Hypertension in Obese Patients: Hemodynamic and Volume Studies

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SUMMARY Distinct hemodynamic and volume characteristics have been suggested for established hypertension in severe obesity, namely, a high cardiac output, an expanded blood volume, and a normal peripheral resistance. To evaluate whether hypertension in moderately obese patients represents a separate entity that can be defined by hemodynamic and volume profiles, we studied these in 50 such patients and compared results with those obtained in 59 nonobese essential hypertensives and 25 normal subjects. Both obese and nonobese hypertensives had a normal cardiac index (men, 2.8 ± 0.1 vs 2.8 ± 0.09 liter/min/m²; women, 2.9 ± 0.1 vs 2.8 ± 0.1 liter/min/m², respectively) and similarly elevated total peripheral resistance (men, 47.1 ± 2.3 vs 46.5 ± 1.9 U·m⁻¹; women, 45.0 ± 2.4 vs 44.0 ± 1.3 U·m⁻¹, respectively) as compared to normals (cardiac index: men, 2.9 ± 0.09 liter/min/m², women, 3.4 ± 0.2 liter/min/m²; total peripheral resistance: men, 29.4 ± 1.0 U·m⁻¹, women, 28.3 ± 2.8 U·m⁻¹). Volume measurements corrected to body surface area showed that both obese and nonobese hypertensive patients had lower blood volume (men, 2.6 ± 0.05 vs 2.5 ± 0.05 liter/m²; women, 2.2 ± 0.05 vs 2.1 ± 0.05 liter/m², respectively) than normals (men, 2.9 ± 0.08 liter/m²; women, 2.5 ± 0.08 liter/m²). The results of this study suggest that hypertension in moderately obese subjects is similar in its hemodynamic and volume profiles to hypertension in the nonobese and that the presence of obesity does not alter the hemodynamic characteristics of established essential hypertension. (Hypertension 4: 84-92, 1982)

KEY WORDS • obesity • hypertension • hemodynamics • blood volume

HYPERTENSION and obesity are two closely associated conditions; epidemiologic studies have suggested that obesity predisposes one to hypertension, and clinical studies that weight loss reduces blood pressure. The reason for this close association is not known, nor whether the relationship is causative. Increases in cardiac output, blood volume, sodium intake, and steroid production, as well as alterations in receptors for various pressor substances, have been suggested as factors in the observed association, but none definitely proven. Inherent is the assumption that hypertension in the obese represents a distinct entity and that any factor above or a combination of them is causative in its pathogenesis. While many studies of the hemodynamics of hypertension are available, few characterize the hemodynamics in obesity or the hypertension that accompanies it.

In this study, we evaluated the hemodynamic, volume, and humoral characteristics of established hypertension in obese subjects, and whether these characteristics are different from those of normal subjects or of nonobese hypertensive patients. Our goal was to determine if any of these characteristics, or the way they relate to each other, would define the obese hypertensives as a separate group. Our results suggest, however, that hypertension in the obese cannot be defined by a single functional abnormality such as high cardiac output or expanded blood volume, nor can it be separated from essential hypertension in the nonobese by the ways various factors, are interrelated (hemodynamic, intravascular volume, or humoral).

Materials and Methods

Subjects

This hemodynamic study included all subjects with essential hypertension investigated in the last 5 years at the Research Division of the Cleveland Clinic; none had evidence of secondary forms of hypertension. All were included without preselection or subsequent elimination analysis by the following criteria: they had been untreated or had had their treatment dis-
continued for at least 4 weeks before the study; they did not have malignant hypertension; and they had no clinical or laboratory evidence of cardiac decompensation or renal failure. The total was 109 patients, mostly caucasians, 66 men and 43 women. During the same period, a group of 25 normal subjects, 17 men and eight women, were also studied by the same methods with normal diet and activity.

