

# Obesity-Hypertension: The Effects on Cardiovascular and Renal Systems

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Longitudinal and cross-sectional studies suggest that a large number of obese patients have a high prevalence of hypertension. This association causes the following changes: insulin and leptin resistance with a suppressed biologic activity of natriuretic peptide, which contributes to sodium retention with concomitant expanded cardiopulmonary volume and increased cardiac output. The cellular metabolism of cations may be altered in obesity and may lead to changes in vascular responsiveness and increased vascular resistance. These changes lead to structural adaptations in the heart characterized by concentric–eccentric left ventricular hypertrophy. The hypertrophic condition provides the basis for the development of congestive heart failure and cardiac arrhythmias that may explain the higher rates of cardiac sudden death in those patients. In

the kidneys, obesity hypertension may initiate a derangement of renal function. The increased deposit of interstitial cells and of extracellular matrix between the tubules induces higher interstitial hydrostatic pressure and tubular sodium reabsorption. The consequent increase in renal flow and glomerular filtration enhances albuminuria excretion and the susceptibility to the development of renal damage. In summary, the hemodynamic and structural adaptations related to obesity hypertension is the cause of greater risk for adverse cardiovascular and renal events. *Am J Hypertens* 2000;13:1308–1314 © 2000 American Journal of Hypertension, Ltd.

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**O**besity is a common disorder that affects more than one-third of adult Americans.<sup>1</sup> It is associated with numerous comorbid conditions such as hypertension (HTN), diabetes, dyslipidemia, atherosclerosis, osteoarthritis, cancer, and chronic renal failure.<sup>2–4</sup> Epidemiologic studies suggested that up to 50% of obese individuals, as defined by body mass index (BMI) > 27 kg/m<sup>2</sup>,

have concomitant HTN.<sup>3,5</sup> Studies in animals and humans show that weight gain raises blood pressure (BP) and that weight loss reduces BP in both normotensive and hypertensive subjects.<sup>6</sup>

Obesity-associated HTN has a complex, multifactorial mechanism including activation of sympathetic and renin systems, insulin resistance, abnormal renal sodium handling, and possibly leptin-resistance and natriuretic peptide downregulation. In this review, we will discuss the effects and subsequent consequences of obesity on the cardiovascular and renal systems.

## EFFECTS OF OBESITY ON THE CARDIOVASCULAR SYSTEM

**Systemic Hemodynamic** The hemodynamic profile of obese subjects is characterized by high intravascular volume, high cardiac output, and inappropriately nor-

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mal peripheral resistance.<sup>7,8</sup> Because heart rate remains unchanged, the increase in cardiac output in response to the elevated metabolic requirement and expanded intravascular volume occurs chiefly through increased stroke volume.

In the lean subject with HTN, the hemodynamic profile is characterized by high total peripheral resistance and contracted circulating intravascular volume. Cardiac output increases in the early stage of HTN development, but tends to decrease thereafter with established HTN.<sup>9</sup>

The hemodynamic changes in obese-hypertensive subjects have a mixed profile resulting from the interplay of the individual components of obesity and HTN. In the obese-hypertensive patient, intravascular volume, total peripheral resistance and cardiac output are all elevated. However, due to the effect of the obesity component, total peripheral resistance is less elevated than would be expected in the lean hypertensive subject, and may be completely normal in some obese-hypertensive patients.<sup>10,11</sup>

Obesity also appears to change the normal circadian variation of BP. In a recent study, we found that up to 70% of obese-hypertensive subjects failed to show an appropriate fall in both systolic and diastolic pressures during sleep.<sup>12</sup> There also are important hemodynamic differences in response to stress between obese and nonobese hypertensive patients. When subjected to mental stress, obese hypertensives responded with a higher increase in total peripheral resistance and lower increases in heart rate, stroke volume, and cardiac output compared with nonobese counterparts. When exposed to isometric handgrip stress, obese individuals responded with an exaggerated increase in BP and heart rate.<sup>13</sup> These maladaptive hemodynamics and abnormal responses to stress also contribute to the development of HTN in obesity.

