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Obesity-Related Hypertension

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ABSTRACT

Obesity-associated arterial hypertension is characterized by activation of the sympathetic nervous system, activation of the renin-angiotensin system, and sodium retention, among other abnormalities. In this review, the following 3 facets of the obesity/hypertension nexus will be discussed: the potential mechanisms by which obesity can lead to elevated arterial pressure, the interaction of obesity with the sequelae of hypertension, and the therapies that are believed to optimally treat obesity-related hypertension.

INTRODUCTION

Obesity increases the risk of the development of hypertension. This linkage has been the subject of several recent reviews.[1–4] Herein, the following 3 facets of the obesity/hypertension nexus will be discussed: (1) the potential mechanisms by which obesity can lead to elevated arterial pressure, (2) the interaction of obesity with the sequelae of hypertension, and (3) the therapies that are believed to optimally treat obesity-related hypertension. Each of these issues is the subject of ongoing research and debate, so definitive answers to many related questions cannot be given. However, enough is known to inform therapeutic decisions and to provide a basis for the evaluation of emerging experimental results.

PATHOPHYSIOLOGIC MECHANISMS

According to the Guyton hypothesis, sustained hypertension can occur only when the relationship between arterial pressure and natriuresis is abnormal (ie, when pressure-natriuresis is deranged). If a normal relationship between pressure and renal sodium excretion pertains, increased pressure will result in increased sodium excretion and lowering of pressure.[1] Although the evidence to support this hypothesis is extensive, it must not lead to the assumption that all hypertension results from disease in the kidney because various factors (particularly certain hormones) can alter the pressure-natriuresis relationship in normal kidneys. The clearest example of this is the action of aldosterone, which includes increasing renal tubular sodium reabsorption and the production of hypertension even in patients with normal renal function.

Against this background, one may ask how obesity predisposes to hypertension. In other words, how does obesity affect the pressure-natriuresis relationship? Obesity is associated with increased blood flow, vasodilatation, cardiac output, and hypertension. Although cardiac index (cardiac output divided by body weight) does not increase, cardiac output and glomerular filtration rate do. However, renal sodium retention also increases, leading to hypertension.[2–4] The factors generally considered responsible for obesity-related alterations in the pressure-natriuresis curve include enhanced sympathetic tone, activation of the renin-angiotensin system (RAS), hyperinsulinemia, structural changes in the kidney, and elaboration of adipokines (hormones produced in fat itself) such as leptin. Sympathetic blockade (combined alpha and beta blockade) prevents obesity-related hypertension in experimental animals and in patients.[2–6] Similarly, leptin, a hormone produced in fat that produces satiety and weight loss by diminishing caloric intake and by activating the sympathetic nervous system to enhance thermogenesis, can cause hypertension. Leptin-induced hypertension is also prevented by combined sympathetic blockade. This and other findings strongly suggest that leptin contributes to obesity hypertension primarily through sympathetic activation. The effects of sympathetic activation in obesity hypertension seem to be related to activation of renal nerve traffic and to subsequent alteration of the pressure-natriuresis relationship, as renal denervation prevents the development of hypertension in some animal models of obesity-related hypertension.[2–10] Also, the hypothalamic leptin-melanocortin pathway is an important modulator of weight, and hyperleptinemia stimulation of this hypothalamic pro-opiomelanocortin pathway likely contributes to high sympathetic outflow. Recent

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work involving investigations of mutations in the melanocortin 4 receptor shows that the melanocortin pathway can produce hypertension in man, thereby demonstrating that this system directly regulates hypertension and weight.[5,11]

There is also activation of the RAS in hypertension with elevations of circulating renin, angiotensinogen, and angiotensin II, despite the fact that renal sodium retention is augmented.[3–4,8,10,12] The reasons for this RAS activation are not completely understood, but a clue comes from the observation that adipose tissue synthesizes angiotensinogen. Because the circulating concentration of angiotensinogen is close to the rate constant, km, for the renin reaction, any increase in circulating angiotensinogen will lead to increased production of angiotensin I and secondarily of angiotensin II.[12] The elevation of renin activity observed in obesity could be the result of increased sympathetic activity. In any case, elevations in angiotensin II directly increase renal tubular reabsorption of sodium and stimulate synthesis of the sodium-retaining hormone aldosterone. Similarly, obesity is associated with hyperinsulinenmia.[8,9] Because insulin can in some circumstances produce enhanced tubular reabsorption of sodium, insulin also could help support an elevated arterial pressure. The roles for the RAS and hyperinsulinemia in this process are indirectly supported by the beneficial effects on blood pressure of angiotensin-converting enzyme inhibitors and peroxisome proliferator-activated receptor gamma agonists.[13–15]

