

Contrasting Clinical Properties and Exercise Responses in Obese and Lean Hypertensive Patients

Michael A. Weber, MD, FACC,*† Joel M. Neutel, MD,† David H. G. Smith, MD†

Long Beach, California and Brooklyn, New York

- OBJECTIVES** We sought to test whether the differences in activity of the renin-angiotensin and sympathetic nervous systems at rest or during exercise can explain the differing cardiovascular properties and outcomes of lean and obese hypertensive patients.
- BACKGROUND** Although lean hypertensive patients have fewer metabolic abnormalities than obese hypertensive patients, paradoxically they appear to have a poorer cardiovascular prognosis.
- METHODS** To evaluate the heightened risks in lean hypertensive patients, this study compared metabolic, neuroendocrine and cardiovascular characteristics at rest and during a standardized treadmill protocol in obese (body mass index [BMI] = 32.5 ± 0.3 kg/m², n = 55) and lean (BMI = 24.3 ± 0.2 kg/m², n = 66) hypertensive patients. Normotensive obese (n = 21) and lean (n = 55) volunteers served as control subjects.
- RESULTS** Compared with the lean normotensive subjects, the lean and obese hypertensive patients had greater left ventricular mass index (LVMI) values, but on multivariate analysis, LVMI correlated with plasma renin activity (p < 0.001) and plasma norepinephrine (PNE) (p < 0.01) in the lean but not the obese hypertensive patients. Arterial compliance (stroke volume/pulse pressure ratio) was reduced in the lean hypertensive patients, in whom it correlated (p = 0.033) with PNE. The PNE rose less (22%) in the obese than in the lean (55%) hypertensive patients in response to standing (p < 0.05). Likewise, during treadmill exercise, there were lesser increases in renin (65% vs. 145%, p < 0.01) and epinephrine (200% vs. 500%, p < 0.05) in the obese hypertensive patients. These changes were also less in obese patients than in lean control subjects, indicating attenuated neurohormonal responses to stress in obesity.
- CONCLUSIONS** Compared with obese hypertensive patients, cardiovascular properties in lean hypertensive patients are more dependent on catecholamines and the renin system. The different neuroendocrine responses to dynamic stimuli in lean and obese patients also might help to explain the disparity in their cardiovascular outcomes. (J Am Coll Cardiol 2001;37:169-74)
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Both hypertension and obesity are risk factors for cardiovascular events or death (1,2). Excess body weight, independent of hypertension, is associated with several other cardiovascular risk factors. For example, increased blood levels of low-density lipoprotein cholesterol, low levels of high-density lipoprotein cholesterol (3), increased left ventricular muscle mass (4) and renal hyperfiltration (5). Because many of these findings are also associated with hypertension, it could be anticipated that the obese hypertensive patient would have an exaggerated susceptibility to these abnormalities. Paradoxically, though, it has been reported that lean hypertensive patients might have a worse cardiovascular prognosis than obese hypertensive patients (6,7). This apparent advantage to obese hypertensive patients appears to persist even when other risk factors are taken into account (8). This has led to speculation that obese hypertension and lean hypertension represent two genetically distinct forms of hypertension (8), but no clear-cut genetic differences have been established that can explain the differences in clinical outcomes between the two types of hypertension. It should also be recognized that

although obese hypertensive patients might have better clinical outcomes than lean hypertensive patients, their prognosis is still poorer than that of lean people with normal blood pressures (6,8).

The main goal of the present study was to test the hypothesis that differences in catecholamine and renin values might discriminate between obese hypertension and lean hypertension. In particular, we have examined whether responses to standardized treadmill testing might reveal properties of these two conditions that might further explain the differences in their clinical outcomes. In addition, we have performed the same observations in obese and lean normotensive control subjects to determine which characteristics can be attributed to hypertension and which to obesity.

METHODS

A total of 197 volunteers participated in this study. Of these, 121 were hypertensive and were classified into those who were obese (body mass index [BMI] >30 kg/m², n = 55) and those who were lean (BMI <25 kg/m², n = 66). These two groups were matched for age and blood pressure. There were 76 normotensive subjects; 21 were obese and 55 were lean (defined the same as for the hypertensive patients). The two normotensive groups were matched with

From the *State University of New York Downstate Medical Center, Brooklyn, New York; and the †Veterans Affairs Medical Center, Long Beach, California. This work was supported by Merit Review funding of the Department of Veterans Affairs.

