The Problem of Obesity and Hypertension

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SUMMARY  Hypertension and obesity are two disorders that have been closely related, each occurring in greater frequency with the other than in an otherwise normal population. Although a causal relationship has not been established between the two, their coincidence carries increased risk of cardiovascular morbidity and mortality. This report summarizes the pathophysiological studies from our laboratory concerning their interrelationship and offers a rational hypothesis for the mechanisms underlying this enhanced risk. Patients with hypertension demonstrate an increased total peripheral resistance that explains hemodynamically the rising arterial pressure with advancing vascular disease. In response to this increased afterload imposed upon the heart, the left ventricle adapts itself structurally through a process of concentric hypertrophy. In addition, in most patients with essential hypertension, plasma volume progressively contracts and renal vascular resistance increases in proportion to the rise in arterial pressure and total peripheral resistance. In contrast, in obesity-hypertension there is a superimposed factor of volume overload upon the hemodynamic abnormality. The result is an additional cardiac stimulus for eccentric hypertrophy due to the increased ventricular preload. This factor enhances left ventricular stroke work and its attendant myocardial oxygen demands, thereby providing a dual overload on cardiac function that can explain the increased risk of heart failure related to these associated conditions. In contrast to the compounding adverse hemodynamic effects on the heart, there does not seem to be an additive hemodynamic effect of obesity on hypertensive renal vascular disease. With respect to introduction of appropriate antihypertensive therapy, use of an effective weight reduction diet (alone or in conjunction with pharmacological agents) will provide specific amelioration of the pathophysiological changes. It therefore follows that the unidirectional consequences of these two commonplace disorders are remediable and with proper attention can be prevented. (Hypertension 5 (supp III): III-71-III-78, 1983)

KEY WORDS  • obesity • systemic hemodynamics • intravascular volume • renal hemodynamics • renal blood flow • ventricular hypertrophy • cardiac enlargement

HYPERTENSION and obesity are two diseases that have been directly related.1-4 Thus, the incidence of hypertension in an obese population is far greater than in otherwise normal people;5-8 and hypertensive patients, as a group, consistently weigh more than age-, race-, and sex-matched normotensive subjects.9-12 Nevertheless, a causal relationship between the two disorders has not been established. Our investigative group has been interested in the pathophysiological correlates of the two disorders for a number of years, and this report will summarize our series of studies.

Materials and Methods

We have studied a large number of men and women who were normotensive, borderline hypertensive, and established essential hypertensive by comparing systemic and regional hemodynamic, cardiac, fluid volume, and humoral factors associated with arterial pressure control.10 Borderline hypertensive patients had diastolic pressures that were greater than 90 mm Hg on at least two outpatient visits but at normotensive levels (less than 90 mm Hg) at other times. In contrast, patients with established essential hypertension had diastolic pressures that persisted above 90 mm Hg at each outpatient visit. Each of our studies was accomplished with the patients in the fasting state and having remained off all anti-hypertensive therapy for at least 4 weeks. All patients were instructed to eat a normal diet without sodium restriction prior to all studies. However, in one study involving a weight reduction program, the patients were instructed to follow a caloric-restricted diet; but for the several days preceding the hemodynamic study, all patients returned to a normal caloric, normal sodium diet. All patients said to have remained on a normal sodium diet ingested over 100 mEq sodium daily.

Hemodynamic evaluation of patients was conducted as described in detail previously.11,12 In brief, polyethylene tubing was inserted into an antecubital vein and brachial artery by the Seldinger technique and then
advanced to subclavian level. Cardiac output was determined in triplicate using indocyanine green dye while the patient remained in the supine position. Renal blood flow was determined by the single injection of 131I-iodinated paraamminohippurate. Plasma volume was measured using 131I-iodinated human serum albumin. Plasma catecholamine levels were determined with the radioenzymatic method of Peuler and Johnson. Plasma renin activity was measured by radioimmunoassay.