**Vascular Adaptations** Cellular metabolism of cations and other molecules may be altered in obesity and lead to changes in vascular responsiveness.<sup>14</sup> Insulin has been shown to be a vasodilator that regulates peripheral vascular resistance. Insulin not only inhibits voltage-gated  $\text{Ca}^{2+}$  influx, but also stimulates glucose transport and phosphorylation of glucose to glucose-6-phosphate, which further activates  $\text{Ca}^{2+}$  ATPase transcription and increases cellular  $\text{Ca}^{2+}$  efflux. Both actions result in a net decrease in intracellular  $\text{Ca}^{2+}$  and, therefore, decrease vascular resistance. These effects are blunted in obesity due to insulin resistance, leading to increased vascular resistance.<sup>15</sup>

With the use of magnetic resonance imaging to evaluate the aorta of normal and hypertensive subjects, Resnick et al found that increased abdominal visceral fat, decreased intracellular magnesium and advanced age were closely associated with reduced aortic dis-

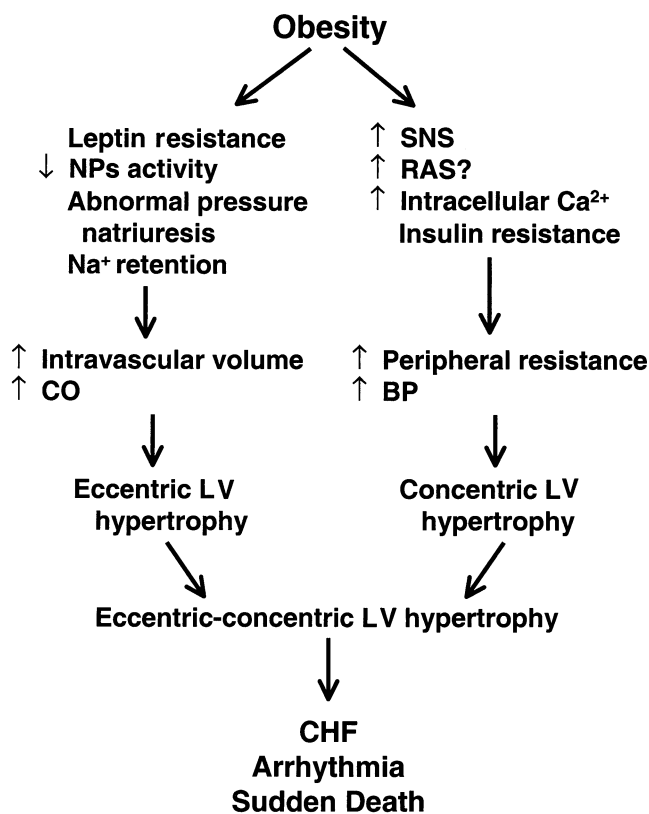
tensibility vessels.<sup>16</sup> Obesity is often accompanied with structural changes in peripheral resistance vessels; the nature of such changes remain to be known.<sup>14,17</sup>

**Cardiac Adaptations** In nonobese hypertensive patients, cardiac adaptation is “concentric” hypertrophy due to the elevated peripheral resistance, increased ventricular afterload, and wall stress. Contractile elements are added in parallel, resulting in the thickening of chamber walls, partially at the expense of chamber volume. Cardiac dilation is not observed until the later stages when cardiac decompensation eventually occurs due to uncontrolled progressive disease.<sup>18</sup>

As opposed to the “concentric” cardiac hypertrophy seen in essential HTN, the characteristic finding in obese individuals is “eccentric” cardiac hypertrophy<sup>19</sup> due to increased intravascular and left ventricular volume or filling pressure. This eccentric hypertrophy can be demonstrated by echocardiographic studies. An earlier autopsy study of obese subjects showed increased heart weight—associated thickening and hypertrophied ventricles.<sup>20</sup> Not surprisingly, congestive heart failure has been documented as a common complication of morbid obesity, regardless of the presence of HTN.<sup>21,22</sup>

The coexistence of both obesity and HTN in the same patient results in a mixed “eccentric-concentric” hypertrophy.<sup>23</sup> Obesity-HTN produces an extensive rise in left ventricular stroke work, as the result of increased afterload associated with HTN and increased preload associated with obesity.<sup>18</sup> The combined hemodynamic burden increases the risk for congestive heart failure. Autopsy data from the Mayo Clinic revealed that the average heart weight was 467 g in obese hypertensive subjects, compared with 367 g in obese individuals without heart disease and only 272 g in nonobese hypertensive subjects.<sup>24</sup> These hypertrophic changes in obesity may provide the basis for the development of cardiac arrhythmias.<sup>25</sup> A recent study of obese individuals showed the presence of mononuclear cell infiltration in and around the sinoatrial node, with marked fat throughout the conduction system.<sup>26</sup> Lipomatous hypertrophy of the interatrial septum has also been noted in obesity.<sup>27</sup> Such changes may contribute to the high rate of sudden cardiac death in morbidly obese patients.<sup>28</sup>

