Central Obesity and Hypertension
Relationship Between Fasting Serum Insulin, Plasma Renin Activity, and Diastolic Blood Pressure in Young Obese Subjects

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This study was designed to evaluate the role of fasting serum insulin and plasma renin activity in obesity-induced hypertension. In view of this, plasma catecholamines, fasting serum insulin (IRI), urinary sodium excretion (NaU), plasma renin activity (PRA), and plasma aldosterone (PA) levels were assessed in young (age less than 40 years) normotensive (n = 27) and hypertensive (n = 14) subjects with central obesity and in lean normotensives (n = 20). Central obesity was evaluated by waist-to-hip ratio (WHR) according to the indication of the Italian Consensus Conference of Obesity.

PRA, PA, IRI, and plasma norepinephrine levels were significantly ($P < .05$) higher in both obese groups than in lean normotensives.

PRA was significantly ($P < .05$) higher and NaU was significantly ($P < .05$) lower in obese hypertensives than in obese normotensives. Diastolic blood pressure correlated directly with WHR and PRA in normotensive and hypertensive obese subjects and with IRI but only in normotensive obese subjects.

Multiple regression analysis indicated that diastolic blood pressure values increased with WHR ($P < .05$), IRI ($P < .005$), and PRA ($P < .002$), but not with body mass index, NaU, and norepinephrine levels.

Our results indicated that increased PRA could play an important role in the development of hypertension in subjects with central obesity. Am J Hypertens 1994;7:314–320

KEY WORDS: **Central obesity, hypertension, insulin, renin-angiotensin-aldosterone system.**

Obesity has been shown to be associated with essential hypertension.[1] In fact, some prospective studies indicated that weight gain was positively associated with future blood pressure[2,3] and with the risk of developing primary hypertension.[4]

However, human obesity is not a homogeneous condition. Some studies have indicated that the distribution of excess adipose tissue to central or peripheral areas is associated with different prevalence rates of associated metabolic abnormalities as well as risk for cardiovascular disease.[5,6] In addition, hypertension appears to be related to obesity (defined as enlargement of body fat mass) as such, as well as to central distribution of body fat.[7,8] There is consistent evidence that hypertension associated with visceral excess of body fat is particularly harmful as a risk factor for development of cardiovascular disease.[7,9]

Although this strong association is known, the mechanisms of obesity-induced hypertension are still unclear.[10–16] Some abnormalities have been suggested to explain the higher susceptibility of obese subjects to developing hypertension. They include sodium retention[12] and dysregulation in salt-regulating hormones,[13] increased plasma volume and

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cardiac output,[14] hyperinsulinemia and insulin resistance,[11,15] and enhanced sympathetic nervous system activity.[16]

Despite these indications, few studies have addressed the evaluation of these abnormalities in a particular subset of young normotensive or hypertensive obese subjects, ie, those with central obesity.

In this study, plasma catecholamine levels, fasting serum insulin, urinary sodium excretion, plasma renin activity, and plasma aldosterone were evaluated in young hypertensive and normotensive subjects with central obesity, and in lean normotensives.

Our final goal was to recognize the relationship between hormonal profile and blood pressure, to improve the understanding of the mechanisms responsible for obesity-induced hypertension.

SUBJECTS AND METHODS

Subjects A total of 41 obese subjects, 14 with established hypertension and 27 normotensives, and 20 lean normotensive subjects with ages less than 40 years were included in the study. Obese subjects were recruited from the obese population attending the obesity center of the Internal Medicine Department at the University of Palermo, Italy. Lean controls were volunteer subjects chosen from a group of subjects undergoing a clinical checkup and found to be healthy.

The subjects were defined as obese according to Garrow's criteria[17] and to body mass index values (BMI $\geq$ 30 kg/m^2). Subjects were considered lean when BMI values were $\leq$25 kg/m^2.

