Relation of Central Hemodynamics to Obesity and Body Fat Distribution

Sverker Jern, Anders Bergbrant, Per Björntorp, and Lennart Hansson

Central obesity increases the risk for cardiovascular disease, but little is known about its hemodynamic effects. The aims were to investigate the influence of obesity (as defined by body mass index) and abdominal fat accumulation (as defined by the waist/hip ratio) on hemodynamics at rest and during mental stress. Invasive hemodynamic studies were performed in 20 healthy, normotensive young men (aged 18–22 years) recruited from an unbiased population sample. Their body mass index and waist/hip ratio ranged between 18.5 and 30.2 (mean 24.1) and 0.77 and 0.98 (mean 0.87), respectively. Hemodynamics were related to the two anthropometric indexes by bivariate regression analyses. Cardiac output and stroke volume were positively correlated to body mass index ($p=0.05$ and $p=0.005$), but inversely to waist/hip ratio ($p=0.01$ and $p=0.01$). Mental stress augmented the hemodynamic patterns. Total peripheral resistance during stress correlated inversely to body mass index ($p=0.02$), whereas high waist/hip ratio was associated with higher systemic vascular resistance ($p=0.002$). The ΔCO/ΔMAP ratio, i.e., relative contribution of cardiac output for the stress-induced increase in mean arterial pressure, showed a strong positive association with body mass index ($p=0.004$), but was inversely related to the waist/hip ratio ($p=0.002$). Serum insulin correlated significantly to the stress-induced change in total peripheral resistance ($r=0.54; p=0.02$), whereas the increase in cardiac output was inversely related to insulin ($r=-0.59; p=0.007$). Thus, central obesity is associated with a specific hemodynamic pattern characterized by higher total peripheral resistance, lower cardiac output, and a vasoconstrictor response to psychosocial stress. (Hypertension 1992;19:520–527)

**Key Words** • obesity • body mass index • hemodynamics • cardiac output • stress, psychological

Epidemiological studies have demonstrated a rather close relation between hypertension, obesity, and disturbances of glucose and lipid metabolism. Hypertensive individuals, selected at random from the population, frequently have obesity and metabolic derangements, and conversely, there is a high prevalence of hypertension in obese subjects. However, human obesity is not a homogenous condition. Several studies have shown that the distribution of excess adipose tissue to central or peripheral depots is associated with different prevalence rates of associated metabolic perturbations as well as risk for development of cardiovascular disease (for reviews, see References 5 and 6).

Hypertension appears to be related both to obesity (defined as enlargement of body fat mass) as such, as well as to central distribution of body fat. There is suggestive evidence that hypertension associated with central excess of body fat is particularly harmful as a risk factor for development of cerebrocardiovascular disease. In addition, abdominal fat accumulation appears to be associated with a complex endocrine aberration, including glucose intolerance, hyperactivity of the hypothalamopituitary-adrenocortical axis, and derangements of sex steroid hormone secretions. Despite these differences in associated pathology between central and peripheral obesity, and the pathophysiological importance of the relation of central obesity to cardiovascular disease and hypertension, little is known about the influence of the abdominal type of obesity on central and peripheral hemodynamics. The present study was designed to investigate the effects of degree of obesity (as defined by body mass index [BMI]) and central distribution of body fat (as defined by the waist/hip circumference ratio [WHR]) on central and peripheral hemodynamics.

Since we have recently shown that the hemodynamic effects of metabolic alterations may be quite different during resting conditions and during cardiovascular activation in response to increased arousal, hemodynamic studies were performed both at rest and during exposure to highly standardized mental stress. To avoid secondary consequences of established hypertensive cardiovascular disease, young men with blood pressure within strictly normotensive limits were selected for the study from a random population sample.