In summary, obesity can cause marked changes in systemic hemodynamics as well as structural adaptations in blood vessels and in the heart. Coexistence of obesity and HTN exerts a double burden on the heart, resulting in distinct cardiac pathologic changes, which increase the risk for congestive heart failure and sudden cardiac death. Fig. 1 summarizes the effects and consequences of obesity-HTN on the cardiovascular system.



**FIG. 1.** Effects of obesity-hypertension on the heart. NP = natriuretic peptides; CO = cardiac output; LV = left ventricular; CHF = congestive heart failure; SNS = sympathetic nervous system; BP = blood pressure; RAS = renin-angiotensin system.

## EFFECTS OF OBESITY ON THE KIDNEY

**Renal Hemodynamic Changes** In an earlier study, we showed that obese patients, both normotensive and hypertensive, have reduced renal vascular resistance and increased renal blood flow compared with lean subjects.<sup>29</sup> Others have shown that obese subjects have an elevated glomerular filtration rate (GFR)<sup>30</sup> and abnormal pressure natriuresis, which shift toward higher BP.<sup>6,31</sup> This resetting of pressure natriuresis and sodium retention in obesity is primarily due to increased renal tubular reabsorption, which may contribute to the raising of BP. The increased sympathetic nervous system (SNS) and renin-angiotensin system (RAS) activity, together with the insulin resistance and hyperinsulinemia that occur in obesity, have been postulated to cause renal sodium retention in obesity.<sup>6</sup> The structural changes in renal medulla, which also cause an increased interstitial hydrostatic pressure, may also play an important role in the sodium reabsorption.<sup>31</sup>

Microalbuminuria and, later, proteinuria often accompany obesity even before histologic changes become evident in the kidneys.<sup>32,33</sup> Increased glomerular

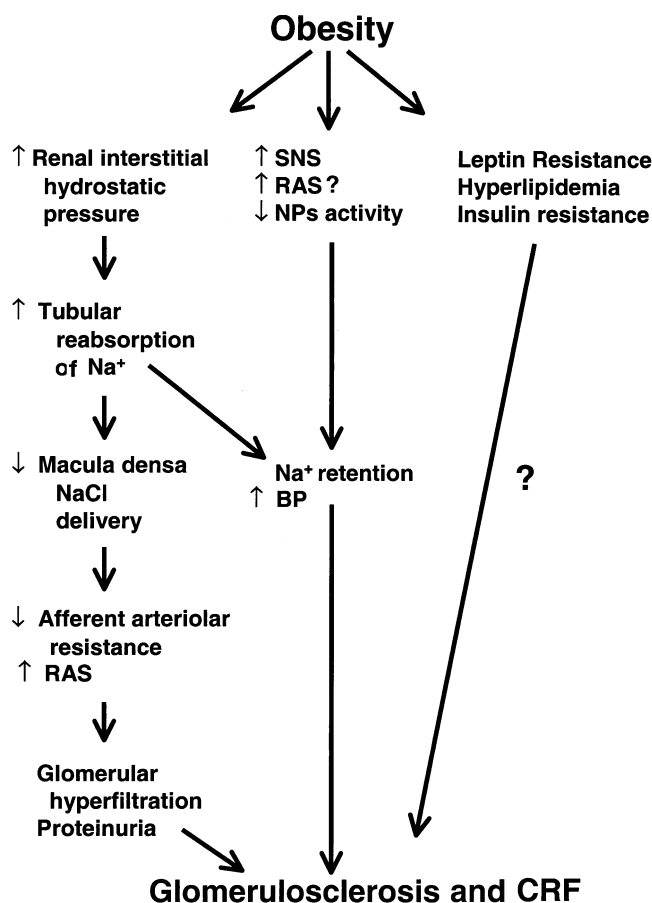
protein traffic and tubular protein load have been shown as direct causes of tubular injury, and contribute to the progression of renal damage.<sup>34</sup> Therefore, the combination of hyperperfusion, hyperfiltration, proteinuria, and HTN together put the obese subject at a great risk for development of glomerulosclerosis and renal failure.