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Abbreviations and Acronyms

AER	=	albumin excretion rate
BMI	=	body mass index
LVMI	=	left ventricular mass index
PNE	=	plasma norepinephrine
SV/PP	=	stroke volume/pulse pressure ratio

each other for age and blood pressure, and with their respective hypertensive counterparts for age and BMI. The hypertensive patients either had never been treated for hypertension or had been free of treatment for at least six months. They were identified by a hospital-sponsored screening program. They were excluded from the study if they had a history or any clinical findings indicative of secondary hypertension. Diastolic blood pressures were in the range 90 to 109 mm Hg. The blood pressures for analysis in the study were based on an average of three readings in each patient measured at 2-min intervals after the patient had been comfortably seated for 5 min.

All subjects were carefully instructed in the collection of a 24-h urine sample. Collections were regarded as adequate if 24-h urinary creatinine measurements exceeded 10 mg/kg body weight in women and 15 mg/kg in men. Blood samples for insulin were drawn after an overnight fast. Blood samples for measurement of plasma renin activity were drawn from an indwelling venous port after at least 1 h in the upright position. Blood samples for catecholamine measurements were also drawn from an indwelling venous port after the patient had been quietly recumbent for 30 min. In addition, samples for renin and catecholamines were drawn from an indwelling venous port immediately before treadmill exercise (with the patient standing ready on the treadmill) and immediately on completion of the exercise protocol. Urinary protein values were measured by nephelometry. Plasma values of renin activity (9) and insulin (10) were measured by radioimmunoassay techniques, and plasma catecholamine concentrations were measured by a radioenzyme method (11).

M-mode and two-dimensional echocardiographic studies were performed from parasternal and apical windows. Standard views were obtained by using a commercially available, phased-array, Doppler echocardiographic instrument (General Electric, Pass II or RT500). Standard M-mode echocardiograms were recorded from the parasternal window on strip chart paper at a speed of 50 mm/s. Left ventricular mass was calculated in grams with the equation: left ventricular mass = $1.05 ([LVDD + PWT + VST]^3 - [LVDD]^3)$, where VST = ventricular septal thickness; LVDD = left ventricular diastolic dimension; and PWT = (left ventricular) posterior wall thickness (12). The ratio of echocardiographically derived stroke volume to pulse pressure (SV/PP ratio—the difference between systolic and diastolic blood pressures measured in close proximity to the echocardiographic procedure) was used as an index of total body arterial compliance.

Each participant underwent a full treadmill test on two separate occasions, according to a modified Balke-Ware treadmill protocol (13). The data from the initial study were used to individualize the protocol for each subject during the definitive study treadmill session, which was performed between 7 and 14 days after the initial session (14). After a 1-min warm-up at 2.0 mph/0% grade, the changes in speed and grade were then computer-adjusted (based on each subject's exercise capacity during the baseline test) to yield a test duration of 10 min. The walking speed was increased in ramp fashion to a level between 2.7 and 4.2 mph, where it remained constant; after that, the treadmill grade began increasing at a rate ranging from 1.0% to 2.5%/min. For a given subject, the overall ramp rate was constant during changes in both speed and grade (14). Exercise was continued until volitional fatigue. A standard 12-lead electrocardiogram was obtained throughout the exercise test for safety purposes and to exclude from analysis any patient who revealed evidence of cardiac disease (there were no such instances).

The principal analytic technique was to compare measurements or responses to exercise among the four separate groups (obese and lean hypertensive patients and obese and lean normotensive subjects) using two-way analysis of variance. One factor was lean/obese, and the other was normotension/hypertension. The interaction term between these two factors was also tested (although, in fact, it did not reach significance for any of the values measured in this study). Regression analysis was done using the Pearson method. Data are shown as the mean value \pm SEM. All participants in the study signed an informed consent approved by the Institutional Review Board of the Long Beach Veterans Affairs Medical Center.