Patients were categorized according to body weight using the Metropolitan Life Insurance Company's Desirable Weight Tables. They were defined as being: lean, if their body weight was 5% less than ideal body weight; obese, if their body weight exceeded 50% of ideal weight; or mildly obese, if body weight was between 15% and 50% greater than ideal body weight.

Statistical comparison was accomplished with one-, two-, or three-way analyses of variance and Tukey's honestly significant range tests. When indicated, paired or unpaired data analyses using Student's t tests were made, and linear regression analysis was performed by the related values when necessary.

Relationship of Obesity and Hypertension

A direct relationship between body mass and height of arterial pressure has been repeatedly reported over the years. This has been attributed to several factors, but recent studies have emphasized that the height of pressure is not solely related to an artificial error of indirect pressure measurement because of arm girth. Moreover, other studies have demonstrated that simple increased body mass may be responsible for the elevated pressure, and this factor may not depend on the amount of dietary sodium ingested. Indeed, these concepts have been reinforced by specific studies in which caloric restriction was associated with a maintained dietary sodium intake.

Nevertheless, despite this close association, it is clear that not all obese individuals develop hypertension and, conversely, not all patients with essential hypertension are necessarily obese. Despite these discrepancies with a cause-effect relationship for these two abnormalities, it is important to underscore that even in normotensive obese individuals there is an increased risk of cardiovascular morbidity and mortality.

Hemodynamics of Hypertension

Most authorities agree that the hemodynamic hallmark of increased arterial pressure is that of elevated total peripheral resistance produced by arteriolar constriction. Nevertheless, there are exceptions; recent reports have indicated that most forms of clinical and experimental hypertension are associated with increased smooth muscle tone in the venules (capacitance vessels) as well as in arterioles (resistance vessels). Indeed, this increased venomotor tone, particularly during the early phases of hypertension, is associated with a translocation of the circulating intravascular volume from the peripheral circulations to the cardiopulmonary area. This increased venous return to the heart serves to augment a normal cardiac output (even in the absence of an expanded intravascular volume). It may also be associated with increased myocardial contractility, providing a hyperdynamic circulatory state in the early phases of hypertension, particularly in younger individuals.

With advancing vascular disease, there is increasing arterial pressure associated with a rising total peripheral resistance (due to arteriolar vasoconstriction), persistent venoconstriction, but a diminishing plasma volume. As a result, the earlier increased cardiac output returns toward normal as less circulating volume returns to the heart. As the heart can no longer functionally adapt (by hyperfunction) to the increasing afterload imposed on the left ventricle, structural adaptation (i.e., ventricular hypertrophy) occurs. This ventricular hypertrophy is concentric in structure and tends to maintain cardiac output at normal levels until, despite these structural changes, the heart can no longer adapt to the overload. At that point, contractility of the myocardium decreases, and this eventually is followed by a fall in cardiac output. Ultimately, congestive heart failure occurs.

Hemodynamics in Obesity with Hypertension

When we compared three groups of normotensive, borderline hypertensive, and established essential hypertensive patients and classified them as lean, mildly obese, and obese, we found that, even in the normotensives, arterial pressure tended to rise progressively from the lean subgroup to the mildly obese to the obese (fig. 1). Of great interest were the other hemodynamic findings. The lean borderline hypertensive patients demonstrated increased heart rate, cardiac output, and cardiac index, findings comparable with previous studies. The heart rate of the lean established-essential hypertensive patients was also somewhat faster than normal, but cardiac output and index were within normal limits. In contrast, cardiac output was elevated in both the mildly obese and obese borderline hypertensive patients and was either similar to or greater than that of the mildly obese and obese normotensive subjects. Most important was the finding that cardiac output in established essential hypertension was elevated in the mildly obese and obese patients instead of being normal or reduced (fig. 1). These findings were corroborated in part by others. Unexplained at the time is the normal cardiac index (the output is increased) in the mildly obese and obese borderline and established essential hypertensive patients, a finding that might be related to the lack of definition of appropriate indices to express blood flow for patient groups having different body masses. Nevertheless, it seems clear that the absolute volume pumped by the heart (cardiac output) is an appropriate reference to relate to the absolute circulating blood volume or to make comparisons with hemodynamic changes in the same individual.