**Methods**

**Subjects**

Twenty normotensive, apparently healthy young men (aged 18–22 years) participated in the study. The sub-
jects were recruited as a random normotensive sample from a population consisting of all subjects examined during 1989 at the military enlistment center of the Göteborg area. Since military enlistment is compulsory in Sweden, only subjects with severe chronic diseases are exempted from this examination. Thus, the original population consists of all healthy men of this age group living in the area of Göteborg.

The selection of subjects for the study was performed in two steps. In the first step, we obtained a random sample of 122 subjects born 1960 and later, who lived in the city of Göteborg and had screening systolic and diastolic blood pressures within the range 110-130 and 60-80 mm Hg, respectively. In the second step, each subject was invited by letter to two additional blood pressure check-ups at our laboratory. The first 20 of those who fulfilled the blood pressure criteria (same as at screening) and were willing to participate in the hemodynamic investigation were included in the hemodynamic study.

To rule out the possibility that any bias had been introduced by the selection in the second step, we compared the participant group (n=20) with those who did not participate in the hemodynamic study (n=102). This analysis revealed no differences between the two groups at screening regarding age, weight, height, BMI, aerobic physical performance scores, or systolic and diastolic blood pressure (p > 0.10 throughout). Thus, it was concluded that the sample investigated in the present study was representative of the population.

Only three subjects were smokers (range, 3-15 g tobacco per day). Average self-reported alcohol consumption per week was 66.3 g alcohol (range, 20-200 g/wk). None of the subjects had plasma y-glutamyl transferase and aspartate aminotransferase levels above 0.45 μkat/l and 0.70 μkat/l, respectively. Neither self-reported alcohol consumption nor biochemical indexes of excessive use of alcohol correlated to any of the hemodynamic variables evaluated in the study.

Two subjects had a positive family history for essential hypertension, and one subject had a parent with diabetes mellitus.

Informed consent was obtained from each subject before inclusion in the study after the rationale, nature, and potential risks of the research had been carefully explained. The protocol was approved by the Ethics Committee of the University of Göteborg, and the study was performed according to the declaration of Helsinki.

Anthropometric Indexes

The BMI was calculated from the weight divided by height squared (kg/m²). The WHR was determined as the ratio of the waist circumference at the umbilical level to the hip circumference at the level of the anterior iliac spine in the standing position.

Experimental Protocol

All experiments were performed in the heart catheterization laboratory according to a highly standardized procedure after an overnight fast. After introduction of arterial and venous catheters and application of recording devices, the subject was left alone in the recumbent position in the dimly lit, soundproof room for a 60-minute rest period. Throughout the nonstress periods of the experiment, great care was exercised to maintain a calm and friendly atmosphere to allow the subjects to relax comfortably.

After the rest period, assessments of central hemodynamics were performed at rest, and during and after 10 minutes of a standardized mental stress test. Two hours after conclusion of the first part of the experiment, peripheral hemodynamics were studied at rest and during maximal vasodilation for determination of minimal vascular resistance.

Central Hemodynamics

An 18-gauge arterial polyethylene catheter (Viggo Products, British Viggo, Swindon, UK) was introduced percutaneously into the brachial artery of the nondominant arm by the Seldinger technique and advanced some 15 cm in the proximal direction. The catheter was connected to an electrical transducer (EMT 35, Siemens-Elema, Stockholm, Sweden). Intra-arterial blood pressure was recorded on a Mingograph 82 (Siemens-Elema). Mean arterial pressure was obtained by electrical damping of the pressure signal.

Another indwelling cannula (Venflon, Viggo, Helsingborg, Sweden) was introduced percutaneously into an antecubital vein of the nondominant arm for blood sampling and dye injection.

Cardiac output was determined with the dye dilution technique using indocyanine green dye (Cardiogreen, Hynson, Westcott & Dunning Products, Becton Dickinson and Co., Cockeysville, Md.) and a cuvette densitometer (Brechtelstuber, Munich, FRG). Each dye dilution curve was computer-integrated. At each point of measurement (i.e., at rest, during stress, and 10 minutes after stress) two to four separate cardiac output determinations were performed, and the mean of those was computed and used for further analysis.