RESULTS

Of the hypertensive patients in this study, 55 (8 women) met the criteria for obese hypertension and 66 (9 women) for lean hypertension. There were 21 obese normotensive subjects (3 women) and 55 lean normotensive subjects (10 women). There were 41 non-Caucasian participants (32 Asian), again distributed evenly among the groups. Table 1 shows the values for age, BMI, blood pressure and heart rate for each of the four study groups. There was no difference in age among the groups, but by definition, BMI in both obese groups was significantly greater than that in the lean groups. However, there was no difference in BMI values between the obese hypertensive patients and normotensive subjects or between the lean hypertensive patients and normotensive subjects. There were no differences in blood pressures between either of the hypertensive groups or either of the normotensive groups, although the differences between hypertensive patients and normotensive subjects were significant. Heart rate was similar across all groups. Values for the four groups in blood concentrations of lipids, insulin, catecholamines and renin activity are shown in Table 2.

Table 1. Clinical Characteristics

	Obese HTN (n = 55)	Lean HTN (n = 66)	Obese Norm (n = 21)	Lean Norm (n = 55)
Age (yr)	46 ± 2	45 ± 2	45 ± 2	45 ± 2
BMI (kg/m ²)	32.5 ± 0.3	24.3 ± 0.2	31.8 ± 0.6	23.9 ± 0.2
Systolic BP (mm Hg)	145 ± 2*	144 ± 2*	126 ± 2	124 ± 2
Diastolic BP (mm Hg)	100 ± 1*	98 ± 1*	82 ± 1	81 ± 1
Heart rate (beats/min)	70 ± 1	70 ± 1	67 ± 2	68 ± 2

Data are presented as the mean value ± SEM.
 BMI = body mass index; BP = blood pressure; HTN hypertensive; Norm = normotensive.

Lipid values in the obese hypertension group differed from those in each of the other three groups, including the obese normotensive group. Insulin concentrations were significantly higher in the obese groups than in the lean groups. There were no differences in catecholamine or renin values between the four study groups.

Values for the cardiovascular measurements of left ventricular mass index (LVMI) and total body compliance (SV/PP ratio), as well as the renal measurements of creatinine clearance and urinary albumin excretion rate (AER), are shown in Table 3. As compared with the lean normotensive subjects, both the obese and lean hypertensive patients, as well as the obese normotensive subjects, had significantly higher LVMI values. Even the lean normotensive group had a relatively high LVMI; this might reflect the method used to calculate this value (12), or possibly a tendency toward borderline changes in apparently normal individuals who choose to attend a screening program. The SV/PP ratio was significantly lower in the lean hypertensive group than in any of the other groups. As compared with the lean normotensive group, creatinine clearance was significantly higher in both of the obese groups; AER was higher in the obese hypertensive group than in any of the other groups.

Correlations between the dependant variable LVMI and the three principal neuroendocrine values—plasma renin activity, plasma norepinephrine (PNE) and plasma epinephrine—are shown in Figure 1. Each of these three independent variables correlated significantly with LVMI in the lean hypertensive patients, but these correlations were not significant in the obese hypertensive patients. For the dependent variable SV/PP ratio, there was a significant

relation ($r = -0.36, p = 0.018$) with norepinephrine in the lean hypertensive patients. This correlation was not significant in the obese hypertensive patients ($r = -0.06$); however, in the obese but not the lean hypertensive patients ($r = -0.11$), the SV/PP ratio correlated significantly with plasma insulin concentration ($r = -0.34, p = 0.033$).

The effects of standing (10 min in the upright posture) on PNE concentrations were greater in the lean hypertensive patients (104 ± 17 pg/ml) than in the obese hypertensive patients (47 ± 11 pg/ml) or in the lean or obese (54 ± 15 and 48 ± 17 pg/ml) normotensive subjects ($p = 0.044$ by analysis of variance for obese vs. lean). The effects of standing on PNE concentrations or plasma renin activity were not different between any of the groups. Likewise, there were no differences in changes in blood pressures or heart rate between the groups on assuming the upright posture. During treadmill exercise, there were no differences between the four groups (obese and lean hypertensive patients and obese and lean normotensive subjects) in either maximal changes in systolic blood pressure ($60 \pm 3, 61 \pm 3, 60 \pm 5$ and 60 ± 3 mm Hg, respectively) or maximal changes in diastolic blood pressure ($-4 \pm 2, -5 \pm 2, -5 \pm 1$ and -6 ± 2 mm Hg, respectively). The changes during treadmill exercise in plasma concentrations of epinephrine and in plasma renin activity are shown in Figure 2 for the two hypertensive groups and the two normotensive groups. The changes in norepinephrine during treadmill testing were not significantly different between the two groups. However, the increases in both PNE concentration and plasma renin activity were significantly greater in lean participants as compared with obese ones.