Associated with the higher cardiac output in obesity is an increased total blood volume due to an expanded
plasma volume. These findings had been reported earlier in normotensive obese subjects and were later confirmed in our laboratory in obese borderline hypertensive as well as established essential hypertensive patients. Even when one relates the plasma volume (or total blood volume) to body height, there is a persistently expanded plasma volume that tends to increase in the mildly obese and definitely obese categories (fig. 1). Thus, the expected decrement in plasma volume that is usually associated with rising arterial pressure was not found in the obese borderline and established essential hypertensive patients. Clearly, the “normal” plasma volume observed in obese patients with essential hypertension is inappropriate for those patients for that level of arterial pressure. Moreover, the findings of an expanded (plasma) intravascular volume that was associated with an increased cardiopulmonary volume, venous return, and cardiac output were even more striking when we compared lean patients with grossly obese (greater than 50% overweight) established essential hypertensive patients whose arterial pressures were matched (table 1).

Cardiac Structure and Function in Obesity Hypertension

As indicated earlier, the heart adapts to increasing arterial pressure, total peripheral resistance, stroke work, and overall ventricular afterload by increasing its mass through adaptive structural responses. The lean hypertensive patient does this by a process of concentric hypertrophy in order to maintain cardiac output. However, the obese established essential hypertensive patient, at any level of arterial pressure, has greater stroke work and higher cardiac output.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lean (Mean ± SE)</th>
<th>Obese (Mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>37.7 ± 0.4</td>
<td>37.7 ± 0.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.7 ± 1.3</td>
<td>101.6 ± 3.0</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>110 ± 4.6</td>
<td>118 ± 4.5</td>
</tr>
<tr>
<td>Cardiac output (liter/min)</td>
<td>5.20 ± 0.39</td>
<td>6.97 ± 0.29</td>
</tr>
<tr>
<td>Cardiac index (liter/min/m²)</td>
<td>3.01 ± 0.18</td>
<td>3.29 ± 0.13</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>74 ± 4.1</td>
<td>101 ± 4.5</td>
</tr>
<tr>
<td>Plasma volume (ml)</td>
<td>2573 ± 220</td>
<td>3344 ± 183</td>
</tr>
<tr>
<td>Total blood volume (ml)</td>
<td>4041 ± 323</td>
<td>5429 ± 332</td>
</tr>
<tr>
<td>Total blood volume (ml/cm)</td>
<td>23.6 ± 1.9</td>
<td>31.7 ± 1.9</td>
</tr>
<tr>
<td>Total blood volume (ml/kg)</td>
<td>65.2 ± 3.8</td>
<td>52.1 ± 0.5</td>
</tr>
</tbody>
</table>

*P < 0.05.