Each subject's fat distribution was assessed by measurement of waist-to-hip girth ratio (WHR) in the standing position, as previously reported.[18] Central fat distribution was defined on the basis of sex-specific 85th percentile of WHR values as suggested by the Italian Consensus Conference on Obesity.[19] In view of this, the cutoff value of central obesity was considered $\geq$0.81 for women and $\geq$0.92 for men. According to these criteria obese subjects with peripheral obesity (WHR values <0.81 for women and <0.92 for men) were excluded. Duration of obesity (DO) was evaluated by accurate medical history,[20,21] and it was 176 ± 107 months in normotensive obese subjects and

TABLE 1. DETAILS OF LEAN NORMOTENSIVES AND OF THE TWO GROUPS OF SUBJECTS WITH CENTRAL OBESITY

	Lean subjects	Obese subjects	
	Normotensives (n = 20)	Normotensives (n = 27)	Hypertensives (n = 14)
Gender (M/F)	10/10	12/15	6/8
Age (years)	31 ± 4.9	30.3 ± 5.4	30.9 ± 5.2
Weight (kg)	61 ± 8.1	90.7 ± 19.9*	90.3 ± 18.5*
Height (cm)	165 ± 8.3	161 ± 11	163 ± 10
BMI (kg/m^2)	22.2 ± 2.1	34.6 ± 5.9*	35.5 ± 4.3*
WHR (%)	0.85 ± 0.07	0.93 ± 0.07*	0.94 ± 0.05*
SBP (mm Hg)	123 ± 4.2	126 ± 12	160 ± 5.2*†
DBP (mm Hg)	77.6 ± 8.1	78 ± 9	101 ± 4.9*†
MBP (mm Hg)	93 ± 6.9	94 ± 8.5	121 ± 6.1*†
HR (beats/min)	71 ± 4.1	75.6 ± 4.5*	76.5 ± 5.2*
DO (months)	—	176 ± 107	185 ± 99
FBS (mg/dL)	88.8 ± 2.9	90 ± 3.7	90.9 ± 4.3
CHOL (mg/dL)	180 ± 8.5	182 ± 7.5	180 ± 7.7
TRIG (mg/dL)	120 ± 18	115 ± 22	114 ± 32
IRI (μU/mL)	9.1 ± 3.2	15.6 ± 9.7*	19 ± 9.5*
PRA (ng/mL/h)	1.5 ± 0.9	2.3 ± 0.2*	2.9 ± 0.7*†
PA (pg/mL)	250 ± 27	276 ± 41*	301 ± 53*
NOR-EP (pg/mL)	278 ± 30	332 ± 23*	344 ± 25*
EP (pg/mL)	173 ± 38	179 ± 41	180 ± 32
NaU (mmol/L/24 h)	117 ± 39	134 ± 24.3	105 ± 31†

*P < .05 v *lean normotensives.*

†P < .05 v *obese normotensives.*

BMI, body mass index; WHR, waist/hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; DO, duration of obesity; FBS, fasting blood sugar; CHOL, total cholesterol; TRIG, serum triglycerides; IRI, immunoreactive insulin; PRA, plasma renin activity; PA, plasma aldosterone; NOR-EP, plasma norepinephrine; EP, plasma epinephrine; NaU, 24-hour urinary sodium excretion.

185 ± 99 months in hypertensive obese subjects. This difference was statistically not significant (Table 1).

According to Joint National Committee (JNC)[22] criteria, essential hypertension was defined when diastolic blood pressure was ≥90 mm Hg with the subjects in the supine position on at least three visits at 1-week intervals. Arterial pressure was measured with an appropriate large cuff in obese subjects.[23] According to these criteria the subjects were subdivided as follows:

Group 1 (Lean Normotensive Subjects) This group consisted of subjects (10 men and 10 women) aged 24 to 39 years (mean age 31 ± 4.9) with BMI mean value of 22.2 ± 2.1 and WHR mean value of 0.85 ± 0.07.

Group 2 (Normotensive Subjects With Central Obesity) This group consisted of subjects (12 men and 15 women) aged 27 to 40 years (mean age 30.9 ± 5.2) and with BMI mean value of 34.6 ± 5.9 and WHR mean value of 0.93 ± 0.07.

Group 3 (Hypertensive Subjects With Central Obesity) This group consisted of subjects (6 men and 8 women) aged 25 to 40 years (mean age 30.3 ± 5.4) with BMI mean value of 35.5 ± 4.3 and WHR mean value of 0.94 ± 0.05.