Definitions

Hypertension was defined as a persistent systolic pressure $\geq 140$ mm Hg and/or a diastolic pressure $\geq 90$ mm Hg on repeated sphygmomanometric measurements in the clinic, over follow-up observation, comparison, another index of obesity was also used, was calculated as wt/ht $^2$ (weight in kg and height in meters). A value of BMI $\geq 29$ for both sexes was used as denoting obesity. In our subjects groups, there was complete concordance between the two definitions.

Hemodynamic Studies

The procedures were explained to each subject, and all gave their informed consent. The subjects fasted overnight and did not receive sedation. After they had rested 40 minutes in the supine position, cardiac output (CO) was determined by the dye-dilution (indocyanine green) method; details of the procedure have been described previously. Values reported are averages of at least three successive determinations over 10 to 15 minutes, with less than 10% variation from curves. Arterial BP was recorded continuously from a catheter introduced percutaneously (modified Seldinger technique) through the brachial artery and advanced to the subclavian artery or to the root of the aorta. Mean arterial pressure (MAP) was calculated from the sum of diastolic pressure and one third of the arterial pulse pressure. Heart rate (HR) was measured from the electrocardiogram during cardiac output determinations.

Since MAP is not related to body size as cardiac output is, some investigators have used the total peripheral resistance index (TPRi) = MAP/cardiac index; others, however, have criticized the validity of cardiac index (CI) for that calculation. For this reason, total peripheral resistance has been expressed in both ways; as arbitrary units (U) when cardiac output was used in its calculation, and as U-m$^2$ when cardiac index was used.

Aortic distensibility index (ADLc) was calculated as the ratio of pulse pressure to stroke volume and expressed as mm Hg/ml. The expected index (ADLc) was calculated from the equation:

$$ADLc = 0.0048 \times DBP + 0.0069 \times age + 0.009 \times HR - 0.64.$$
Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Hypertensives</th>
<th>Normals</th>
<th>Hypertensives</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nonobese</td>
<td>Obese</td>
<td>Nonobese</td>
</tr>
<tr>
<td>Number</td>
<td>17</td>
<td>36</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>33.1</td>
<td>±1.7</td>
<td>48.6</td>
<td>±2.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>177.1</td>
<td>±1.8</td>
<td>176.0</td>
<td>±1.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.7</td>
<td>±1.8</td>
<td>74.0</td>
<td>±1.4</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.87</td>
<td>±0.03</td>
<td>1.89</td>
<td>±0.02</td>
</tr>
<tr>
<td>BMI</td>
<td>22.5</td>
<td>±0.4</td>
<td>23.6</td>
<td>±0.3</td>
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</table>

Values are means ± SEM. BSA = body surface area; BMI = body mass index.

For both sexes, normal subjects were on the whole younger than hypertensive patients (table 1). The mean age in hypertensives, however, was not significantly different between the obese and nonobese.

Clinical Characteristics

Age

For both sexes, normal subjects were on the whole younger than hypertensive patients (table 1). The mean age in hypertensives, however, was not significantly different between the obese and nonobese.
### Table 2. Hemodynamic Studies

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
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<tr>
<td></td>
<td>Normals</td>
<td>Hypertensives</td>
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<tr>
<td></td>
<td>Nonobese</td>
<td>Obese</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>87.4 ± 1.7</td>
<td>127.6 ± 2.8</td>
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<tr>
<td>HR (beats/min)</td>
<td>66.7 ± 1.5</td>
<td>70.7 ± 1.5</td>
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<tr>
<td>CO (liter/min)</td>
<td>5.6 ± 0.2</td>
<td>5.4 ± 0.1</td>
</tr>
<tr>
<td>CI (liter/min/m²)</td>
<td>2.9 ± 0.09</td>
<td>2.8 ± 0.09</td>
</tr>
<tr>
<td>TPRi (U/m²)</td>
<td>29.4 ± 1.0</td>
<td>46.5 ± 1.9</td>
</tr>
<tr>
<td>TPR (U/m³)</td>
<td>15.7 ± 0.6</td>
<td>24.6 ± 1.0</td>
</tr>
<tr>
<td>SI (ml/m²)</td>
<td>46.1 ± 1.5</td>
<td>40.7 ± 1.3</td>
</tr>
</tbody>
</table>

Values are means ± 1 SEM.