Stroke volume was computed by dividing cardiac output by heart rate. To obtain total peripheral resistance, mean arterial blood pressure was divided by cardiac output. To assess the relative contribution of the increase in cardiac output for the blood pressure increment in response to stress, the Δcardiac output/Δmean arterial pressure ratio (ΔCO/ΔMAP) (1·min⁻¹·mm Hg⁻¹) was defined for each individual.

Electrodes for electrocardiographic recordings were fixed to the precordium, and electrocardiogram was recorded on a Mingograph 81 (Siemens-Elema). Heart rate was continuously monitored by a computerized vectorcardiograph (MIDA 1000, Orthivus Medical AB, Täby, Sweden).

Mental Stress Test

All experiments followed the highly standardized procedure we have previously described in detail (see Reference 20 for reproducibility data). The experiment commenced with the first 10-minute prestress baseline period with the subject alone in the quiet and dimly lit room. The investigator then entered the room, which was now fully lit, and gave an approximately 40-second oral instruction, after which the stress test was started.

The subject performed forced mental arithmetic for 10 minutes with serial subtractions of 7 from 700, trying to keep pace with a metronome at a rate of approximately 90 beats per minute. After a positive and reas-
Hemodynamics at Rest and During Mental Stress

A summary of the major hemodynamic variables for the whole group is shown in Table 2. Univariate analyses only showed weak and insignificant correlations between either BMI or body fat distribution and the hemodynamic variables at rest. However, during mild cardiovascular activation in response to stress a strong inverse relation was disclosed between WHR and cardiac output (r = -0.63, p = 0.003; Figure 1). Accordingly, total peripheral resistance during stress was directly correlated with degree of central obesity (r = 0.49, p = 0.03), whereas a weak indirect relation emerged between mean arterial blood pressure and WHR.

Since BMI and WHR were partly interrelated (r = 0.52), their relative contribution to the hemodynamic patterns was further analyzed by bivariate regression models. These analyses revealed that resting cardiac output was positively correlated to the degree of obesity (BMI), but was inversely related to abdominal adipose tissue distribution (WHR; Table 3). In turn, this was explained by rather strong but opposite associations of stroke volume to the anthropometric indexes, whereas heart rate was unrelated both to BMI and WHR. Neither total peripheral resistance nor mean arterial pressure were significantly correlated to BMI or WHR at rest. Peripheral blood flow at rest or during maximal vasodilation did not correlate significantly with either BMI or body fat distribution, neither in univariate nor in bivariate analyses (p > 0.10 throughout; data not shown).

During mental stress, the direct and inverse relations of cardiac output and stroke volume to BMI and WHR, respectively, were further accentuated (Table 3). In fact, taken together the two anthropometric indexes explained more than 50% of the variance in cardiac output and stroke volume during stress. Also, heart rate during the stress test tended to be inversely correlated to the WHR (p = 0.054). In contrast, a reversed pattern was observed for total peripheral resistance. During stress, there was a significant negative correlation of peripheral resistance to the degree of obesity (p = 0.02), whereas a high WHR was associated with higher systemic vascular resistance (p = 0.002).

Hemodynamic Stress Response Patterns

As shown in Table 2, mental stress induced highly significant increases of mean arterial pressure, cardiac output, and heart rate (p < 0.0001 throughout), whereas total peripheral resistance fell slightly but significantly.

