Hypertension Highlights

Should We Target the Sympathetic Nervous System in the Treatment of Obesity-Associated Hypertension?

Italo Biaggioni

An estimated 60% to 70% of hypertension may be attributed to obesity. As our population increases in weight and girth, obesity-associated hypertension will be an increasing medical problem, contributing to greater health care costs and reversing the gains that we have achieved in the treatment of hypertension. Considering that 30% of hypertensive subjects are undiagnosed, 40% remain untreated, and, of those being treated, 65% do not meet treatment goals, the opening of the spigot of obesity-associated hypertension will result in an ever-growing number of patients with uncontrolled hypertension, particularly because obesity is a predictor of poor blood pressure control.

It is important, therefore, to understand the pathophysiology of obesity-associated hypertension. This commentary focuses on the role that the sympathetic nervous system plays in this condition and its relevance to treatment.

Sympathetic Activity and Obesity-Associated Hypertension

Landsberg postulated that obesity induces sympathetic activation as a compensatory mechanism to increase resting energy expenditure and restore energy balance; sympathetically mediated hypertension is the price to pay for this beneficial metabolic effect. A competing MONA LISA (Most Obesities Known Are Low In Sympathetic Activity) hypothesis postulates that lower sympathetic activity is an initiating event leading to decreased energy expenditure and obesity. In white populations, in whom most of the studies have been done, the preponderance of evidence supports the concept that sympathetic activation accompanies obesity-associated hypertension. There is less agreement about the cause of sympathetic activation; potential culprits include the increase in insulin, leptin, and angiotensin II; the decrease of adiponectin; and the sleep apnea associated with obesity. Despite the disparity of these mechanisms, it is interesting that all of them act in the central nervous system to increase sympathetic outflow. This central sympathetic activation is not generalized; rather, it is selectively increased in organs relevant to blood pressure regulation, including the kidney, heart, and skeletal muscle vasculature.

To determine whether sympathetic activation indeed contributed to obesity-associated hypertension, Wofford et al used combined α- and β-blockade with doxazosin and atenolol and showed a greater decrease in blood pressure in obese compare with lean hypertensive subjects. We recently used a similar approach, inducing complete but transient autonomic withdrawal with the ganglionic blocker trimethaphan, and showed that most of the increase in blood pressure observed in obese subjects was mediated by the autonomic nervous system. As expected, resting energy expenditure was higher in obese subjects but, in contrast to blood pressure, it remained significantly elevated after autonomic blockade. We found that the increase in energy expenditure was likely because of the increase in muscle mass that usually accompanies obesity; in our patients, a 30-kg increase in fat mass was accompanied by a 12-kg increase in lean (muscle) mass, and lean mass explained 83% of the variability in resting energy expenditure.

Current evidence, therefore, supports the hypothesis that sympathetic activity is increased in obesity and contributes to hypertension but brings into doubt the concept that it provides a beneficial metabolic effect. An interesting parallel can be drawn with leptin; the levels of this hormone are increased in animal models of obesity and act in the hypothalamus to increase blood pressure through sympathetic activation but are no longer effective in reducing appetite or having a beneficial metabolic effect (“selective leptin resistance”).

Treating Obesity-Associated Hypertension With Weight Loss

The obvious solution to treat obesity-associated hypertension is to lose weight. Weight reduction reduces central sympathetic outflow, lowers blood pressure by 0.3 to 1.0 mm Hg for every kilogram lost, and decreases the risk of cardiovascular disease and all-cause mortality. Unfortunately, success rate for long-term weight loss is in the 5% to 10% range. Furthermore, the reduction in blood pressure may be transient even if weight loss is maintained. It is likely, therefore, that the vast majority of patients with obesity-associated hypertension will require medical treatment.

Does It Matter What Antihypertensive Agents We Use as Long as We Lower Blood Pressure?

Current guidelines for the treatment of hypertension do not recommend specific antihypertensive agents for obesity hy-
Are Adrenergic Blockers Effective in the Treatment of Hypertension?

\(\alpha\)-Adrenoceptor antagonists are effective antihypertensive agents and improve insulin sensitivity,\(^9\) but there are concerns about their safety profile. In the ALLHAT Trial, the \(\alpha\)-blocker doxazosin arm was stopped prematurely because of an increased risk of cardiovascular events, particularly heart failure.\(^9\)

Similarly, \(\beta\)-blockers are particularly effective in obesity-associated hypertension,\(^6\) but reduce energy expenditure, lipolysis, and insulin sensitivity. Their negative metabolic effect is associated with a small but significant weight gain (average: 1.2 kg)\(^10\) and an increased risk of new-onset diabetes.\(^21\) \(\beta\)-Blockers are not as effective in stroke prevention compared with other antihypertensive regimens.\(^22\) Newer vasodilating \(\beta\)-blockers with \(\alpha\)-blocking activity appear to be devoid of this negative metabolic profile,\(^23\) but their effectiveness in improving cardiovascular outcomes in obesity-associated hypertension has not been determined.