Table 2. Metabolic and Neuroendocrine Measurements

	Obese HTN (n = 55)	Lean HTN (n = 66)	Obese Norm (n = 21)	Lean Norm (n = 55)	p Value (ANOVA)
Total cholesterol (mg/dl)	225 ± 6	208 ± 6	203 ± 9	195 ± 4	0.009*
LDL cholesterol (mg/dl)	153 ± 4	135 ± 6	131 ± 5	123 ± 7	0.048†, 0.037*
HDL cholesterol (mg/dl)	44 ± 2	54 ± 3	52 ± 3	59 ± 4	0.012†
Triglycerides (mg/dl)	182 ± 18	133 ± 10	120 ± 12	117 ± 12	0.037*
Insulin (μU/ml)	17.7 ± 1.3	11.1 ± 1.1	15.4 ± 2.2	10.9 ± 1.5	0.0004†
Norepinephrine (pg/ml)	252 ± 20	259 ± 21	231 ± 18	224 ± 17	NS
Epinephrine (pg/ml)	34 ± 3	39 ± 3	37 ± 4	37 ± 3	NS
Plasma renin activity (ngAI/ml per h)	2.2 ± 0.2	2.3 ± 0.2	2.2 ± 0.4	2.1 ± 0.2	NS

*Analysis of variance (ANOVA) for hypertensive patients vs. normotensive subjects. †ANOVA for lean vs. obese patients. There were no significant interactions between the obesity and blood pressure factors with the two-way ANOVA. Data are presented as the mean value ± SEM.

HDL = high density lipoprotein; LDL = low density lipoprotein; NS = not significant; other abbreviations as in Table 1.

Table 3. Cardiac and Renal Measurements

	Obese HTN (n = 55)	Lean HTN (n = 66)	Obese Norm (n = 21)	Lean Norm (n = 55)	p Value (ANOVA)
LVMI (g/m ²)	137 ± 7	135 ± 4	133 ± 4	120 ± 4	0.031*
SV/PP (ml/mm Hg)	2.17 ± 0.12	1.90 ± 0.08	2.26 ± 0.24	2.21 ± 0.13	0.042*
creatinine clearance (ml/min)	121 ± 5	115 ± 4	127 ± 9	104 ± 4	0.005†
Urine sodium (mEq/day)	167 ± 13	159 ± 10	163 ± 16	153 ± 10	NS
AER (mg/day)	144 ± 16	101 ± 10	108 ± 13	85 ± 6	0.034†

*Analysis of variance (ANOVA) for hypertensive patients vs normotensive subjects. †ANOVA for lean versus obese patients. There were no significant interactions between the obesity and blood pressure factors with the two-way ANOVA. Data are presented as the mean value ± SEM.

AER = albumin excretion rate; LVMI = left ventricular mass index; SV/PP = stroke volume to pulse pressure ratio; other abbreviations as in Table 1.

DISCUSSION

This study has compared the characteristics of obese and lean hypertension in two groups of patients matched for age and blood pressure and, with additional control subjects, has compared groups of normotensive subjects matched for age and BMI with the respective hypertensive groups. The study included relatively young patients with mild hypertension who were identified primarily by a screening process. For this reason, there was no overt clinical evidence of cardiovascular or renal pathology in the participants, and the findings were not confounded by current or recent antihypertensive therapy. Reflecting the population served by our institution, the participants in this study were predominantly white and male; in future studies, it would be important to extend this work to a more diverse community.