<table>
<thead>
<tr>
<th>Hemodynamic variable</th>
<th>Rest</th>
<th>Change rest–stress</th>
<th>Change stress–post-stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>79.3 (1.4)</td>
<td>+15.8 (1.5)*</td>
<td>-10.2 (1.4)*</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>6.54 (0.29)</td>
<td>+2.73 (0.48)*</td>
<td>-2.19 (0.57)†</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>54.1 (1.5)</td>
<td>+20.1 (2.1)*</td>
<td>-15.4 (2.5)*</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>119 (4)</td>
<td>+7.56 (4.12)</td>
<td>-5.55 (5.53)</td>
</tr>
<tr>
<td>Total peripheral resistance (resistance units)</td>
<td>12.7 (0.6)</td>
<td>-1.92 (0.42)*</td>
<td>+1.47 (0.55)§</td>
</tr>
</tbody>
</table>

Values are mean ±(SEM). bpm, Beats per minute. 
Significance levels of absolute changes from rest to stress and from stress to post-stress (t test): *p < 0.0001; †p < 0.01; ‡p < 0.001; §p < 0.05.
during stress \((p<0.001)\). Stroke volume did not change significantly in response to the stress test. Figure 2 shows a scatterplot of the relation between blood pressure and cardiac output responses to the stress test. For the whole group, the stress-induced increase in mean arterial pressure was accomplished through an increase in cardiac output \((r=0.68, p=0.001)\). In turn, the increase in cardiac output was mainly dependent on an increased heart rate \((r=0.77, p<0.0001; \text{Figure 2})\).

However, both amplitudes and patterns of the hemodynamic responses showed a rather large interindividual scatter. Figure 3 illustrates the individual patterns of the hemodynamic stress responses. In the majority of the subjects the circulatory adjustment to stress was characterized by a cardiac output–mediated pressor response, which was associated with a decrease in peripheral resistance. This vasodilatory response was attenuated in some individuals, and a stress response characterized by net systemic vasoconstriction was observed in four individuals.

A further analysis of the relative contribution of the stress-induced change in cardiac output for each millimeter of mercury increment in mean arterial pressure was performed by calculation of the \(\Delta CO/\Delta MAP\) ratio. On the average, the increase in cardiac output was 170 ml/min per mm Hg during the stress test, with an interindividual variation ranging from −19 to 322 ml/min per mm Hg. The \(\Delta CO/\Delta MAP\) ratio showed a strong positive association with BMI \((p=0.004)\), but was inversely related to WHR \((p=0.002)\). This indicated a mainly cardiac output–dependent pressor response in subjects with high BMI, whereas a pressor response characterized by peripheral vasoconstriction was observed in subjects with high WHR.

There was a positive relation between fasting serum insulin and WHR \((r=0.50, p=0.03)\), but fasting insulin did not correlate significantly to BMI. Resting central or peripheral hemodynamics were not correlated to serum insulin \((r<0.03 \text{ throughout; data not shown})\), but the stress-induced changes were. As shown in Figure 4, there was a significant positive correlation between insulin and the stress-induced change in total peripheral resistance \((r=0.54; p=0.02)\), indicating a less effective vasodilation in subjects with higher insulin levels. The
TABLE 3. Bivariate Correlations of Hemodynamic Variables to Body Mass Index and Waist/Hip Ratio

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>BMI</th>
<th>WHR</th>
<th>Adjusted $R^2$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
<td>$p$</td>
<td>$\beta$</td>
</tr>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>1.02</td>
<td>NS</td>
<td>-31.98</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>0.25</td>
<td>=0.047</td>
<td>-15.59</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>-0.43</td>
<td>NS</td>
<td>-26.90</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>4.94</td>
<td>=0.005</td>
<td>-214.95</td>
</tr>
<tr>
<td>Total peripheral resistance (resistance units)</td>
<td>-0.38</td>
<td>NS</td>
<td>24.08</td>
</tr>
<tr>
<td>During stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>0.20</td>
<td>NS</td>
<td>-62.70</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>0.44</td>
<td>=0.026</td>
<td>-42.07</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>-0.91</td>
<td>NS</td>
<td>-93.23</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>7.22</td>
<td>=0.001</td>
<td>-425.52</td>
</tr>
<tr>
<td>Total peripheral resistance (resistance units)</td>
<td>-0.54</td>
<td>=0.02</td>
<td>38.98</td>
</tr>
<tr>
<td>Change rest–stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta CO/\Delta MAP$</td>
<td>0.02</td>
<td>-0.004</td>
<td>-1.40</td>
</tr>
</tbody>
</table>