**Renal Structural Changes** Kidneys from obese animals and humans are encapsulated tightly with fat tissue in the capsules. Some of the fat penetrates the renal hilum into the sinuses surrounding the renal medulla.<sup>31</sup> Hall et al reported that in obese dogs, there were large increases in the numbers of interstitial cells and extracellular matrix.<sup>31</sup> Similar histologic changes were noted in the renal medulla of obese humans. The interstitial fluid hydrostatic pressure is elevated to 19 mm Hg in obese dogs compared with only 9 to 10 mm Hg in lean dogs.<sup>31,32</sup> The elevated interstitial hydrostatic pressure reduces medullary blood flow (vasa recta) and causes tubular compression, which slows the tubular flow rate and increases fractional tubular reabsorption. The tubular compression may be especially important in the loop of Henle, which is very distensible and normally has a luminal hydrostatic pressure of only 10 to 12 mm Hg. Increased sodium reabsorption in the loop of Henle would reduce macula densa sodium chloride delivery, which leads to a feedback-mediated renal vascular dilation, elevation of GFR and stimulation of RAS despite the volume expansion. Renal vasodilation, hyperfiltration, and RAS activation from these compensatory responses aim to overcome the increased tubular reabsorption and maintain sodium balance. However, persistent glomerular hyperfiltration in combination with glucose intolerance, hyperlipidemia, and HTN will cause glomerulosclerosis and renal failure.

In summary, the association of obesity-HTN can be the cause of some renal disorders. Persistent obesity can cause renal injury and functional nephron loss, which worsens BP and finally leads to glomerulosclerosis and kidney failure, as summarized in Fig. 2.

## NATRIURETIC PEPTIDES IN OBESITY

There are at least three natriuretic peptides (NP) that have been identified: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type peptide (CNP).<sup>35</sup> The ANP and BNP are secreted mainly by the heart atria in response to an increase in atrial pressure or stretch. C-type natriuretic peptide appears to be produced in the brain and in the endothelial cells. The NP act by binding to specific NP receptors (Npr).<sup>36</sup> The biologically active receptors, including type A (Npr-A) and type B (Npr-B), are coupled with guanylyl cyclase (GC). The cGMP is generated as second messenger and mediates the functional effects of



**FIG. 2.** Effects of obesity on the kidney. CRF = chronic renal failure; other abbreviations as in Fig. 1.

NP. The biologically inactive receptor type C (Npr-C) is not coupled with GC, and it does not mediate any of the known functional effects of NP. Therefore, Npr-C was presumed to function as a “buffering and clearance” of the circulating NP.

Natriuretic peptides are important regulators of volume homeostasis and arterial pressure.<sup>37</sup> In the kidneys, NP modulate renal vascular resistance and increase GFR, decrease inner medullary hypertonicity, and inhibit sodium reabsorption. They also inhibit RAS activity, and decrease systematic vascular resistance and BP.

Few studies have examined the role of NP in obesity. Licata et al reported that obese subjects have delayed urinary sodium excretion and blunted the response of plasma ANP to saline load.<sup>38</sup> Maoz et al showed that weight loss induced by caloric restriction led to a significant natriuresis and diuresis, together with an early increase of circulating ANP level.<sup>39</sup> Both biologically active receptor Npr-A and inactive receptor Npr-C were expressed in rat and human adipose

tissues, as demonstrated by Sarzani et al.<sup>40,41</sup> However, the Npr-A:Npr-C mRNA ratio was significantly lower in obese hypertensive patients as compared with nonobese hypertensives. Dessi-Fulgheri et al reported that after caloric restriction for 4 days in obese hypertensive patients, ANP infusion caused more profound diuresis, natriuresis, reduction of BP, and elevation of plasma cGMP levels than did ANP infusion before caloric restriction, although the infusions achieved plasma ANP levels that were similar.<sup>42</sup> These studies suggest that relative overexpression of inactive receptor Npr-C in adipose tissue may trap and clear more ANP from circulation, reduce its biologic effects on the kidney, and therefore may contribute to sodium retention and HTN in obesity. Weight loss increases the biologic activity of NP that is abnormally suppressed in obesity.

In summary, obesity is associated with suppressed biologic activity of NP, which contributes to sodium retention and HTN. Weight loss in obesity may reverse such a suppression, and it increases the biologic activity of NP and induces natriuresis and diuresis.