All the subjects were matched as closely as possible with regard to age, gender, and body height.

Exclusion criteria included secondary form of hypertension, severe hypertension, cardiovascular diseases, renal disease and renal failure (serum creatinine > 1.4 mg/dL), insulin-dependent or -independent diabetes mellitus, electrolyte imbalances, moderate or severe Keith-Wagener hypertensive retinopathy, alcoholism, or psychiatric problems.

The patients with concomitant left ventricular hypertrophy assessed by echocardiographic criteria or with other target organ damage were also excluded.[24]

All the patients were untreated for at least 4 weeks before the study, and they maintained a normal sodium intake (120 mEq/day). During this withdrawal period no significant changes in body weight were observed. Each patient gave informed consent after receiving a detailed description of the study procedure; the study was also approved by the Ethical Committee of our institution.

Preliminary investigations included measurements of blood and urinary electrolytes, creatinine clearance, fasting blood sugar and oral glucose tolerance test, serum cholesterol, triglyceride levels, and liver function tests.

Laboratory Methods Venous blood samples were drawn after an overnight fast to determine immunoreactive insulin (IRI), plasma renin activity (PRA), plasma aldosterone (PA), and plasma catecholamines.

Insulin Immunoreactive insulin levels were detected by the radioimmunoassay (RIA) double-antibody method using a commercial kit (Sorin, Saluggia, Italy). Intraassay variation was 7.5% and interassay variation was 8%. Sensitivity for detection of insulin was 2.5 μU/mL.

Plasma Renin Activity and Plasma Aldosterone PRA was measured by radioimmunoassay according to the method described by Menard and Catt[25] and PA levels were estimated by the RIA method using a commercial kit (Sorin).

Intraassay variations were 5% for PRA and 9.5% for PA, whereas interassay variations were 7% for PRA and 11.2% for PA. Sensitivity of methods was 0.12 ng/mL for PRA and 15 pg/mL for PA.

Plasma Catecholamines Samples were prepared and assayed by high-perfusion liquid chromatography as described by Goldstein et al.[26] Sensitivity for detection of norepinephrine was 15 pg and for epinephrine, 25 pg.

Urinary Excretion of Sodium To evaluate urinary sodium excretion (NaU), three consecutive 24-h urine collections were used. NaU values were expressed as the mean value of the three determinations. Sodium levels in urine were measured by the current ion-selective electrode method (Beckman).

Statistical Analysis Data are presented as mean value ± SD. Comparisons among the three groups were performed by one-way analysis of variance and Newman-Keuls *t* test.

Linear and multiple regression analyses were utilized to calculate coefficients of correlation among diastolic blood pressure (DBP) and both hormonal measurements and obesity parameters. Independent variables in multiple regression analysis were IRI, BMI, WHR, PRA, plasma norepinephrine, and 24-h NaU.

A P value $<.05$ was considered statistically significant.

RESULTS

Characteristics of Lean and Obese Subjects The three groups were comparable with regard to gender, age, and body height. Lean and obese normotensive subjects were also comparable with regard to systolic, diastolic, and mean blood pressure. Duration of obesity and WHR were similar in both obese groups (Table 1).

A mild but significant ($P < .05$) increase in heart rate was found in both obese groups in comparison with lean normotensives (Table 1).

Subjects With Central Obesity *v* Lean Normotensives PRA, PA, fasting serum insulin, and norepinephrine levels were significantly ($P < .05$) higher in both obese groups than in lean normotensives. No significant differences in fasting blood sugar, total cholesterol, triglycerides, urinary sodium excretion, and epinephrine values were observed among the obese and lean groups (Table 1).

Obese Hypertensives *v* Obese Normotensives Plasma renin activity was significantly ($P < .05$) higher and urinary excretion of sodium was significantly ($P < .05$) lower in obese hypertensive than in obese normotensive subjects. No significant changes in the remaining measurements were observed between the two obese groups (Table 1).

Correlations Linear and multiple correlation analyses were performed in all subjects with central obesity and separately in normotensive and hypertensive obese subjects.