From Messerli et al., Arch Intern Med 141:81–85, 1981 (see ref. 10). Values are means ± SE; numbers in parentheses are SE.
Table 2. Hemodynamic and Cardiac Functional Characteristics in Lean and Obese Normotensive (34 Subjects) and Hypertensive (40) Patients without ECG Evidence of Left Ventricular Hypertrophy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lean</th>
<th>Obese</th>
<th>Lean</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>61 (8)</td>
<td>110 (19)</td>
<td>65 (11)</td>
<td>108 (23)</td>
</tr>
<tr>
<td>Overweight (%)</td>
<td>-0.2 (6)</td>
<td>70 (22)</td>
<td>-0.9 (9)</td>
<td>74 (24)</td>
</tr>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>126 (15)</td>
<td>125 (6)</td>
<td>170 (19)</td>
<td>166 (22)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>75 (8)</td>
<td>75 (5)</td>
<td>97 (12)</td>
<td>98 (18)</td>
</tr>
<tr>
<td>Mean</td>
<td>92 (10)</td>
<td>92 (5)</td>
<td>121 (13)</td>
<td>120 (15)</td>
</tr>
<tr>
<td>Cardiac output (liter/min)</td>
<td>5.33 (0.78)</td>
<td>7.16 (1.45)</td>
<td>5.40 (1.30)</td>
<td>6.36 (1.07)</td>
</tr>
<tr>
<td>Stroke work (U)</td>
<td>123 (32)</td>
<td>172 (36)</td>
<td>171 (44)</td>
<td>200 (45)</td>
</tr>
<tr>
<td>Left atrium (cm)</td>
<td>2.84 (0.52)</td>
<td>4.01 (0.35)</td>
<td>2.98 (0.54)</td>
<td>3.84 (0.61)</td>
</tr>
<tr>
<td>Diameters (cm):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>4.96 (0.62)</td>
<td>5.95 (1.01)</td>
<td>4.66 (0.71)</td>
<td>5.67 (0.91)</td>
</tr>
<tr>
<td>Systolic</td>
<td>3.18 (0.56)</td>
<td>3.91 (0.86)</td>
<td>3.10 (0.68)</td>
<td>3.54 (0.83)</td>
</tr>
<tr>
<td>Aortic root</td>
<td>2.98 (0.46)</td>
<td>3.54 (0.66)</td>
<td>3.16 (0.56)</td>
<td>3.52 (0.66)</td>
</tr>
<tr>
<td>Fractional fiber shortening (%)</td>
<td>36.2 (0.06)</td>
<td>34.6 (0.08)</td>
<td>33.7 (0.07)</td>
<td>37.8 (0.09)</td>
</tr>
<tr>
<td>Vcf (circ/sec)</td>
<td>113 (18)</td>
<td>112 (25)</td>
<td>109 (37)</td>
<td>118 (27)</td>
</tr>
</tbody>
</table>

Each value represents the mean ± 1 standard deviation (indicated in parentheses).

Even before left ventricular hypertrophy is demonstrated by electrocardiogram (ECG), the lean patient with hypertension may develop early ventricular hypertrophy manifested by left atrial enlargement, as demonstrated by ECG or echocardiogram. This finding is not one of atrial disease; the left atrium enlarges to overcome the reduced compliance of a hypertrophying left ventricle.

Even in normotensive obese individuals, the left atrial size is increased. And the left atrium is enlarged to the same degree in the obese established essential hypertensive patients who demonstrate no ECG evidence of left ventricular hypertrophy. Moreover, even when the arterial pressure of the obese patients was of the same level as that of their lean counterparts, the atrial size was similarly increased (table 2). These echocardiographic findings of left atrial enlargement support the thesis that atrial enlargement is caused by reduced ventricular compliance regardless of whether resulting from obesity (volume overload) or hypertension (pressure overload). Most important, echocardiographic measurements of other chambers in both obese normotensive and hypertensive subjects showed similarly increased diastolic, systolic, and aortic root diameters. These augmented diameters were related to the volume overload that was imposed upon the heart by the chronic volume expansion of obesity. Therefore, the early cardiac enlargement resulted first from obesity and not hypertension; and the normotensive and hypertensive patients demonstrated similar chamber diameters and myocardial contractile indices (table 2).

