Resting Metabolic Rate and Substrate Use in Obesity Hypertension

Iris Kunz, Ulrike Schorr, Susanne Klaus, Arya M. Sharma

Abstract—There is substantial evidence that obesity is a prime risk factor for the development of hypertension. Although hyperinsulinemia and an increased activity of the sympathetic nervous system have been implicated in the pathogenesis of “obesity hypertension,” their effects on energy metabolism have not been studied thus far. In the present study, we therefore examined resting metabolic rate (RMR) and basal substrate oxidation in subjects with obesity and obesity-related hypertension. A total of 166 subjects were characterized for RMR and basal substrate use through indirect calorimetry. Blood pressure was measured at rest and with 24-hour ambulatory monitoring. Blood samples were collected for the measurement of plasma catecholamines, leptin, and the insulin response to an oral glucose load. In our study population, 116 subjects were defined as hypertensive and 91 were defined as obese. Hypertensive patients under β-adrenergic blockade (n=42) had a significantly lower RMR than did patients without β-blockade (P<0.05) and were therefore excluded from further analyses. Univariate regression analysis revealed a significant relationship between RMR and body fat mass, as well as body fat-free mass, in both groups. Compared with obese normotensive control subjects (n=27), obese hypertensives (n=43) had a 9% higher RMR (P<0.05), higher plasma catecholamine (P<0.05) and leptin (P<0.05) levels, and an increased insulin response to oral glucose (P<0.01). Together, these findings are compatible with the idea that chronic neurogenic and metabolic adaptations related to obesity may play a role in the development of obesity hypertension in susceptible individuals. (Hypertension. 2000;36:26-32.)

Key Words: energy expenditure ■ blood pressure ■ nervous system, sympathetic ■ glucose ■ obesity ■ leptin

Obesity is an increasingly common disorder in both developed and developing countries.1 There is substantial clinical and epidemiological evidence that obesity represents an independent risk factor for the development of cardiovascular diseases,2,3 including hypertension.4 Hypertension in obesity is a result of complex interactions among hormonal, hemodynamic, and nutritional factors, but the relationship between these factors remains poorly understood. Nevertheless, both increased activity of the sympathetic nervous system and hyperinsulinemia, secondary to insulin resistance, have been implicated in the pathogenesis of “obesity hypertension.”5

The sympathetic nervous system plays an important role in the regulation of energy intake and energy expenditure.6 Although several investigators have shown an acute thermogenic effect of catecholamines on energy expenditure,7–9 there is no evidence regarding the chronic adaptation of energy expenditure to hormonal and endocrine alterations in obesity-related hypertension.

The aim of our study was therefore to examine resting metabolic rate (RMR), which accounts for 65% to 75% of total energy expenditure,10 and basal substrate oxidation in subjects with obesity and obesity-related hypertension. All patients were also characterized for blood pressure, sympathetic nervous system activity, and glucose tolerance.

Methods

Subjects
A total of 166 subjects (51 men and 115 women) with a wide range of body weights (body mass index [BMI] range 19.4 to 52.2 kg/m²), with and without hypertension, volunteered for the study. Patients with known diabetes mellitus, congestive heart failure, abnormal renal or liver function, and intentional weight reduction during the past 3 months were excluded from the study. Obesity was defined as a BMI of ≥30 kg/m²,1 and ambulatory blood pressure measurement (90207; SpaceLabs Medical Inc) was performed for the definition of hypertension in untreated patients. Patients with a mean 24-hour ambulatory blood pressure level of >135/85 mm Hg11 or on any antihypertensive medication were defined as hypertensive. Furthermore, the intake of thyroid hormone and other medications was recorded. The study protocol was approved by the institutional ethics committee, and all subjects gave informed consent before participation in the study.

Study Protocol
All subjects were characterized for weight, height, and waist and hip circumference, and body composition was determined with bioelec-
Impaired glucose tolerance was defined according to the World Health Organization criteria. A minimum of 7 days after the oral glucose tolerance test, all subjects underwent a measurement of energy expenditure. For this measurement, subjects were admitted to a metabolic ward on the evening before the test and were given a light evening snack. After a 12-hour overnight fast, RMR was measured in the sitting awake subject in a temperature-controlled room over two 25-minute periods with an open-circuit indirect calorimetry system (standardized for temperature, pressure, and moisture) fitted with a face mask (Sensor Medics 2900 Z; NewMedics Medizinlektronik GmbH). During the measurement of energy expenditure, complete urine samples were collected for the assessment of nitrogen excretion. For each measurement, the first 5 minutes were discarded to allow subjects to adapt to the measurement procedure, and data from the remaining 20 minutes were averaged and used to calculate energy expenditure and substrate oxidation based on oxygen consumption, carbon dioxide production, and urinary nitrogen excretion.