A less well-understood system that may have a role in obesity and hypertension is the endocannabinoid system. Obesity is associated with increased levels of endocannabinoids in tissues and in the circulation.[13–15] Notably, the cannabinoid receptor 1 inverse agonists rimonabant and taranabant produce weight loss and ameliorate obesity-related metabolic disorders, suggesting a role for endocannabinoids in obesity and possibly in obesity-related hypertension.[13–15]

Finally, structural changes in the kidney secondary to obesity seem to be important. The pressure of fat deposits around the kidneys, coupled with increased abdominal pressure secondary to central obesity, has been suggested as an additional cause of disordered renal sodium reabsorption. Glycoprotein deposition in the renal medulla may contribute as well.[3,4] Moreover, the hyperfiltration observed in obesity sets the stage for progressive glomerular loss and loss of renal function and associated increases in arterial pressure.[3,4]

OBESITY AND HYPERTENSION SEQUELAE

Hypertension is associated with well-known sequelae, including coronary artery disease, cerebrovascular disease, renal insufficiency, atherosclerosis, left ventricular hypertrophy, atrial fibrillation, and congestive heart failure. Obesity-related hypertension is no different in this regard in that it predisposes to these conditions as well.[2–5] However, there seem to be subtle differences between the sequelae observed in obese vs lean individuals with hypertension. Indeed, the so-called obesity paradox has recently been described, meaning that, while obese individuals are more likely to develop cardiovascular structural abnormalities, they may have better survival than lean individuals with hypertension. Although controversial, this idea is intriguing, as is the notion that obese individuals with hypertension may have an increased risk of renal insufficiency.[2–5,16]

Hypertension is associated with an increased risk of left ventricular hypertrophy, itself a powerful risk factor for cardiovascular death, as shown by the Framingham Heart Study.The increased intravascular volume associated with obesity leads to increased cardiac output.[2–6] Hypertension leads to concentric adaptive hypertrophy. Therefore, the obese individual with hypertension demonstrates eccentric left ventricular hypertrophy in addition to concentric hypertrophy. That is, left ventricular hypertrophy in the obese individual tends to manifest as eccentric hypertrophy, a form of left ventricular hypertrophy in which ventricular diameter is unchanged and left ventricular wall thickness increases (to be contrasted with concentric hypertrophy typically seen in the lean individual with hypertension that is associated with decreased ventricular diameter and increased wall thickness).[2,3,17] Recently, the relationship between obesity and eccentric hypertrophy has been studied in detail in the Bogalusa Heart Study,[17] and again a relationship between obesity and eccentric hypertrophy was found in young adults. Moreover, a recent large study[16] of cardiac geometry in lean and obese patients with hypertension produced intriguing results. Work in the Department of Cardiology at the Ochsner Medical Center demonstrated the following:

> Abnormal LV [left ventricular] geometry occurred more commonly in obese than nonobese patients (49% vs 44%, p <0.0001 for the difference in the 4 patterns). In obese patients, CR [concentric remodeling] was the most prevalent abnormal pattern (34%), with eccentric and concentric LV hypertrophy occurring in 7% and 8%, respectively, compared with nonobese patients (32%, 6%, and 6%, respectively). Overall mortality was considerably lower in obese than nonobese (3.9% vs 6.5%, p <0.0001). In both groups, progressive increases in mortality compared with normal structure occurred with CR, eccentric and concentric LV hypertrophy (obese patients 2.8%, 4.8%, 5.3%, and 6.9%, respectively; and nonobese patients 4.3%, 8.4%, 9.6%, and 11.8%, respectively).[16(p 1460)]

This is the obesity paradox (ie, lower mortality in obese as opposed to lean individuals with hypertension).[16] Assuming that the obesity paradox is real, the question arises as to whether the subtle changes in left ventricular geometry associated with obesity-related hypertension can account for the differences in mortality or if other subtle differences in the nature of cardiovascular sequelae are operative. This question is indirectly being approached by investigations of the transcriptome (the pattern of gene expression) in left ventricular hypertrophy. Results in dogs fed a high-fat diet to induce obesity show distinctive patterns of gene expression in the left ventricle, including upregulation of the transforming growth factor-beta pathway.[18] This is a notable observation given the known ability of angiotensin II to upregulate transforming growth factor-beta and given the upregulation of the RAS in obesity.[10,19] Similar studies may shed light on the nature of the obesity paradox at the genomic level.

