Adrenergic and Reflex Abnormalities in Obesity-Related Hypertension

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Abstract**—**Previous studies have shown that essential hypertension and obesity are both characterized by sympathetic activation coupled with a baroreflex impairment. The present study was aimed at determining the effects of the concomitant presence of the 2 above-mentioned conditions on sympathetic activity as well as on baroreflex cardiovascular control. In 14 normotensive lean subjects (aged 33.5±2.2 years, body mass index 22.8±0.7 kg/m^2 [mean±SEM]), 16 normotensive obese subjects (body mass index 37.2±1.3 kg/m^2), 13 lean hypertensive subjects (body mass index 24.0±0.8 kg/m^2), and 16 obese hypertensive subjects (body mass index 37.5±1.3 kg/m^2), all age-matched, we measured beat-to-beat arterial blood pressure (by Finapres device), heart rate (HR, by ECG), and postganglionic muscle sympathetic nerve activity (MSNA, by microneurography) at rest and during baroreceptor stimulation and deactivation induced by stepwise intravenous infusions of phenylephrine and nitroprusside, respectively. Blood pressure values were higher in lean hypertensive and obese hypertensive subjects than in normotensive lean and obese subjects. MSNA was significantly ($P<0.01$) greater in obese normotensive subjects (49.1±3.0 bursts per 100 heart beats) and in lean hypertensive subjects (44.5±3.3 bursts per 100 heart beats) than in lean normotensive control subjects (32.2±2.5 bursts per 100 heart beats); a further increase was detectable in individuals with the concomitant presence of obesity and hypertension (62.1±3.4 bursts per 100 heart beats). Furthermore, whereas in lean hypertensive subjects, only baroreflex control of HR was impaired, in obese normotensive subjects, both HR and MSNA baroreflex changes were attenuated, with a further attenuation being observed in obese hypertensive patients. Thus, the association between obesity and hypertension triggers a sympathetic activation and an impairment in baroreflex cardiovascular control that are greater in magnitude than those found in either of the above-mentioned abnormal conditions alone. **(*Hypertension*. 2000;36:538-542.)**

Key Words: nervous system, sympathetic ■ nervous system, autonomic ■ baroreceptors ■ hypertension, essential ■ obesity

Studies on the sympathoadrenal function in animal and human obesity have provided somewhat heterogeneous results.[1–5] However, several recent data have shown that sympathetic activity, as directly assessed by regional norepinephrine (NE) spillover or by microneurographic recording of muscle sympathetic nerve activity (MSNA), is increased in normotensive overweight subjects.[6–9] A similar increase has been shown to occur in lean individuals with essential hypertension.[10–14] However, whether this increase and the one characterizing obesity are additive in an obese hypertensive individual is not clear. In one study, the renal spillover of NE was shown to be greater in obese hypertensive than in obese normotensive subjects.[15] However, this was not the case in the cardiac and systemic circulation and in obese and lean hypertensive individuals, who have been reported to display similar NE spillover values in the kidney also.[5,15] Furthermore, in another study, MSNA was not found to be greater in normotensive and hypertensive obese subjects, although obesity was defined only by a mild increase in body weight.[16]

In the present study, we investigated whether sympathetic activity is further increased in individuals with hypertension and a marked increase in body weight compared with either condition alone. Sympathetic activity was assessed by microneurography and by plasma NE assay. The present study included evaluation of the baroreceptor sympathetic reflex (a major modulator of sympathetic drive), because this reflex has been shown to be impaired in obesity but not in hypertension.[8,14]

Methods

The study population consisted of 57 subjects of both genders (47 men, 10 women) and an age ranging from 22 to 50 years who were classified as (1) normotensive if blood pressure (BP) was

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Received December 27, 1999; first decision February 15, 2000; revision accepted April 25, 2000.