### Analytical Measurements

Plasma electrolytes and glucose were measured according to standard laboratory techniques. Radioimmunoassays were used for the measurement of plasma insulin (Biermann) and leptin (DRG). The area under the curve (AUC) was calculated for glucose and insulin response during oral glucose tolerance test according to the trapezoidal rule. Plasma epinephrine and norepinephrine levels were measured with HPLC with electrochemical detection as described previously.

### Statistical Analysis

Statistical analysis was performed with the SPSS-PC software package (SPSS Inc). Data are reported as mean ± SD. Differences and correlations were considered significant at *P* < 0.05.

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### Baseline Characteristics and Blood Pressure in Nonobese and Obese Normotensive and Hypertensive Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nonobese (n=23)</th>
<th>Hypertensive (n=31)</th>
<th>Normotensive (n=27)</th>
<th>Hypertensive (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/M, %</td>
<td>57/43</td>
<td>68/32</td>
<td>78/22</td>
<td>58/42</td>
</tr>
<tr>
<td>Age, y</td>
<td>45.6 ± 13.4</td>
<td>53.5 ± 12.6</td>
<td>49.9 ± 10.9</td>
<td>54.4 ± 8.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.7 ± 3.3</td>
<td>26.3 ± 2.8</td>
<td>35.0 ± 4.6</td>
<td>36.4 ± 5.0</td>
</tr>
<tr>
<td>Body fat–free mass, %</td>
<td>74.8 ± 7.9</td>
<td>70.0 ± 7.4</td>
<td>63.7 ± 7.0</td>
<td>64.5 ± 7.1</td>
</tr>
<tr>
<td>Body fat mass, %</td>
<td>25.2 ± 7.9</td>
<td>30.0 ± 7.4</td>
<td>36.3 ± 7.0</td>
<td>35.1 ± 6.9</td>
</tr>
<tr>
<td>WHR, F</td>
<td>0.94 ± 0.05</td>
<td>0.97 ± 0.02</td>
<td>0.92 ± 0.05</td>
<td>0.90 ± 0.05</td>
</tr>
<tr>
<td>WHR, M</td>
<td>0.94 ± 0.05</td>
<td>0.97 ± 0.02</td>
<td>0.98 ± 0.03</td>
<td>1.00 ± 0.02</td>
</tr>
<tr>
<td>Resting measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>111/66 ± 13/10</td>
<td>133/74 ± 22/12</td>
<td>115/66 ± 10/8</td>
<td>134/75 ± 19/12</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>62 ± 8</td>
<td>62 ± 9</td>
<td>65 ± 6</td>
<td>67 ± 9</td>
</tr>
<tr>
<td>24-h ambulatory measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime blood pressure, mm Hg</td>
<td>127/81 ± 11/8</td>
<td>146/90 ± 17/12</td>
<td>128/80 ± 7/5</td>
<td>145/91 ± 14/9</td>
</tr>
<tr>
<td>Daytime heart rate, bpm</td>
<td>79 ± 8</td>
<td>81 ± 7</td>
<td>81 ± 6</td>
<td>84 ± 10</td>
</tr>
<tr>
<td>Nighttime blood pressure, mm Hg</td>
<td>116/70 ± 12/10</td>
<td>129/75 ± 15/12</td>
<td>117/70 ± 9/6</td>
<td>129/77 ± 12/10</td>
</tr>
<tr>
<td>Nighttime heart rate, bpm</td>
<td>66 ± 8</td>
<td>69 ± 10</td>
<td>70 ± 7</td>
<td>74 ± 12</td>
</tr>
<tr>
<td>Fasting insulin, mU/L</td>
<td>12.7 (4.2–26.5)</td>
<td>17.0 (4.4–42.4)*</td>
<td>17.1 (2.6–40.0)</td>
<td>21.3 (3.1–66.5)</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.4 (4.6–7.5)</td>
<td>5.4 (4.1–10.0)</td>
<td>5.5 (4.5–18.4)</td>
<td>5.8 (3.8–11.5)</td>
</tr>
<tr>
<td>Treated hypertensives, %</td>
<td>68</td>
<td></td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Thyroid hormones, %</td>
<td>4</td>
<td>13</td>
<td>19</td>
<td>9</td>
</tr>
</tbody>
</table>

WHR indicates waist-to-hip ratio.

*P* <= 0.05, †*P* <= 0.0001 vs nonobese/obese normotensive subjects.
Differences between groups were tested for significance with 2-tailed Student’s t test for independent samples or the nonparametric Mann-Whitney U test as appropriate. The $\chi^2$ statistic was used to detect differences in the distribution between men and women, obese and nonobese subjects, and subjects with impaired and normal glucose tolerance. Univariate and stepwise multiple linear regression analyses were performed with RMR and basal fat oxidation as dependent variables to explore their dependence on gender, age, body weight, body composition, waist-to-hip ratio, hypertension, impaired glucose tolerance, epinephrine, norepinephrine, leptin, drugs, and thyroid hormones. Associations between blood pressure, heart rate, and fat oxidation were explored with Pearson correlation coefficients, after we established that the data were normally distributed.