MAP = mean arterial pressure; HR = heart rate; CO = cardiac output; CI = cardiac index; TPR = total peripheral resistance; SI = stroke index.

The difference did not achieve statistical significance in this group. In women, there was no significant difference in mean heart rate among all three groups. Normal women had a higher heart rate than normal men.

### Cardiac Output

Because of lack of universal agreement on normalization for cardiovascular data, cardiac output was expressed both in absolute terms and after normalization for body surface area (cardiac index). Values for cardiac output varied over a wide range in each of the groups: in men, values for normals ranged between 4.3 and 7.1 liter/min; for nonobese hypertensives, between 3.3 and 7.5 liter/min; and for obese hypertensives, between 3.6 and 8.9 liter/min. In women, values for normal cardiac output ranged between 3.7 and 7.2 liter/min; for nonobese hypertensives, between 2.8 and 5.7 liter/min; and for obese hypertensives, between 3.4 and 9.3 liter/min. For both sexes there was considerable overlap in the distribution of cardiac output values between the groups (fig. 2).

For both sexes, analysis of variance showed no difference in the means of cardiac index among different groups. For cardiac output, the mean values for the male groups were also not significantly different; in women, although analysis of variance showed the group means for cardiac output to be different, comparison of group pairs by Bonferroni test did not show a statistically significant difference.

Normal men and women had similar mean values for stroke index (46.1 vs 44.0 ml/m²), indicating that the higher cardiac index in women was due to the higher heart rate. Stroke index (SI) in all hypertensive patients was lower than normal except for nonobese hypertensive men, in whom the difference did not reach statistical significance.
Total Peripheral Resistance

Total peripheral resistance (TPR) had a non-normal distribution in obese hypertensive men and non-obese hypertensive women; hence, group comparisons were performed by the nonparametric Kruskall Wallis test. There was no significant difference in the medians of TPR between nonobese hypertensives and obese patients (medians were 2.47 vs 2.58 liter/m² for men and 2.28 vs 2.15 liter/m² for women).

When TPR was normalized to body surface area (BSA), nonobese hypertensives had a significantly higher TPR than nonobese hypertensives (p < 0.016). Although TPR/BSA in nonobese hypertensives was lower than in normals, the difference reached marginal significance (p = 0.0172) only in men.

When TPR was normalized to weight, the results were again similar in both sexes. Normals had significantly higher values than hypertensive groups (p < 0.001); among the latter, nonobese hypertensives had a higher value than obese hypertensives (p < 0.01). In both sexes, mean values for plasma volume followed a pattern identical with total blood volume (fig. 4).

Plasma Renin Activity

In both sexes there was no significant difference in supine PRA between nonobese hypertensives and obese hypertensives.

<table>
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<tr>
<th>TABLE 3. Volume and Hormonal Studies</th>
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<td><strong>Men</strong></td>
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<tr>
<td>TBV/height (ml/cm)</td>
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<td>TBV/BSA (liter/m²)</td>
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<td>PRA (ng/ml)</td>
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<td><strong>Women</strong></td>
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<td>PRA (ng/ml)</td>
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Values are means ± 1 SEM. TBV = total blood volume; BSA = body surface area; wt = weight; PRA = plasma renin activity.
Figure 4. Total blood volume in hypertensives expressed as a percent of values found in normals, using various indices of normalization. Males and females shown separately.

Correlations

Correlations between hemodynamic, volume, and humoral variables were examined in the various groups to determine whether obese hypertensives could be distinguished from the other groups. There was no correlation between weight and BP in any of the groups.

Cardiac output correlated significantly with weight only in obese hypertensive men ($r = 0.44, p < 0.025$). When the correlation was corrected for effect of TBV, $r$ became 0.25 with $p > 0.05$, suggesting that weight in this group was related to CO through blood volume changes.