Responses to exercise. The primary goal of this investigation was to determine whether obese and lean hypertensive patients could be differentiated by their responses to a standardized treadmill protocol. In fact, there was no difference between the two hypertensive groups, or their respective normotensive control groups, in their maximal systolic or diastolic blood pressure changes during the procedure. However, there were significantly greater increases in both plasma epinephrine concentrations and plasma renin activity in the lean hypertensive patients as

compared with the obese ones. The corresponding changes in the normotensive groups were virtually identical to those in the hypertensive patients, indicating that obesity—regardless of whether or not hypertension is present—may have an inhibitory effect on the neuroendocrine response to physical stress. We also observed that the increase in PNE concentrations on standing, possibly a reflection of acute sympathetic activation, was greater in the lean hypertensive patients than in the obese ones.

Cardiovascular and renal findings. The role of sympathetic factors in hypertension in the obese individual is not clear. In a large number of studies reporting measurements of plasma or urinary norepinephrine levels at rest or during unspecified activity, approximately equal numbers of studies

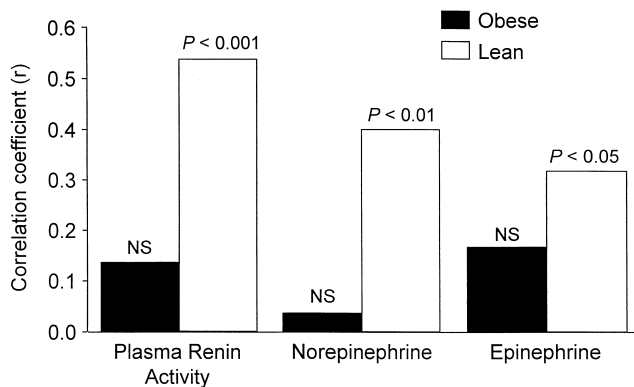


Figure 1. Correlation coefficients for the relations between left ventricular mass index (LVMI) and plasma renin activity or plasma concentrations of norepinephrine and epinephrine in obese and lean hypertensive patients. The r values are significant by univariate analysis for each of the variables in the lean patients; however, by multivariate analysis, only the plasma renin activity and norepinephrine relations remain in the model.

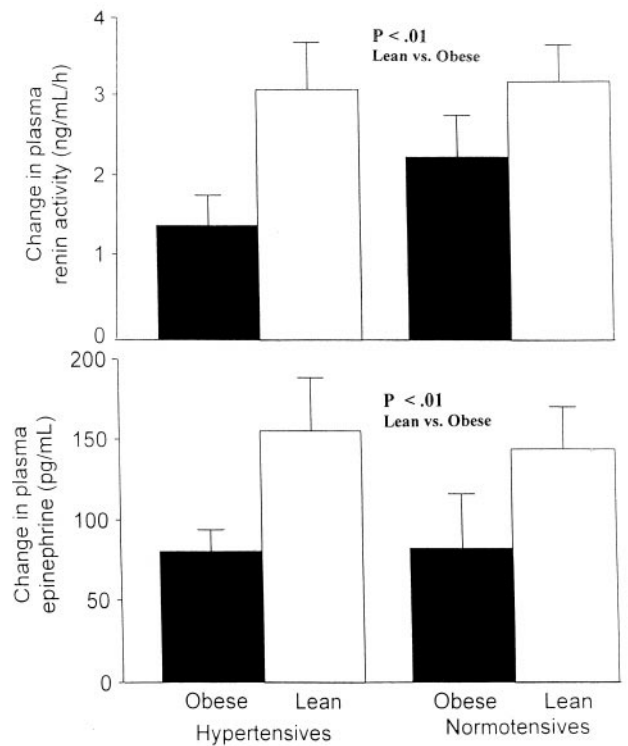


Figure 2. Changes in plasma renin activity and in plasma norepinephrine (PNE) concentrations during treadmill testing in obese and lean hypertensive patients and normotensive volunteers. By two-way analysis of variance, the differences between the obese and lean patients were significant, but not the differences between hypertensive patients and normotensive subjects