Even though the left ventricle posterior wall and septal thicknesses and increased left ventricular mass index were the same in the obese hypertensive and obese normotensive patients, there were striking differences in the ratio of ventricular radius to wall thickness between the two groups (fig. 2). These data are...
presented as absolute measurements of chamber size and wall thicknesses and were not corrected for body surface area. As indicated above for hemodynamic data, reference indices may reflect disparate results. Until a proper index is arrived at for obese subjects, absolute data may be the most valid basic information. Moreover, using this presentation, pre- and posttreatment data can be compared in the same patient. The normotensive obese subjects demonstrated a lower radius-to-wall thickness ratio, whereas the hypertensive subjects revealed a greater ratio compared with their matched lean counterparts. The obese patient with hypertension develops dimorphic structural changes in response to two coincidental cardiovascular diseases.

Renal Hemodynamics

Because of the aggravating effect of obesity on cardiac structure and function, it was of particular importance to determine the role of obesity on renal hemodynamic function.44 We therefore compared our findings in lean and obese patients with similar renal function (i.e., glomerular filtration rate) and arterial pressure. These data demonstrated that the obese individual (normotensive or hypertensive) has a greater renal blood flow and lesser renal vascular resistance than the lean individual. More specifically, in patients with established essential hypertension, the obese patient has lesser renal vascular resistance than the lean established hypertensive (table 3). Indeed, renal vascular resistance may even be "normal" in the obese essential hypertensive individual compared with lean normotensive subjects; however, the renal vascular resistance of the obese patient with hypertension may be higher than that of the obese normotensive patient.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lean</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>4/6</td>
<td>4/6</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>43 (±2)</td>
<td>43 (±1)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61 (3)</td>
<td>93 (4)†</td>
</tr>
<tr>
<td>Overweight (%)</td>
<td>1 (1)</td>
<td>58 (5)†</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>111 (4)</td>
<td>110 (4)</td>
</tr>
<tr>
<td>Cardiac output (liter/min)</td>
<td>5.1 (0.3)</td>
<td>6.1 (0.3)*</td>
</tr>
<tr>
<td>Total peripheral resistance (U)</td>
<td>22 (2)</td>
<td>19 (1)†</td>
</tr>
<tr>
<td>Total blood volume (ml)</td>
<td>3913 (213)</td>
<td>5171 (380)†</td>
</tr>
<tr>
<td>Renal blood flow (ml/min)</td>
<td>876 (52)</td>
<td>1128 (85)†</td>
</tr>
<tr>
<td>Renal vascular resistance</td>
<td>13 (1)</td>
<td>10 (1)†</td>
</tr>
</tbody>
</table>

Each value represents the mean ± 1 SEM (indicated in parentheses).

*p < 0.05.
†p < 0.01.

Effects of Weight Reduction

Recently our group reported its findings in 21 patients with essential hypertension and obesity who were treated with prolonged caloric-restricted diet in order to reduce weight and, hopefully, arterial pressure.45 Twelve of these patients demonstrated a significant weight loss and nine were unable to lose weight. It is significant that only the patients demonstrating a weight reduction also showed a fall in arterial pressure. The pretreatment systemic hemodynamic findings in the two groups of patients were similar (fig. 3). The data obtained from the patients who lost weight corroborated the role of expanded intravascular (plasma)
volume in the pathogenesis of obesity hypertension. Thus, cardiac output, cardiopulmonary volume, and total blood volume failed to change over the course of this study in the group of patients who had no reduction in arterial pressure and no reduction in body weight. However, in the group of patients who demonstrated a decrease in pressure there was also a reduction in body weight associated with a fall in plasma and total blood volume, cardiopulmonary volume, and cardiac output (fig. 2).

Conclusions

The literature has established a close association between increased body mass and elevated arterial pressure. Indeed, overweight is a characteristic of the essential hypertensive population. However, obesity need not be a constant feature of all patients with hypertension. In lean patients with essential hypertension, the pathophysiological alteration is one of an increased total peripheral resistance that is in proportion to the rising arterial pressure. In response to these hemodynamic changes producing an increased ventricular afterload, the left ventricular mass increases by concentric hypertrophy. Additionally, the increase in systemic vascular resistance is proportionately distributed to the renal circulation in patients with essential hypertension.