Diastolic blood pressure correlated directly with WHR (r = 0.334; $P < .05$), PRA (r = 0.575; $P < .0001$), and IRI (r = 0.522; $P < .002$) in all the subjects with central obesity.

On the contrary, DBP did not correlate with BMI, NaU, and catecholamines. WHR correlated directly with IRI (r = 0.370, $P < .05$) and with PRA (r = 0.381; $P < .05$) but not with the remaining measurements.

DBP correlated directly with PRA (r = 0.51; $P < .005$), IRI (r = 0.74; $P < .0001$), and WHR (r = 0.44; $P < .005$) in normotensive obese subjects (Figure 1). DBP correlated directly with PRA (r = 0.61; $P < .03$), WHR (r = 0.80; $P < .0001$) but not with IRI (r = 0.49) in hypertensive obese subjects (Figure 2).

Multiple regression analysis indicated that DBP values increased with WHR ($P < .05$), IRI ($P < .005$), and PRA ($P < .002$) but not with NaU or norepinephrine levels.

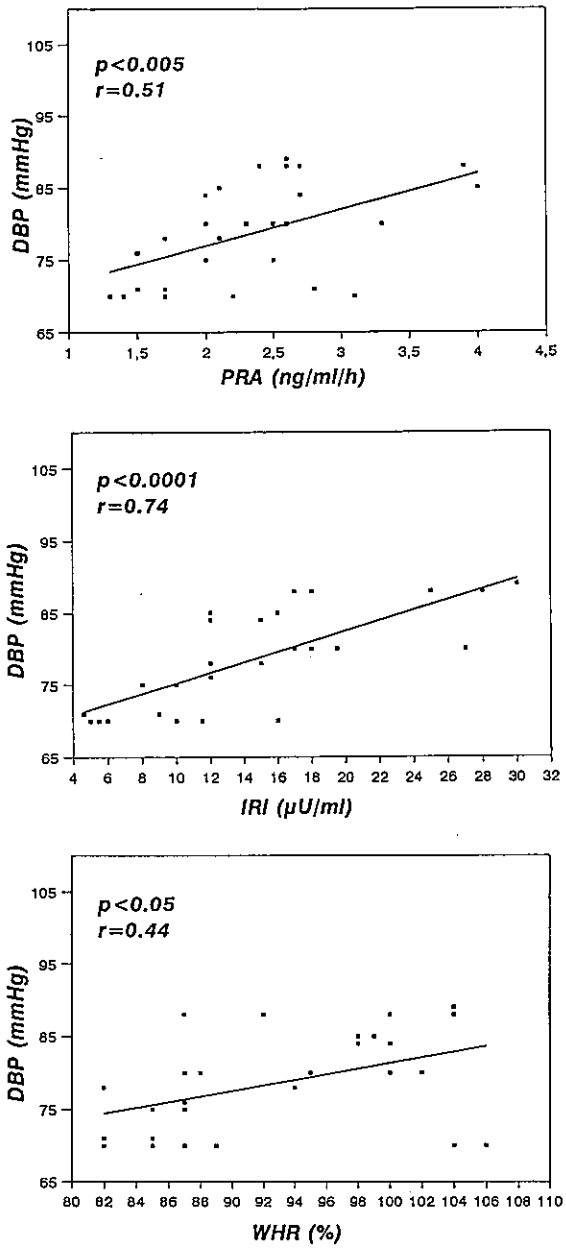

FIGURE 1. *Relationships between diastolic blood pressure (DBP) and plasma renin activity (PRA), fasting insulin (IRI), and waist-hip ratio (WHR) in 27 normotensive obese subjects.*

DISCUSSION

This study indicated that subjects with central obesity, both normotensives and hypertensives, were characterized by remarkable changes in salt-regulating hormones in comparison with lean normotensive subjects.

In particular, PRA, PA, fasting serum insulin, and norepinephrine levels were higher in both obese groups than in lean normotensives. Some of these differences seem to be related to body fat distribution rather than to BMI.