Covariance analysis showed significant correlation between CO and TBV ($p < 0.01$). Comparison of group pairs showed no difference in slopes or intercepts of that correlation, between obese and nonobese hypertensives in either sex. There was no significant correlation between CO and MAP except in nonobese hypertensive women ($r = 0.55, p < 0.005$). Similarly, there was no significant correlation between TBV and MAP except in nonobese hypertensive women ($r = 0.55, p < 0.01$); in the latter, correcting for the effect of CO made the correlation non-significant, suggesting that TBV affected MAP through its effect on CO.

Renin values did not correlate significantly with any of the hemodynamic or volume measurements.

Discussion

The association between hypertension and obesity is multifaceted and bidirectional, the two conditions being related in various stages of their development. In children and young adults, weight is a risk factor for the development of hypertension.\cite{1, 5, 27-30} Overweight and subsequent weight gain are important predictors of whether early increases in BP evolve into sustained hypertension.\cite{31, 32} Furthermore, hypertensives have an increased tendency to develop obesity.\cite{27, 33} and the two conditions may share a common genetically determined predisposition.\cite{34} The two conditions are also strongly linked in their established stages. Hypertensives are more commonly obese than normotensives.\cite{3, 7, 27, 39, 38} and hypertension is more common in obese than in nonobese subjects.\cite{39, 40, 38}

Finally, interventions leading to weight loss have repeatedly led to reduction in BP levels in normotensive and hypertensive subjects;\cite{1, 2, 3, 7, 38, 39} whether this reduction is related to low salt intake remains unsettled.\cite{1, 2}

The present study reports the hemodynamic, volume, and humoral aspects of established hypertension in obese patients, and suggests that hypertension in the obese cannot be defined by a single functional abnormality, nor can it be separated from essential hypertension in the nonobese by the ways in which various BP determinants are interrelated. Because the present study was carried out in the established stage of both conditions, any conclusions refer to the steady state of hypertension and obesity. Because very few obese normotensives were studied, the patients investigated were compared with two other groups. Comparison with both normotensive subjects and nonobese hypertensives allowed a more detailed study of BP determinants, and helped evaluate the effects of hypertension and obesity, singly and combined, on these determinants. The validity of this approach is obviously dependent on the degree to which the reference groups are representative of their respective populations. In fact, the hemodynamic, volume, and humoral characteristics of the two reference groups in this study (viz, the normotensives and essential hypertensives) were comparable to findings reported in the literature by various investigators;\cite{16-18} hence, they could be taken as adequate representatives of their respective populations.

Hemodynamic Characteristics

The present study showed that both hypertensive groups shared common hemodynamic characteristics. Compared to normals, both the obese and nonobese had normal cardiac output (both in absolute values and in reference to body surface area), and similar elevations in total peripheral resistance. Stroke volume indices were similarly reduced in both. These results do not agree with some current concepts. Whyte\cite{4} suggested that hypertension in obesity results from a discrepancy between an increased cardiac output due to increased body mass and a relatively unchanged arterial capacity. The implications of this hypothesis are that a high cardiac output is
chronically maintained in the obese hypertensive state, that adipose tissue has a reduced vascularity, and that obese hypertensives would have a predominance of systolic hypertension. Direct determinations in our patients showed that a consistent elevation of cardiac output was not a universal characteristic of the established obese hypertensive state, but that cardiac output values in such hypertensive patients overlapped to a significant degree with values found in their non-obese counterparts and in normotensive subjects (fig. 2). In addition, the vascularity of adipose tissue has been found to be extensive, resembling that of muscle so that the total vascular bed in overweight subjects is actually expanded. Finally, we did not find an increased frequency of inappropriately elevated systolic BP in our obese hypertensives, and analysis of their aortic distensibility indices did not reveal any additional abnormality.