Results

According to these criteria, 116 subjects were hypertensive and 91 were obese. Of the hypertensive patients, 73% were on antihypertensive medication, but multiple regression analysis revealed no influence of diuretics, calcium channel blockers, and ACE inhibitors on RMR. However, in obese patients under $\beta$-adrenergic blockade (n=42), RMR was 12% lower than in patients without $\beta$-blockade (6717±775 versus 7478±1292 kJ/24 h; $P<0.05$, Figure 1). Patients with $\beta$-blockade were therefore excluded from further analyses. Although 12% of the subjects were on thyroid hormone supplements, multiple regression analyses did not show an effect of this medication on RMR. These patients were therefore included in the analyses. Characteristics of the remaining subjects are presented in the Table. There were no significant differences in gender distribution, BMI, and body composition between hypertensive and normotensive subjects. Hypertensive subjects were slightly older and, as expected, revealed a significantly higher 24-hour ambulatory blood pressure. Because resting blood pressure was measured under standardized conditions over 60 minutes at complete rest, blood pressure levels in the hypertensive group, although significantly higher than in normotensive subjects, were within the normotensive range.

Multiple stepwise regression analysis revealed significant effects of body fat-free mass (FFM), body fat mass (FM), gender, and age on RMR. Together, these variables accounted for 75% of the variation in RMR ($P<0.0001$; $\sqrt{SE}$=586 kJ) (see equation at bottom of page). Univariate regression analysis revealed a significant relationship between RMR and FM as well as FFM in both groups (Figure 2).

There was no overall difference in RMR between normotensive and hypertensive subjects (6651±1046 versus 6903±1302 kJ/24 h). However, in subjects with BMI of $>30$ kg/m$^2$ RMR was significantly higher in hypertensive subjects (Figure 3). Furthermore, plasma epinephrine and norepinephrine levels and the insulin response to an oral glucose load were higher in the obese hypertensive than in the obese normotensive subjects (Figure 3). In nonobese subjects, fasting insulin levels were significantly

![Figure 2. Relationship between RMR and FFM (a) and FM (b) in normotensive and hypertensive male and female subjects.](image)

<table>
<thead>
<tr>
<th>RMR(kJ/24h)</th>
<th>4348 + 45.0 × FFM + 39.0 × FM − 882.1 × gender (for female) − 15.8 × age</th>
</tr>
</thead>
<tbody>
<tr>
<td>($\pm 492$)</td>
<td>($\pm 6.7$)</td>
</tr>
<tr>
<td>($P=0.0001$)</td>
<td>($P=0.0001$)</td>
</tr>
</tbody>
</table>
Figure 3. RMR, basal fat oxidation, plasma catecholamines, AUC glucose, and AUC insulin after glucose load and plasma leptin in nonobese (n=23) and obese (n=27) normotensive (open columns) and nonobese (n=31) and obese (n=43) hypertensive (filled columns) subjects (mean±SEM).
higher in the hypertensive than in the normotensive group (P<0.05), and AUC glucose (P<0.01) and AUC insulin (P=0.07) also appeared higher in the hypertensive than in the normotensive groups. Leptin levels appeared higher in hypertensive compared with normotensive subjects in both the obese and nonobese groups, but this difference achieved statistical significance only in obese men (Figure 3). The RMR was not different between the nonobese hypertensive and normotensive groups.

Neither relative nor absolute basal substrate oxidation was significantly different between obese normotensive and hypertensive subjects (Figure 3). Stepwise multiple regression analysis revealed FM, gender, and AUC glucose as independent determinants of basal fat oxidation (kJ/h), accounting for 40% of the variation (P≤0.001; √SE=28.2 kJ/h), whereas age, FM, catecholamines, leptin, blood pressure, and hypertension had no significant effect. Although there was no relationship between blood pressure and basal fat oxidation, resting heart rate was significantly associated with basal fat oxidation in both obese normotensive (r=0.41, P≤0.001) and obese hypertensive (r=0.35, P≤0.001) subjects (Figure 4).

**Discussion**

The main finding of the present study was that obese hypertensive subjects have a small but significant increase in RMR compared with age- and BMI-matched obese normotensive control subjects. Furthermore, obese hypertensive patients have higher plasma catecholamine and leptin levels and an increased insulin response to an oral glucose load compared with obese normotensive subjects.