A direct and independent relationship between diastolic blood pressure and WHR, a sensitive index of body fat distribution,[7,8] was recognized in normotensive and hypertensive subjects with central obesity. This relation indicates that WHR may be considered a predictor of diastolic blood pressure above all in obese hypertensive subjects when we also considered PRA, IRI, NaU, and norepinephrine levels.

A direct influence of WHR on blood pressure has been recently reported by Gerber et al[27] and by Troisi et al.[28]

WHR is a widely used index of fat distribution and has been shown to correlate strongly with abdominal fat masses in both men and women.[29]

Excessive alcohol use might have confounded the WHR measurement.[28] For this reason we have

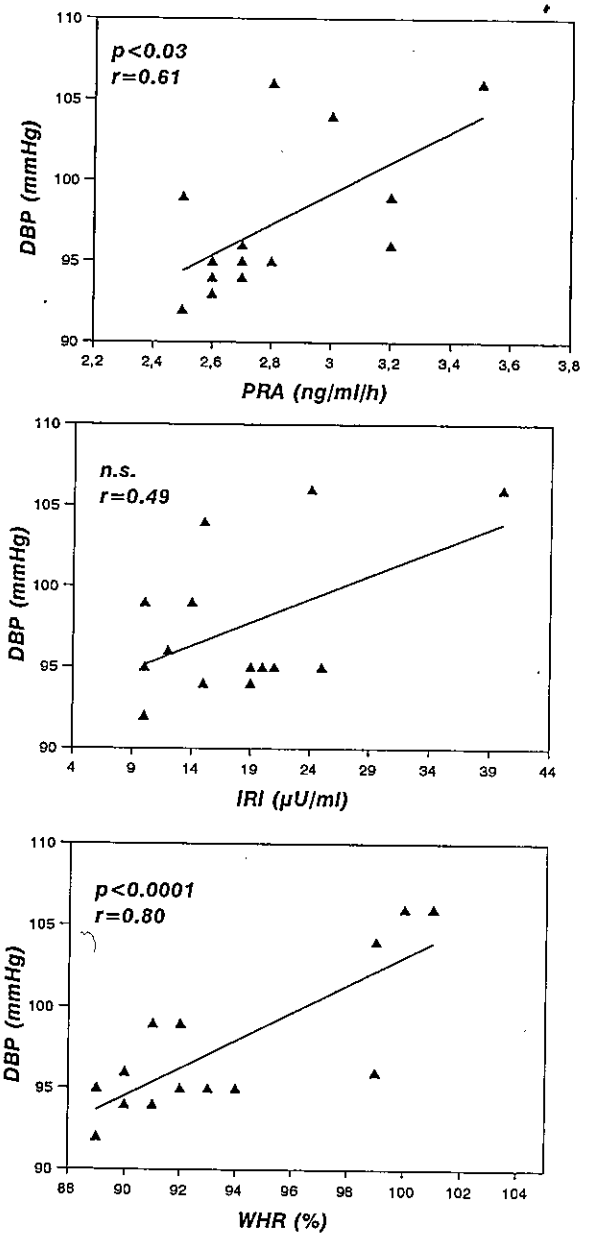

FIGURE 2. *Relationships between diastolic blood pressure (DBP) and plasma renin activity (PRA), fasting insulin (IRI), and waist-hip ratio (WHR) in 14 hypertensive obese subjects.*

excluded all subjects with a history of alcohol consumption.

The principal endpoint of this investigation was to analyze the role of fasting serum insulin and plasma renin activity in obesity-induced hypertension. Several studies reported that hyperinsulinemia and insulin resistance could explain the strong association between obesity and hypertension.[10,15,16,30–34] It has been suggested that hyperinsulinemia and insulin resistance cause blood pressure elevation by stimulating sodium reabsorption and activation of the sympathetic nervous system.[16,31,32]

These changes were also observed in the current study. In fact, increased fasting serum insulin levels and norepinephrine values were found in the hypertensive subjects with central obesity. However, our data cannot indicate whether increased fasting serum insulin levels are responsible for hypertension in these subjects. In fact, despite fasting serum insulin levels remaining an independent determinant of diastolic blood pressure, they were not significantly different between hypertensive and normotensive subjects with central obesity, as also reported by Istfan et al.[30]