A maintained elevation of cardiac output and chronic expansion of blood volume in obese subjects has been described by Alexander et al. and others. The populations they studied, however, were severely obese, had manifest cardiorespiratory dysfunction, and represented a mixture of normotensive and hypertensive subjects. The cardiac output data were frequently not expressed in relationship to any index of body size, in fact, normalization by body surface area of published data in two studies for nonhypoxic subjects resulted in values within the normal range. The high cardiac output reported in these studies cannot, hence, in our opinion be projected to characterize hypertension in obese subjects. The same conclusions can be applied to the suggestion concerning "normal calculated systemic vascular resistance" in obese hypertensives. In our patients with the more common and hence more clinically relevant moderate obesity, the increased arterial pressure was out of proportion to any increase in cardiac output so that their calculated systemic vascular resistance was elevated whether expressed in absolute value or corrected for body surface area (fig. 3). These results are at variance with the conclusions of a recently published study. The reasons for discrepancy seem to be related to group selection, statistical methods, and interpretation of data.

Volume Characteristics

Reference Index for Measurements

In agreement with published reports, blood volume measurements correlated significantly with body size indices (height, weight, surface area) in all subgroups, except in normotensive men. In hypertensives, the correlation was closer with surface area than with height (0.717, p < 0.0001 vs 0.463, p < 0.001 for men), or weight (0.69, p < 0.0001 for men). Analogous results were obtained in normotensives; correlations of blood volume with surface area and height were closer than with weight. Since blood volume depends, albeit in different degree, on both body height and weight, it follows that neither index alone can be used exclusively for data normalization.

Body surface area, which is a function of both height and weight, seems therefore to be the better index for normalization. This conclusion is based not only on the correlations described but also on the mathematical requisite that an index for normalization of data should be the one that correlates best with the absolute measurements as well as least with the normalized measurements. Surface area correlated best in our experience with absolute blood volume measurements. When these measurements were normalized to weight and height, they still correlated significantly with these indices (e.g., for hypertensive men TBV/ht vs ht r = -0.47, p < 0.001; TBV/ht vs wt r = 0.26, p < 0.05). However, when they are normalized to surface area, the correlation with this index was not significant (for hypertensive men: TBV/BSA vs BSA r = 0.22). Hence, body surface area seems to be the best index by which to express blood volume measurements.

Findings in Obesity

Blood volume expressed in absolute values was normal in obese hypertensives and reduced in non-obese hypertensives. This pattern persisted when height was used as an index of reference. If weight was used as the reference index, values for obese patients showed significant reduction; that expression (ml/kg) has been considered by most investigators as open to question. When expressed as a function of body surface area, blood volume tended to be slightly lower than normal in both hypertensive groups, but the difference was not significant (fig. 4). These observations do not support, therefore, the contention that hypervolemia is a consistent finding in obese hypertensives, but rather suggest the pattern described for essential hypertensives in general, namely, a slight reduction of blood volume per m² as compared to normals. These observations also contrast with findings in subjects with hypervolemic essential hypertension whose blood volume was consistently higher than essential hypertensives, whatever the index of reference used (fig. 5).

In obese subjects, there was a declining level of correlation between the following measurements in the sequence shown: weight and total blood volume (r = 0.74, p < 0.0001); total blood volume and cardiac output (r = 0.39, p < 0.005); cardiac output and MAP (r = 0.19, p > 0.1). This gradually decreasing level of correlation reflects the interference of different factors in the sequential translation from weight to BP through the intermediate steps of blood volume and cardiac output. Blood volume was significantly correlated with weight; cardiac output was less influenced by blood volume, probably because of the intervening effect of possible relocation of intravascular volume and of cardiac performance. The lack of correlation between cardiac output and BP reflects the many factors controlling peripheral resistance.

In conclusion, established hypertension in the moderately obese does not constitute a separate hemodynamic entity; its hemodynamic and volume characteristics appear similar to those in hypertension in the
nonobese. The maintenance of an increased arterial pressure is not dependent on high cardiac output or expanded blood volume, but rather on an elevated total peripheral resistance. The role of hemodynamic and volume factors in the development of the two conditions and during therapeutic weight manipulations remains to be explored.

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