6,22), a class of antihypertensive agents that may improve insulin sensitivity in some hypertensive subjects (58,59), raises the interesting possibility that there might be a mechanistic link between these two features of nonmodulation. This suggests the equally intriguing possibility that inhibition of the renin-ANG system may have favorable effects on the cardiovascular risk profile of this high-risk subset of hypertensive patients.

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