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<140 mm Hg systolic or <90 mm Hg diastolic or hypertensive if BP was ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic at repeated sphygmomanometric measurements performed over 2 visits in the outpatient clinics, (2) obese if body mass index (BMI, body weight in kilograms divided by the square of the height in meters) was >27 kg/m^2, and (3) lean if BMI was <25 kg/m^2. Exclusion criteria were (1) secondary hypertension, (2) a family history of hypertension, (3) an overt diabetes mellitus, (4) history, physical evidence, or laboratory evidence of congestive heart failure, coronary heart disease, or other major cardiovascular disease, (5) history of major organ damage (eg, serum creatinine >1.5 mg/dL, proteinuria, or echocardiographic left ventricular ejection fraction $<50\%$), and (6) history of smoking and/or excessive alcohol consumption. All subjects were studied as outpatients in the absence of antihypertensive or other cardiovascular or metabolic drugs. In hypertensive subjects, antihypertensive drugs were withdrawn at least 10 days before the study. All subjects gave written informed consent to the study, whose protocol was approved by the ethics committee of our institution.

Measurements

Supine BP was initially measured 3 times with a mercury sphygmomanometer; the first and fifth Korotkoff sounds identified systolic and diastolic values, respectively, and a standard cuff and a tight cuff (bladder, 150×330 mm and 150×360 mm) were used in lean and obese subjects, respectively. In addition, arterial BP was monitored by a finger photoplethysmographic device (Finapres 2300, Ohmeda), capable of providing accurate and reproducible beat-to-beat systolic and diastolic values.[17] Heart rate (HR) was continuously monitored by a cardiotachometer triggered by the R wave of an ECG lead. Respiration rate was monitored by a strain-gauge pneumograph positioned at the midchest level. Plasma NE was assayed the same day of the study by high-performance liquid chromatography[18] on a blood sample withdrawn from a cannula placed in an antecubital vein of the arm contralateral to that used for BP measurements.

MSNA was obtained from a microelectrode inserted in the right or left peroneal nerve posterior to the fibular head, as previously described.[6–8,11–14] The microelectrode was made of tungsten and had a diameter of 200 μm in the shaft, tapering to 1 to 5 μm at the uninsulated tip. A reference electrode positioned subcutaneously 10 to 30 mm from the recording electrode served as the ground. The nerve signal was amplified ×70 000, fed through a band-pass filter (700 to 2000 Hz), and integrated with a custom nerve traffic analysis system (Bioengineering Department, University of Iowa, Iowa City). Integrated nerve activity was monitored by a loudspeaker, displayed on a storage oscilloscope (model 511A, Tektronix), and recorded with BP, HR, and respiration rate on an ink polygraph (Gould 3800, Gould Instruments). The muscle nature of the MSNA was assessed according to the criteria outlined in previous studies,[3–5,8–11] and the recording was accepted only if the signal-to-noise ratio was >3. Under baseline resting conditions, MSNA was quantified either as number of bursts per minute or as number of bursts per 100 heart beats. MSNA assessment by this quantification has been shown to be highly reproducible, ie, to differ by only 3.8% when assessed on the same tracing on 2 occasions by a single investigator.[19]

Baroreflex Evaluation

Baroreceptor modulation of MSNA and HR was assessed by the technique on the basis of infusion of vasoactive drugs.[8,14,19] Briefly, phenylephrine was incrementally infused in an antecubital vein at doses of 0.3, 0.6, and 0.9 μg/kg per minute, with each step being maintained for 5 minutes. Nitroprusside was also incrementally infused in an antecubital vein at doses on 0.4, 0.8, and 1.2 μg/kg per minute, with each step being maintained for 5 minutes. In all subjects, the drug initially infused was randomly selected, and the end of the first infusion was separated from the beginning of the second one by a recovery time of 45 minutes. Mean BP (diastolic BP plus one third of pulse pressure), MSNA, and HR were averaged for the 5 minutes before infusion and for the 5 minutes of each step infusion. Baroreceptor modulation of MSNA and HR was estimated by calculating (1) the change in the number of bursts per minute, (2) the percent change in integrated activity (ie, mean burst amplitude times bursts number over time), and (3) the change in HR in relation to the change in mean BP induced by each dose of phenylephrine and nitroprusside.

Protocol and Data Analysis

Obese and lean subjects came to the laboratory in the morning. They were put in the supine position, and they were fitted with intravenous cannulas, microelectrodes for MSNA recording, and other measuring devices. Blood samples for assessment of plasma NE were then taken, and BP was measured 3 times with the mercury sphygmomanometer. After a 30-minute interval, BP, HR, respiration rate, and MSNA were continuously measured during (1) an initial 10-minute basal state, (2) the intravenous infusion of one vasoactive drug, (3) a 45-minute recovery period followed by a second 10-minute basal state, and (4) intravenous infusion of the second vasoactive drug.