showed that catecholamine levels were higher in obese hypertensive patients or were higher in lean hypertensive patients, or were similar in each (15). This is consistent with the findings in the present study, where rest plasma catecholamine levels were similar in obese and lean hypertensive patients. It has been suggested, though, by such techniques as norepinephrine spillover (16) or microneurography (17), that there might be increased sympathetic activity in obesity; but, again, these findings may not be consistent (15). Indeed, cardiac left ventricular muscle mass in the present study correlated significantly with plasma concentrations of norepinephrine and epinephrine, as well as with plasma renin activity, in the lean hypertensive patients but not in the obese ones. However, other investigators have previously shown that left ventricular mass in obese individuals appears to be primarily related to increased body weight (4), perhaps reflecting the known myocardial trophic effects of the peptide hormone leptin, which is produced by adipose tissue (18).

The SV/PP ratio, which is used as an index of total arterial compliance (19), differed between the two hypertensive groups. It was significantly lower, suggesting increased arterial stiffness, in the lean hypertensive patients as compared with the obese hypertensive patients or normotensive control subjects. This finding may be of clinical relevance, for SV/PP has been shown to be predictive of physiologic changes in the vasculature (20) and recently was found to have predictive value, even when adjusted for other risk factors, for subsequent clinical cardiovascular events (21). In the present study, this measure of arterial compliance correlated inversely with plasma concentrations of norepinephrine in the lean hypertensive group, but not in any of the other groups. It is possible, therefore, that arterial stiffening may be a characteristic of lean hypertension that distinguishes it from obese hypertension.

There are differences in renal function between obese and lean hypertensive patients. Obesity appears to increase renal sodium reabsorption (22,23), very likely because of heightened renal sympathetic activity (24). This, in turn, could help explain the increased plasma volume and cardiac output found in obese individuals (25). This study has shown that the glomerular filtration rate, as measured by creatinine clearance, is significantly higher in both hypertensive and normotensive obese individuals as compared with lean normotensive control subjects. The lean hypertensive patients also exhibited an increase in glomerular filtration. Similar findings have been reported previously (5). Likewise, we found an increase in the albumin excretion rate in the obese hypertensive patients, probably reflecting their high glomerular filtration rate. Another finding, also previously well demonstrated (3), was the clearly abnormal lipid profile in the obese hypertensive patients. Obesity, per se, may not fully explain these abnormalities, because as compared with the obese normotensive group, the obese hypertensive group had higher low density lipoprotein and lower high density lipoprotein cholesterol concentrations. Thus,

the combination of obesity and hypertension in this particular group seems to have additive adverse effects on the lipid profile.

Therapeutic implications. The hemodynamic data of obese hypertension are characterized by increased stroke volume but normal peripheral resistance, whereas in lean hypertension, stroke volume is normal but peripheral resistance is increased (26-28). A recently published report based on a re-analysis of the Systolic Hypertension in the Elderly Program (SHEP) has highlighted the prognostic importance of these differing hemodynamic profiles (29). Treatment with the diuretic chlorthalidone was most effective at reducing mortality in overweight hypertensive patients. Indeed, in hypertensive patients with BMI ≤ 24 kg/m², normally considered a desirable weight, the risk of adverse events rose sharply (29). The findings of the present study that cardiovascular changes in lean hypertensive patients are at least partly mediated by activity of the renin-angiotensin and sympathetic systems may help explain why diuretic therapy, which stimulates these systems, is not fully effective in preventing clinical end points in lean patients. It would also be most interesting to test whether such agents as angiotensin-converting enzyme inhibitors might be preferentially effective in thin hypertensive patients.

Overall, these findings emphasize that obese hypertension and lean hypertension are two distinct conditions. As established previously (26), obese patients with hypertension are characterized by abnormalities of insulin and lipid metabolism and have evidence for left ventricular hypertrophy, renal hyperfiltration and albuminuria. Lean hypertensive patients have similar findings, but they are more dependent on the sympathetic and renin systems. Moreover, in this study, there was an attenuated neuroendocrine response to stress in the obese patients, which might also help to explain why they appear to have a cardiovascular prognostic advantage over lean patients (6-8,29).

Reprint requests and correspondence: Dr. Michael A. Weber, 350 Fifth Avenue, Suite 4002, New York, New York 10118. E-mail: michaelwebermd@cs.com.

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