In contrast, in obese patients with essential hypertension, there is an additional hemodynamic alteration: one of volume overload. The increased circulating volume is redistributed to the cardiopulmonary circulation, increasing the ventricular preload and cardiac output. This superimposed cardiovascular stress therefore provides a dual load on the left ventricle: 1) a pressure overload (afterload) that stimulates the myocardium to adapt by concentric myocardial hypertrophy; and 2) a volume overload (preload) that initiates an eccentric type of myocardial hypertrophy.

The pathophysiological studies summarized herein provide prospective data that offer an explanation for the increased cardiovascular risk from obesity in both normotensive and hypertensive patients. They provide a rational means for answering four important questions: Why is there an increased prevalence of congestive heart failure in patients with obesity? Why is this risk further increased in individuals with obesity and hypertension? Why does myocardial oxygen consumption increase in obesity and obesity-hypertension, thereby aggravating a relative or absolute state of ischemic heart disease? Why does renal functional impairment not seem to be exacerbated in obese patients with essential hypertension?

References

Discussion

Discusants: F. Gross
E. Frohlich
P. Vetter
C. Alicandri
S. Julius

Gross: What was the period during which the weight reduction occurred?

Frohlich: Six months.

Gross: How then can you maintain this weight loss over 1 year or more? Recently there have been two papers in the Lancet (one by Stumpe) on the longterm reduction of body weight in obese patients. They recommended not only dietary reduction but also the administration of drugs such as fenfluramine over a long period of time. How does this compare with your experience, and how was the weight loss achieved?

Frohlich: By counseling, by having dietitians working with the patients, and by frequent visits to the clinic. As I have shown, only about half the patients lost weight. Jerry Stamler reported in JAMA about 2 years ago his study of 67 men with mild hypertension who lost about 13 lbs over 5 years of controlled blood pressure — a very difficult program. I think that those who reduced their weight during our study were those who were so obese and so motivated that they lost weight. We continued to follow these individuals after the dietitians had stopped working with them and several began to regain weight. Your question is appropriate — these patients present a very difficult problem of management.

Gross: Would you not agree that one should aim to reduce weight over the long term?

Frohlich: Yes, but we wanted to show this over the short term to show the hemodynamic and other physiological changes.

Vetter: Were your patients receiving individually tailored diets or a fixed prescribed diet? Or did you apply any group dynamic methods?

Frohlich: We used no group dynamics. The diets were individually tailored for our patients so that we could get a well-motivated group who could within a relatively short period lose enough weight so that we could determine the physiological variables associated with weight reduction and blood pressure reduction.

Vetter: To assess the patients, did you use a set questionnaire?
Frohlich: For dietary intake? Yes.

Alicandri: Have you any data on the reactivity of the vessels with the weight reduction on changes in biochemical values or, for example, changes in catecholamines or renin?

Frohlich: Other groups have also studied plasma renin activity. But we did not collect any meaningful data on this. Maxwell and associates in California have studied morbid obese patients and showed an increase in renin and aldosterone. They did not measure the other changes. We did not do reactivity studies in our patients. We tried to motivate them by conducting as short a hemodynamic study as we could. But in rats, we have shown that there are changes in norepinephrine responsiveness.

Julius: Obviously, the overweight hypertensive patients had the same kind of increased cardiac output, so the difference between the two groups was in the blood pressure. If we assume that an increased cardiac output somehow drives the blood pressure, which is an assumption from the weight reduction, what is the difference?

Frohlich: The hypertensive patients had an increased total peripheral resistance. The obese individuals, both normotensive and hypertensive, had an increased volume and cardiac output, but the presence of hypertension did not depend on that. In the hypertensive patients, the pressure was dependent on the vascular resistance. When we reversed the hypertension, cardiac output fell.
The problem of obesity and hypertension.
E D Frohlich, F H Messerli, E Reisin and F G Dunn

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