Data were collected in a quiet room at a constant temperature of 20°C to 21°C. Data were analyzed by a single investigator unaware of the experimental design. Baseline BP, HR, and MSNA values from individual subjects were averaged for each group and expressed as mean±SEM. This procedure was also followed for the changes in mean BP, MSNA, and HR induced by each dose of phenylephrine or nitroprusside. Comparisons between data obtained in control, obese, and lean subjects, with or without hypertension, were made by 2-way ANOVA. The 2-tailed t test for unpaired observations was used to locate between-group differences. The Bonferroni correction was used to account for multiple comparisons. The relationships between MSNA, BP, and BMI were assessed via multiple regression analysis. A value of $P<0.05$ was considered statistically significant.

Results

Basal Values

As shown in the Table, the 4 groups of subjects were matched for age. Body weight and BMI were similarly elevated in normotensive and hypertensive obese groups compared with normotensive and hypertensive lean groups to which they were comparable. Systolic and diastolic BP were similarly elevated in obese and lean hypertensive groups compared with obese and lean normotensive groups to which they were comparable. Respiration rate was superimposable in the 4 groups, whereas HR was significantly greater in the obese hypertensive group than in the other 3 groups. Compared with the lean normotensive control group, MSNA was markedly greater in obese normotensive and lean hypertensive groups; a further increase was observed in the group with the association between obesity and hypertension. Plasma NE showed a similar trend, although (unlike MSNA) the between-group differences were not always statistically significant. In the multiple regression analysis, MSNA values were related to BMI ($r=0.72$, $P<0.001$) and to mean BP ($r=0.54$, $P<0.01$).

Baroreflex Responses

The Figure shows that in all groups the stepwise increase in mean BP induced by phenylephrine caused a progressive bradycardia and reduction in MSNA, whereas the stepwise decrease in mean BP induced by nitroprusside had opposite effects. Compared with lean normotensive control subjects, the reflex HR responses were less in the obese normotensive and lean hypertensive subjects; a further reduction was observed in obese hypertensive subjects. The reflex sympathetic responses were preserved in lean hypertensive subjects,

Baseline Demographic, Anthropometric, Hemodynamic, Microneurographic, and Humoral Data for Lean Normotensive, Normotensive Obese, Lean Hypertensive, and Obese Hypertensive Subjects

Variable	Control Subjects (n=14)	Obese Subjects (n=16)	Hypertensive Subjects (n=13)	Obese Hypertensive Subjects (n=14)
Age, y	33.5±2.2	32.9±2.4	38.5±1.8	38.8±2.3
Gender, M/F	11/3	13/3	11/2	12/2
Body weight, kg	77.3±2.1	108.2±2.9*†	79.0±1.7	109.4±3.1*†
BMI, kg/m^2	22.8±0.7	37.2±1.3*†	24.0±0.8	37.5±1.3*†
Sphygmo BP, mm Hg				
Systolic	127.3±2.5	130.5±3.0	154.2±3.0*§	156.2±3.3*§
Diastolic	75.5±2.0	76.1±2.1	97.1±3.1*§	98.0±2.8*§
Finger BP, mm Hg				
Systolic	124.4±2.1	128.0±2.7	150.4±2.4*§	153.4±3.1*§
Diastolic	74.1±1.7	73.3±1.9	95.6±2.7*§	96.7±2.6*§
Respiration rate, breaths/min	21.2±0.8	22.0±1.0	21.8±0.9	22.2±1.1
Heart rate, bpm	69.9±2.0	69.2±2.4	71.5±2.1	80.1±2.4‡‖¶
MSNA, bursts/min	21.9±1.2	34.3±1.8*	31.8±2.7*	49.9±2.9*‖¶
MSNA, bursts/100 heart beats	32.2±2.5	49.1±3.0*	44.5±3.3*	62.1±3.4*†¶
NE, nmol/L	1.08±0.12	1.59±0.20‡	1.32±0.21	2.08±0.23‡

Values are mean ±SEM. Sphygmo BP indicates sphygmomanometric BP (average of 3 measurements).