Although the association between obesity and hypertension is well recognized, the relationship between energy metabolism and hypertension has not been widely studied. In fact, we are aware of only 2 studies that specifically investigated RMR in small groups of normotensive and hypertensive individuals: 1 in obese Chinese normotensive (n=10) and hypertensive (n=9) women17 and 1 in white normotensive (n=7) and hypertensive (n=8) men.18 Both studies found no difference in energy expenditure, but this may have been due to the rather small number of probands in these studies. Indirect findings on the relationship between energy expenditure and hypertension are limited to early reports that demonstrate a greater increase in oxygen consumption during mental challenge, which was associated with an increased response in heart rate in patients with mild hypertension.19,20 These studies, however, provide no useful information regarding basal metabolic rates in these individuals.

Previous studies demonstrate that a large proportion of variability in RMR is related to differences in body composition.21 Despite the potential effect of increased sympathetic activity on RMR, it is apparent that as in normotensive individuals, RMR in hypertensive subjects was predominantly determined by FFM, FM, gender, and age. This is in line with previous findings that demonstrate FFM alone accounts for 60% to 85% of variation in RMR.21–23 Interestingly, the small but statistically significant effect of FM on RMR observed in the present study is in line with the observation by Nelson et al,24 who have previously shown that although the contribution of FM to the variation of RMR is negligible in lean individuals, it becomes more important with increased FM in obese subjects. Nevertheless, despite this effect of FM, higher RMR in obese subjects is mainly attributable to the higher FFM present in obese individuals.25

Consistent with previous findings,26,27 hypertension was associated with an increased insulin response to oral glucose in obese individuals. Similarly, as in some,28,29 but not all,30,31 studies, the obese hypertensive subjects tended to have higher plasma norepinephrine levels than the normotensive subjects. Previous investigators have suggested that insulin resistance in hypertensive patients may be due in part to increased sympathetic activity,32,33 but insulin has also been shown to increase sympathetic nerve activity.34 More recent studies suggest that leptin may also stimulate sympathetic outflow from the hypothalamus, thereby contributing to increased heart rate and perhaps a rise in blood pressure.35–37 This idea is in line with our observation that plasma leptin levels were higher in obese hypertensive men (P<0.05) and women (P=0.06) than in the obese normotensive control subjects. Clearly, the role of leptin in the development of obesity hypertension deserves further exploration.

In the present study, basal fat oxidation and basal substrate oxidation did not differ between obese hypertensive and normotensive individuals. This finding is in line with the previous report by Natali et al,18 who found no differences in the exchange of lipid substrates (free fatty acids, glycerol, and β-hydroxybutyrate) in the forearm of hypertensive and normotensive individuals. This comes as a surprise, because higher insulin levels, secondary to insulin resistance in hypertensives, may be expected to inhibit fat oxidation.38 On the other hand, higher sympathetic activity in hypertensive subjects could counteract the inhibitory effect of hyperinsulinemia, because catecholamines are known to stimulate fat oxidation.39 The idea that increased sympathetic activity in hypertensive individuals is related to fat oxidation is also supported by the
presence of a positive correlation between resting heart rate and basal fat oxidation in the present study.

The importance of increased sympathetic activity in the maintenance of higher energy expenditure and thus countering an increase in body weight is also illustrated by our observation of a significantly lower RMR in patients on β-blockers. This is consistent with previous reports that β-adrenergic blockade affects energy expenditure by lowering RMR,40,41 as well as glucose-42 and diet-induced thermogenesis. The clinical relevance of this effect is apparent from several clinical trials, including the recent United Kingdom Prospective Diabetes Study,43 in which treatment with atenolol resulted in twice the weight gain compared with that observed in patients on captopril.

Although this is the largest study to date on the relationship between energy metabolism and hypertension, some important study limitations must be considered. Physical activity, an important determinant of lean body mass and energy expenditure, was not assessed in our study; it must, however, be noted that the impact of physical training on RMR is still controversial.44 Furthermore, although not statistically significant, hypertensive subjects were slightly older than normotensive subjects in both groups. Thus, because RMR is known to decrease with age,45 the difference in RMR between obese hypertensive and normotensive subjects may have been underestimated in the present study. On the other hand, hypertensive subjects were also slightly heavier in both groups. It therefore cannot be ruled out that some of the difference in RMR between the obese hypertensive and normotensive individuals is attributable to this small difference in body weight.

In summary, the present study demonstrates a significant, albeit marginal, increase in RMR in obese hypertensive patients. This finding is associated with higher plasma catecholamine levels, a hyperinsulinemic response to an oral glucose load, and higher leptin levels in these individuals. Together, these findings are compatible with the idea that chronic neurogenic and metabolic adaptations related to obesity may play a role in the development of obesity hypertension in susceptible individuals.

Acknowledgments

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