BMI, body mass index; WHR, waist/hip ratio; bpm, beats per minute; $\Delta CO/\Delta MAP$, stress-induced change in cardiac output (CO) divided by change in mean arterial pressure (MAP).

increase in cardiac output during stress showed a significant inverse relation with serum insulin ($r=-0.59$; $p=0.007$), which was mainly due to a negative correlation between change in cardiac output and heart rate ($r=-0.52$; $p=0.02$).

FIGURE 2. Scatterplots show relation between absolute changes of mean arterial pressure and cardiac output (upper panel), and changes of cardiac output and heart rate (lower panel) in response to 10 minutes of mental arithmetic ($n=20$). bpm, Beats per minute.

FIGURE 3. Line plot shows absolute change from rest (○) to stress (arrow) of cardiac output and mean arterial pressure ($n=20$). Isoresistance lines indicate slope of pressor responses without change in total peripheral resistance.

Discussion

The results of the present study show that in normotensive individuals, degree of obesity and abdominal distribution of adipose tissue (as indicated by WHR) are associated with distinctly different hemodynamic patterns and that the differences in hemodynamic patterns between the two fat distribution profiles are more pronounced during mild mental stress than at rest. When distribution of excess body fat was controlled for by bivariate regression analysis, the degree of obesity as such (BMI) was directly correlated to cardiac output and inversely to systemic vascular resistance. This relation is in accordance with previous observations by several groups of investigators.22–25 Also in line with previous findings, we found that the increments in
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Cardiac output in the obese individuals originated from increased stroke volume since heart rate was unrelated to BMI. The increased stroke volume is probably related to an expanded total blood volume, since the latter is known to be directly related to the degree of obesity.

By contrast, a central distribution of body fat, in both univariate and bivariate regression models, was associated with lower cardiac output and higher total peripheral resistance. The decrease in cardiac output was mainly dependent on an inverse relation between stroke volume and WHR, irrespective of BMI. To our knowledge, this relation of central body fat distribution (as indicated by WHR) to a hemodynamic state characterized by higher systemic vascular resistance has not previously been reported.

A weak, insignificant negative correlation between WHR and mean arterial blood pressure emerged in the univariate analysis, but in the bivariate models there were no relations either at rest or during stress between WHR or BMI and blood pressure.

The WHR is a widely used index of fat distribution. This ratio is a composite measurement of the contents of the body encircled by the waist and hip circumferences. The rational for dividing the waist with hip circumference is to adjust for variations in frame size in different subjects. The waist measure encompasses subcutaneous and visceral fat as well as gastrointestinal contents. Among these, the body compartment with the greatest capacity for variation is the adipose tissues included. Therefore, WHR is mainly determined by abdominal adipose tissues. Consequently, it has been shown that WHR correlates strongly with abdominal fat masses in both men and women over a wide range of total body fat mass.

Although the precise masses of the components of the waist-hip measure were not measured in the present work, it is reasonable to assume that WHR was mainly dependent on abdominal adipose tissues. This interpretation is supported by the finding that there was a direct correlation between fasting serum insulin and WHR.

Furthermore, to rule out the possibility that excessive alcohol use might have confounded the WHR measurement, a detailed history of drinking habits was obtained from each subject and were compared with plasma $\gamma$-glutamyl transferase and aspartate aminotransferase levels. None of the subjects had elevated plasma trans-ferase levels, and neither self-reported alcohol consumption nor biochemical indexes correlated with WHR or any of the hemodynamic variables evaluated in the study.