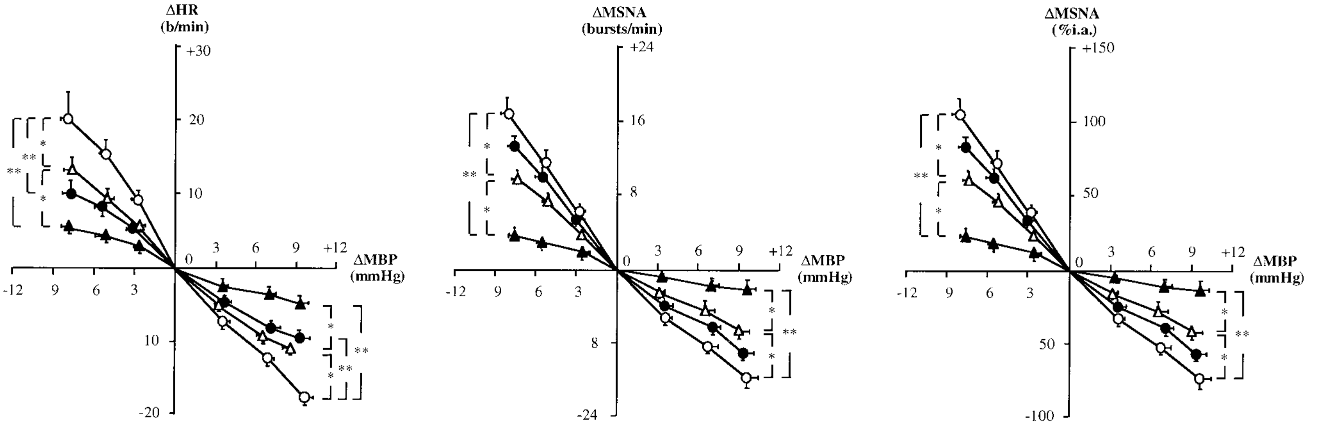
*$P<0.01$ and ‡$P<0.05$ vs control subjects; †P and ‖$P<0.05$ vs hypertensive subjects; and §$P<0.01$ and ‖$P<0.05$ vs obese subjects.

but they were reduced in obese normotensive subjects and more reduced in obese hypertensive subjects.

Discussion

Confirming previous findings of our group and others,[7–9,11–14] the present study determined that MSNA was greater in obese normotensive and lean hypertensive subjects than in lean normotensive control subjects. However, the new finding of the present study is that in patients in whom hypertension was associated with obesity, MSNA showed a further increase, which was so marked as to make the increase caused by only obesity and only hypertension additive. Thus, an additional sympathetic hyperactivity is to be expected when dealing with an increase in body weight accompanied by a BP elevation.

The present study also provides data on the mechanisms that may be responsible for the additive stimulatory effects of obesity and hypertension on MSNA. Confirming previous



Plots showing changes in HR (ΔHR), expressed as beats per minute (b/min), and MSNA (ΔMSNA), expressed as bursts per minute (bursts/min), and percent integrated activity (%i.a.), accompanying stepwise increases and reductions in mean BP (ΔMBP), induced by intravenous infusion of phenylephrine and nitroprusside in lean normotensive control subjects (○), in lean hypertensive subjects (●), in obese normotensive subjects (△), and in obese hypertensive subjects (▲). Data are expressed as mean±SEM. *$P<0.05$ and **$P<0.01$ between groups.