#### LEPTIN IN OBESITY

Leptin is a 167 amino acid hormone that is secreted exclusively by adipocytes.<sup>43</sup> By binding to the leptin receptor (Ob-R) at the hypothalamus<sup>44</sup> and by activating multiple neuropeptide pathways, leptin decreases appetite and increases energy expenditure, thereby decreasing adipose tissue mass and body weight.<sup>45</sup>

Leptin enters cerebrospinal fluid (CSF) by a specific transporter-mediated endocytosis.<sup>47</sup> The Ob-R gene controls several alternatively spliced variants of Ob-R.<sup>44</sup> The Ob-Rb is the full-length receptor, with one transmembrane domain and a long intracellular carboxyl terminal tail. The Ob-Ra, Ob-Rc, and Ob-Rd are prematurely terminated receptor proteins with short intracellular tails, and they are presumed to facilitate the transport of leptin across the brain–blood barrier. The Ob-Re lacks the transmembrane domain and, therefore, it may function as a soluble receptor to bind and inactivate the circulating leptin.<sup>44,45</sup>

Serum leptin level is at low levels (5 to 15  $\mu\text{g}/\text{mL}$ ) in lean individuals, and is elevated in most obese humans.<sup>46</sup> There is a strong correlation between serum leptin levels and body fat mass, suggesting that there is a leptin-resistant mechanism in obesity.<sup>46,47</sup> In addition to regulating body fat mass, leptin also has multiple complex actions on cardiovascular and renal systems, such as sympathetic activation, increased insulin sensitivity, and renal sodium and water excretion.<sup>44</sup>

**The Effects of Leptin on the Cardiovascular System**  
Leptin-treated animals have higher core temperatures and metabolic rates than control animals.<sup>49</sup> Collins et



al found that leptin increased norepinephrine turnover in adipose tissue, indicating an increased sympathetic outflow.<sup>50</sup> However, no BP elevation was noted when leptin was infused acutely,<sup>51</sup> suggesting that a “depressor” action of leptin coexists. Indeed, leptin was recently reported to increase the production of endothelial nitric oxide in isolated blood vessels.<sup>52</sup>

Chronic effects of leptin seem to be predominantly a “pressor” action.<sup>53</sup> Infusion of leptin to Sprague-Dawley rats (SDR) for 12 days increased arterial pressure despite a decrease in food intake. Increased heart rate and renal vascular resistance were also noted, and explained the consistent sympathetic activation by leptin. Transgenic mice overexpressing leptin also developed elevation of arterial pressure. The elevation of pressure was abolished by the  $\alpha$ -receptor blocker, which had no effect on the BP of nontransgenic littermates.<sup>54</sup>

**The Effects of Leptin on the Kidney** Full-length mRNA encoding leptin receptor Ob-Rb was detected in the kidney,<sup>55</sup> suggesting that leptin may have a direct effect on this organ. Jackson and Li reported that the infusion of leptin (0.3 to 30  $\mu\text{g}/\text{min}$ ) into one renal artery of rats produced an ipsilateral increased in sodium excretion (up to threefold) and urine volume, whereas renal blood flow and GFR had no significant changes.<sup>56</sup> The natriuresis and diuresis were confined to the infused kidney, suggesting a direct local effect of leptin on the kidney. When leptin (0.4 to 0.5 mg/kg) was given systemically, it caused a 40% increase in sodium excretion and 50% increase in urine volume.<sup>57,58</sup> However, long-term leptin infusion increased BP, heart rate and urine protein excretion, but did not cause natriuresis in spontaneously hypertensive rats.<sup>57</sup> Also, the dose of leptin used in these animal studies were much higher than the physiologic level in humans; consequently, it remains to be shown whether the physiologic range of leptin contributes to sodium and water homeostasis in humans.

Leptin was found to increase insulin sensitivity and to inhibit glucose-mediated insulin secretion, and thereby to control hyperinsulinemia.<sup>45,59</sup>

In conclusion, leptin not only controls appetite and body fat mass, but also increases sympathetic activity, renal sodium excretion, and insulin sensitivity. Therefore, leptin resistance in obese patients may contribute to their clinical profile, with such effects as low energy expenditure, sodium retention, and intravascular volume expansion (promoting HTN), and to insulin resistance (promoting diabetes and hyperlipidemia).

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