As expected, the overall reaction pattern during mental stress was characterized by increased blood pressure and cardiac output and a slight decrease of total peripheral resistance. However, the responses were different in subjects with various adipose tissue distribution. High WHR was associated with a vasoconstrictor type of stress response, whereas obesity as such correlated directly with a cardiac output—dependent response pattern.

Regional adipose tissue distribution appears to be linked to differences in muscle morphology and capillary density. Subjects with high WHR have fewer type I and more type IIB muscle fibers. The type IIB fibers have a 20–30% lower capillary density, and there is an inverse relation between WHR and capillary density. One may speculate that the physiological muscular vasodilation in response to stress would be attenuated in these individuals, which would result in a less effective counteraction of the vasoconstriction of splanchnic, renal, and skin vascular beds that occurs during the defense reaction. However, in the present study we could not find any relation between WHR and peripheral muscular blood flow in the two vascular beds examined (forearm and calf), either at rest or during maximal vasodilation.

We have recently reported that during physiological hyperinsulinemia, the hemodynamic response to stress is changed into a vasoconstrictor response, a reaction pattern that is very similar to that associated with high WHR in the present study. Abdominal obesity has been shown to be associated with peripheral insulin resistance and hyperinsulinemia, and there was a direct relation between WHR and fasting insulin in the present study. Insulin may modify the sensitivity of the vascular smooth musculature to vasoconstrictor agents by augmenting Na$^+$-H$^+$ exchange, which results in intracellular accumulation of Na$^+$ and Ca$^{2+}$. Our finding that higher serum insulin levels were associated with attenuated vasodilatory responses during stress exposure, but that insulin was unrelated to peripheral or central hemodynamics at rest, is consistent with the hypothesis that insulin may alter vascular responses to sympathetic activation. Thus, both our previous and present observations could be explained by insulin-mediated hyperresponsiveness of vascular smooth muscles to physiological vasoconstrictors released during stress. That hyperinsulinemia does not increase resting blood muscular flow has recently been shown in an elegant study from the Ferrannini group, using the human forearm hemodynamic model.

High WHR was found to be strongly associated with increased systemic vascular resistance, as well as lower

![Figure](image-url)
cardiac output and stroke volume, and these hemodynamic patterns were augmented by mental stress. In particular, the inverse relation between ACO/ΔMAP and WHR clearly indicates that the hemodynamic stress response in these individuals was characterized by greater vasoconstriction and less cardiac activation. A similar stress reaction pattern with generalized sympathetic vasoconstriction has previously been observed in rats by Hallback and coworkers, in response to defeat reactions elicited by short-term immobilization. The possibility may therefore be considered that subjects with abdominal fat distribution react to stress with defenselike rather than defense reactions.

There are some other observations to support this suggestion. Abdominal fat distribution seems to be associated with an increased activity along the hypothalamicadrenocortical axis, a neuroendocrine correlate of the defeat reaction, and this activation is amplified by stress. Such subjects also have prevalent aberrations of metabolism as well as hypertension. Interestingly, recent studies have shown that defeat reactions in primates are followed by increased adrenal cortex activity combined with abdominal accumulation of body fat, as well as by metabolic perturbations and increased blood pressure. Taken together these studies suggest a relation between a defeatlike reaction to stress, activation of the hypothalamicadrenocortical axis, as well as metabolic derangements and hypertension. Thus, the different hemodynamic response to stress could be an additional expression of a different psychophysiological reaction pattern in subjects with abdominal fat distribution. Although the underlying mechanisms are unknown, other observations have suggested that such individuals may be under psychosocial strain, as previously reviewed.

In conclusion, the results of the present study show that both hemodynamics at rest and the behavior of the cardiovascular system during mental stress are differently related to degree of obesity and to central versus peripheral distribution of adipose tissue. The finding that subjects with high WHR have higher total peripheral resistance and lower cardiac output and react with increased systemic vascular resistance to psychosocial stress suggests that this type of fat distribution is associated with structural, endocrine, or both, aberrations with important circulatory effects.

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