findings,[14,20] we found the arterial baroreflex to show a substantial loss of HR but not of MSNA modulation. However, compared with the control value, the baroreflex-sympathetic modulation was clearly impaired in obese normotensive patients and more so in obese hypertensive patients. Therefore, it can be concluded that when obesity and hypertension are present in the same patient, there is a particularly striking impairment of a major mechanism restraining MSNA and that this may be a factor responsible for the additional sympathetic hyperactivity that characterizes this condition. Other factors, of course, might participate as well. When obesity is associated with hypertension, for example, there can be a more pronounced cardiac hypertrophy, which leads to a greater impairment of another reflex that restrains MSNA, ie, the cardiopulmonary reflex.[21] There can also be a greater reduction of insulin sensitivity, a greater increase in plasma renin activity, and a greater increase in leptin and endothelin secretion that may all have a direct sympathostimulating effect.[22–25] Finally, there may be a greater ischemic involvement of the chemoreceptors, triggered by greater anatomic alterations of the arteries that perfuse the carotid and aortic bodies, which may lead to a reflex sympathostimulation greater than that ascribed to the chemoreflex in hypertension and obesity alone.[26–28] The greater chemoreflex involvement may depend on a greater prevalence of sleep apnea (a condition in which sympathetic hyperactivity has been linked to chemoreceptor stimulation[29]), because sleep apnea has been shown to more frequently accompany hypertension than normotension and to be more frequent in obese than in lean hypertensive patients.[30]

Several other findings of the present study deserve to be discussed. First, our results do not agree with those of Gudbjornsdottir et al,[16] who did not find a significant difference in the degree of sympathetic activation between normotensive and hypertensive obese subjects. However, it should be emphasized that the subjects studied by Gudbjornsdottir et al had an elevation in BP that was similar but an elevation in body weight that was much less than that displayed by our subjects. This may have been responsible for the negative findings they obtained, because in previous studies as well as in the present one, MSNA has been shown to be closely related to both body weight and BP.[7–8,11–14] This implies that when one of the latter 2 variables is only modestly increased, an interaction with the other one can be less easily detected. Second, the present study does not clarify the mechanisms responsible for the complex and diversified alterations of the baroreflex seen in obesity and hypertension alone and combined. In previous studies,[14,31] however, we have argued that in hypertension a greater impairment of HR versus peripheral sympathetic influences of the baroreflex may depend on central factors affecting the vagal more than the sympathetic drive, as is the case for the defense-like reaction.[32] This may not be the case in obesity, in which a greater and more diffuse baroreflex impairment may be caused by (1) a reduction in arterial distensibility, ie, of the large-artery function, which determines the activity of baroreceptors to respond to their natural stimuli,[33] and (2) a direct impairment in baroreceptor function by the increased insulin levels secondary to insulin resistance.[34] A further reduction in arterial distensibility and increase in insulin levels when obesity and hypertension are combined may finally be responsible for the fact that in these conditions the baroreflex is further impaired, with no more sparing of its sympathetic component. Third, the technique that we used allows only MSNA to be quantified, which means that the present study cannot make any determinations for an additive sympathostimulating effect of obesity and hypertension in other vascular districts. However, in obese hypertensive patients, there was also a further marked increase in plasma NE (which derives from secretion in different organs and thus represents a more composite marker of sympathetic activity[35]), suggesting that the additive sympathostimulating effects of these 2 conditions were not limited to muscle districts. In this context, it should be emphasized that NE spillover from the kidney has been reported to be greater in obese than in lean normotensive subjects[9] and that compared with obese normotensive individuals, its value has been found to be greater in hypertensive individuals, regardless of the presence of a normal or increased body weight.[15] This suggests that hypertension or obesity alone is accompanied by an increased renal sympathetic drive and also that their effect on this vascular district may not necessarily be additive. It should also be mentioned that cardiac NE spillover has not been reported to be clearly increased in obese normotensive or in hypertensive individuals,[9,15] suggesting no effect of the overweight state on cardiac adrenergic drive. This is not incompatible with our present finding that HR was slightly greater in obese hypertensive subjects than in subjects with obesity or hypertension alone, because absolute HR values are known to be largely determined by vagal influences, which make them an inaccurate marker of cardiac sympathetic influences.[36]

Our results have several clinical implications. For example, given the direct effect of sympathetic activity on myocyte volume and vascular smooth muscle cell replication,[37] the marked sympathetic activations seen in obesity and hypertension may favor structural alterations of the heart, such as left ventricular hypertrophy, and vascular lesions, such as those associated with atherosclerosis. Furthermore, this greater activation may also be responsible, at least in part, for the greater incidence of sudden death reported in obese hypertensive patients.[38] Finally, on the basis of our findings, it can be suggested that in obese hypertensive patients, the use of drugs that reduce centrally or peripherally sympathetic cardiovascular influences is appropriate for achieving BP control and for organ protection.

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