Despite the fact that in our study we did not assess insulin levels during oral glucose tolerance tests or using the euglycemic clamp technique, reported as methods able to recognize insulin resistance,[33] several data suggest the existence of insulin resistance in obese individuals and above all in those with central obesity.[15,30,32] On the other hand, Bonura et al[35] reported that diastolic blood pressure correlated with postglucose plasma insulin levels in lean hypertensives but not in obese hypertensives. Instead, few data are available on the renin-angiotensin-aldosterone system in subjects with central obesity.[13,36,37]

Our previous results indicated an altered response of this system to an acute saline load in young normotensive obese subjects. It consisted of a lack of atrial natriuretic factor (ANF) response and reduction of PRA and PA suppression to saline load. These abnormalities may be involved in the higher susceptibility of obese subjects to develop hypertension.[13] In the current study PRA values were significantly different between normotensive and hypertensive subjects with central obesity.

These results are consistent with our previous indications that a dysregulation in the renin-aldosterone system may be involved in obesity-induced hypertension.[13] This suggestion is further supported by multiple regression analysis indicating that PRA remained one of the best predictors of diastolic blood pressure in normotensive and hypertensive subjects with central obesity, even when WHR and BMI values, fasting serum insulin, norepinephrine levels, and urinary excretion of sodium were considered.

Higher PRA levels in obese hypertensives were associated with reduced values of NaU. This suggests that increased PRA levels may be related to a lower sodium intake in these subjects. In our opinion the lack of relationship between NaU and PRA could indicate a dysregulation in renin secretion in obese hypertensives independent of the amount of sodium intake. The reduced NaU in obese hypertensives could be due to a reduced action of ANF. This has been reported recently in young obese subjects during an acute saline load.[13]

In conclusion, our results indicate that young obese

subjects may be characterized by some hormonal changes related to their body fat distribution. The differences in PRA levels detectable between normotensive and hypertensive subjects with central obesity suggests that increased renin secretion plays an important role in the development of hypertension in these subjects. Additional data have to be provided to indicate the mechanisms responsible for changes in renin secretion in hypertensive subjects with central obesity.