Considerable evidence suggests that obesity hypertension is associated with an increased risk of renal insufficiency. The pathophysiologic mechanisms associated with the onset of obesity-related hypertension that have been discussed herein demonstrate that hyperfiltration, stimulation of the RAS, and obesity-related structural alterations in the kidney all set the stage for progressive renal disease. To these factors must then be added the effects of glucose intolerance and diabetes mellitus that are associated with obesity.[3–5] Therefore, the combination of obesity, diabetes, and hypertension is a potent and dangerous mix insofar as renal function is concerned. Indeed, it may be that the nexus of these 3 factors is at the heart of the current rise in the prevalence of chronic renal disease.

THERAPY

Therapy for obesity-related hypertension for the most part follows the standard line of high blood pressure treatment but perhaps with a greater emphasis on diet. Lifestyle modifications and dietary changes, followed by pharmacotherapy, remain standard. These various treatment options will not be reviewed in detail herein. However, several principles may help to optimize the therapy of patients with obesity-related hypertension.

First, the mainstay of therapy must be weight loss. As difficult as it is to achieve and to maintain weight loss, this must be a primary goal in the therapy of obesity-related hypertension. Weight loss will reverse many of the pathophysiologic mechanisms that sustain hypertension. Although all structural derangements cannot be reversed, at least some can and the risk of further progression mitigated.[2,20–22]

Second, from the discussion herein, it seems likely that interruption of the RAS, inhibition of sympathetic nervous activity, and diuresis should all be helpful in treating obesity-related hypertension.[2–6,20] That said, it is not necessarily the case that each of these approaches is equally efficacious or that these modes of treatment are comparable in reducing cardiovascular risk. For example, diuretic therapy in an obese patient may worsen glucose tolerance or produce frank diabetes, thereby adding additional risk. In patients with diabetes, strict blood pressure control is efficacious, as is glucose control. Both must be achieved. Therefore, it makes sense to try to aim the hypertension therapy along a path that could improve and not worsen glucose metabolism. Similarly, beta sympathetic blockade can be associated with worsening glucose tolerance, and alpha blockade may be associated with postural hypotension and other adverse effects. However, interruption of the RAS in general does not worsen, and may improve, glucose tolerance and is usually well tolerated. However, interruption of the RAS is not without risk. Angiotensin-converting enzyme inhibition can be associated with angioedema, and all drugs that interrupt the RAS are toxic to the fetus and must be discontinued if pregnancy occurs. Nonetheless, clinical experience teaches us that this class of drugs is effective and well tolerated in this patient population, although they often must be supplemented with agents from other drug classes to achieve control of arterial pressure.[23]

Newer agents in time may have a role. Peroxisome proliferator–activated receptor gamma agonists improve insulin resistance and in some cases reduce arterial pressure. The angiotensin receptor blocker telmisartan has been shown to have some intrinsic peroxisome proliferator–activated receptor gamma activity, and it could prove useful to many patients if investigations demonstrate the utility of this agent.[24] Endocannabinoid blockers may also be effective. Rimonabant, the cannabinoid receptor 1 receptor blocker clinically available abroad, lowered blood pressure in patients in weight loss trials, although it raised arterial pressure in rats. Some data suggest that overactivity of the cannabinoid system is associated with increased renal vascular damage, again suggesting a role for inhibitor therapy.[13–15] It is still too early to define what the role (if any) of these newer agents will be.

CONCLUSION

Obesity predisposes to hypertension and alters the course of hypertensive cardiovascular disease in ways that are only now coming to be appreciated. The strong association of obesity with diabetes further complicates the picture in patients with such condi-

tions and complicates the design of effective therapeutic interventions. However difficult to achieve, weight loss must be the first line of therapy. Pharmacotherapy is effective in controlling blood pressure but must be used judiciously to avoid worsening glucose tolerance. Newer agents offer the promise of improved control of arterial pressure, weight, and metabolic parameters, but the true usefulness of these agents remains to be determined. Continued research into the mechanisms responsible for obesity-related hypertension should allow more directed use of pharmacologic therapy and help explain many of the unknowns in this field such as the obesity paradox.

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