Central Sympatholytics in the Treatment of Obesity-Associated Hypertension

Central sympathetic outflow is increased in obesity,\(^6\) and its inhibition by carotid sinus simulation normalizes obesity-induced hypertension in dogs.\(^24\) Central sympatholytics, therefore, would seem like logical treatment candidates in obesity. Sedative adverse effects limit the use of traditional central sympatholytics, but this effect appears to be less prominent with newer imidazoline agonists.\(^25\) Moxonidine and rilmenidine are prototype drugs of this class of agents available in Europe. The antihypertensive effectiveness of moxonidine is comparable to hydrochlorothiazide, angiotensin-converting enzyme inhibitor, and \(\alpha\)‐ and \(\beta\)-blockers.\(^28\)

Although clonidine lowers resting energy expenditure\(^29\) in normal volunteers, moxonidine appears to have a positive metabolic effect, inducing a 1- to 2-kg weight loss\(^30\) (in uncontrolled studies) and improving insulin sensitivity.\(^31,32\) This effect, however, has not been reported with rilmenidine.\(^33,34\)

It is not known whether these positive metabolic effects of moxonidine will translate in improvement of cardiovascular outcomes. Its use in patients with heart failure has been associated with increased mortality because of worsening pump failure.\(^35\) In those trials, however, moxonidine was given at doses (3.0 mg/d; sustained-release preparation) several-fold greater those used in hypertension (0.4 to 1.2 mg/d; immediate release formulation). Furthermore, enrollment included heart failure patients without a substantial sympathetic activation at baseline, in whom no benefit from aggressive sympathoinhibition would be expected. Even if we argue that these concerns are not applicable to obese hypertensive subjects, the fact remains that studies to determine whether moxonidine improves long-term outcomes are lacking.

Clinical outcome trials are needed before we can recommend the preferred use of sympatholytics in treating obesity-associated hypertension. Unfortunately, there are several reasons why these studies may not be forthcoming. The perception, whether valid or not, is that we already have effective medications to treat hypertension and that some of the cheapest ones (ie, thiazides) are as effective as newer ones. Hypertension, therefore, may not be seen as an unmet need that justifies the investment needed to fund these studies. Current sympatholytics are out of patent, and the incentive to develop novel leads, eg, the superoxide scavenger Tempol,\(^36\) may be lacking.

Even if one could fund an outcome trial for central sympatholytics, it is not clear what the primary outcome or the ideal patient population should be. The golden standard outcome is a reduction in mortality or in morbidities such as myocardial infarction or stroke. By practical necessity, such studies have to enroll patients at risk to develop these events.
during the “life” of the trial, which explains the prevailing age of the patients enrolled in previous hypertension outcome trials.37–40 (Figure). This may not be the ideal population in whom to test the beneficial effects of sympatholytics given that the relative importance of sympathetic activation to obesity-associated hypertension appears to be greater in younger patients. Finally, most patients require combination therapy to control their hypertension, so that studying a single agent may not be ethically justified. Despite these challenges, it will be important to determine whether targeting sympathetic activation provides an advantage over current therapies in obesity-associated hypertension.41–43

Conclusions

Obesity is arguably the most common factor predisposing to the development of hypertension and is a predictor of poor hypertension control. As the prevalence of obesity increases, obesity-associated hypertension will become a growing medical problem. Despite its importance, currently guidelines do not provide specific recommendations about pharmacotherapy of obesity-associated hypertension. This is attributable, in part, to the lack of evidence based on outcome trials in obese hypertensive patients. Large outcome hypertension trials have not focused on obesity and have enrolled older patients, in whom the relationship between BMI (and presumably sympathetic activation) and blood pressure is not as strong. Given this state of knowledge, it seems sensible to avoid drugs that worsen insulin resistance, increase the risk of diabetes, or induce weight gain in the treatment of obese hypertensive subjects. These include thiazides and β-blockers. Of available therapies in the United States, current evidence favors the use of drugs targeting the renin-angiotensin system. In large clinical trials that include, but do not target, obese patients, these drugs improve cardiovascular outcomes and mortality. They may also decrease the incidence of diabetes, but this is not entirely clear.

It would seem intellectually appealing to guide therapy of obesity-associated hypertension based on our understanding of the underlying pathophysiology. In this regard, there is growing evidence that increased sympathetic activity contributes to the development of obesity-associated hypertension, at least in white populations. The finding that central sympathetic outflow is increased in obesity-associated hypertension provides strong scientific rationale for the use of central sympatholytics in its treatment. Newer imidazoline agonists are available in Europe, and proof-of-concept clinical studies suggest that they induce weight loss, improve insulin sensitivity, and are effective in controlling hypertension. Outcome trials may be needed before they can be formally be recommended for the treatment of obesity-associated hypertension.

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None.

**References**


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