REFERENCES

1. Chang BN, Perlman LV, Epstein FH: Overweight and hypertension: A review. Circulation 1969;39:403–421.
2. Julius S, Harburg E, McGinn N, et al: Relation between casual blood pressure readings in youth and at age 40. J Chronic Dis 1964;17:397–404.
3. Rose GA: Hypertension in the community. Handbook of Hypertension 1985;6:1–14.
4. Kannel WB, Brand N, Skinner JJ, et al: The relation of adiposity to blood pressure and development of hypertension. Ann Intern Med 1967;67:48–59.
5. Bjorntorp P: Abdominal obesity and the development of non insulin dependent diabetes mellitus. Diabetes Metab Rev 1988;4:615–622.
6. Kissebah AH, Peiris AN: Biology of regional body fat distribution: Relationship to non insulin dependent diabetes mellitus. Diabetes Metab Rev 1989;5:83–89.
7. Lapidus L, Bengtsson C, Hallstrom T, et al: Obesity, adipose tissue distribution and health in women—Results from a population study in Goteborg, Sweden. Appetite 1989;12:25–35.
8. Jern S, Bergbrant A, Bjorntorp P, et al: Relation of central hemodynamics to obesity and body fat distribution. Hypertension 1992;19:520–527.
9. Welin L, Svardsudd K, Wilhelmsen L, et al: Analysis of risk factor for stroke in the cohort of men born in 1913. N Engl J Med 1987;317:521–526.
10. Dustan HP: Mechanism of hypertension associated with obesity. Ann Intern Med 1983;98:860–864.
11. Modan M, Halkin H, Almog S, et al: Hyperinsulinaemia. A link between hypertension, obesity, and glucose intolerance. J Clin Invest 1985;75:809–817.
12. Rocchini AP, Key S, Bondie D: The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. N Engl J Med 1989;321:580–585.
13. Licata G, Volpe M, Scaglione R, et al: Salt regulating hormones in young normotensive obese subjects. Effects of saline load. Hypertension 1994;23(suppl 1):20–24.
14. Licata G, Scaglione R, Capuana G, et al: Hypertension in obese subjects: Distinct hypertensive subgroup. J Hum Hypertens 1990;4:37–41.
15. Rocchini AP: Insulin resistance and blood pressure regulation in obese and non obese subjects. Hypertension 1991;17:837–842.
16. Landsberg L, Young JB: The role of sympathoadrenal system in modulating energy expenditure. Metabolism 1984;13:475–479.
17. Garrow JS, Webster J: Quetelet's index (W/H^2) as a measure of fatness. Int J Obesity 1985;9:147–153.
18. Licata G, Scaglione R, Barbagallo M, et al: Effect of obesity on left ventricular function studied by radionuclide angiocardiography. Int J Obesity 1991;15:295–302.
19. Crepaldi G, Belfiore S, Bosello O, et al: Special report: Italian Consensus Conference—Overweight, Obesity, and Health. Int J Obesity 1991;15:781–790.
20. Scaglione R, Dichiara MA, Indovina A, et al: Left ventricular diastolic and systolic function in normotensive obese subjects: Influence of degree and duration of obesity. Eur Heart J 1992;14:738–742.
21. Licata G, Scaglione R, Paterna S, et al: Left ventricular function response to exercise in normotensive obese subjects: Influence of degree and duration of obesity. Int J Cardiol 1992;37:223–230.
22. The fifth report of the Joint National Committee on detection, evaluation and treatment of hypertension. Arch Intern Med 1993;153:154–183.
23. King GE: Errors in clinical measurements of blood pressure in obesity. Clin Sci 1967;32:223–225.
24. Licata G, Scaglione R, Parrinello G, et al: Rapid left ventricular filling in untreated hypertensive subjects with or without left ventricular hypertrophy. Chest 1992;102:1507–1511.
25. Menard J, Catt KJ: Measurements of renin activity by radioimmunoassay of angiotensin I. Endocrinology 1972;90:422–427.
26. Goldstein DS, Feuerstein G, Izzo JL, et al: Validity and reliability of liquid chromatography with electrochemical detection for measuring plasma levels of norepinephrine and epinephrine in man. Life Sci 1981;28:468–473.
27. Gerber LM, Schnall PL, Pickering TG: Body fat and its distribution in relation to casual and ambulatory blood pressure. Hypertension 1990;15:508–513.
28. Troisi RJ, Weiss ST, Segal MR, et al: The relationship of body fat distribution to blood pressure in normotensive men: The normative aging study. Int J Obesity 1990;14:515–525.
29. Kvist H, Chowdury B, Grangard U, et al: Total and visceral adipose-tissue volumes from measurements with computed tomography in adult men and women predictive equations. Am J Clin Nutr 1988;48:1351–1361.
30. Istfan NW, Plaisted CS, Bistrian BR, et al: Insulin resistance versus insulin secretion in the hypertension of obesity. Hypertension 1992;19:385–392.
31. De Fronzo RA: The effect of insulin on renal sodium metabolism: A review with clinical implications. Diabetologia 1981;21:165–169.
32. Landsberg L, Young JB: Insulin mediated glucose metabolism in the relationship between dietary intake and sympathetic nervous system activity. Int J Obesity 1985;9:63–68.
33. Ferranini E, Buzzigoli G, Bonadonna R, et al: Insulin

resistance in essential hypertension. N Engl J Med 1987;317:350–356.

34. Denker PS, Pollock VE: Fasting serum insulin levels in essential hypertension. Arch Intern Med 1992;152: 1649–1651.
35. Bonura E, Zavaroni I, Alpi O, et al: Relationship between blood pressure and plasma insulin in nonobese and obese nondiabetic subjects. Diabetologia 1987;30:719–723.
36. West DB, Wehberg KE, Kieswetter K, et al: Blunted natriuretic response to an acute saline load in obese hypertensive dogs. Hypertension 1992;19(suppl I):96–100.
37. Messerli FH, Christie B, DeCarvalho JGR, et al: Obesity and essential hypertension. Haemodynamics, intravascular volume, sodium excretion and plasma renin activity. Arch Intern Med 1981;141:81–85.