Resistant Hypertension, Obesity, Sleep Apnea, and Aldosterone : Theory and Therapy

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Resistant Hypertension, Obesity, Sleep Apnea, and Aldosterone
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Abstract—Hypertension resistant to 2 antihypertensive drugs is more common among obese patients than among lean patients. The case we describe and the observations we report suggest that refractoriness among obese hypertensives is frequently caused by obstructive sleep apnea and/or inappropriately high plasma aldosterone levels. In other words, obese hypertensives may have sleep apnea, obese hypertensives without sleep apnea may have inappropriately elevated levels of plasma aldosterone, and a surprising number of obese patients with sleep apnea also have elevated levels of aldosterone. The mechanisms by which obesity and obstructive sleep apnea increase aldosterone levels and raise blood pressure are not understood, but sympathetic nervous system activation and production of nonclassical adrenal stimuli are two possibilities. Obstructive sleep apnea can be detected with a careful history and various sleep studies. Inappropriately elevated aldosterone levels can be detected by measuring the ratio of plasma aldosterone concentration to plasma renin activity. Successful treatment of these resistant hypertensives often can be achieved by devices that provide positive pressure to the upper airway to correct obstructive sleep apnea and by incorporating an aldosterone antagonist in the therapeutic regimen. **(*Hypertension*. 2004;43:518-524.)**

Key Words: obesity ■ aldosterone ■ sleep apnea ■ hypertension ■ fatty acids ■ renin

Although it may appear that hypertension is a condition readily amenable to therapy, with 10 classes of drugs approved in the United States for its management, success is often elusive. Resistance to therapy is particularly vexing in patients with co-morbidities for whom the evidence and the experts dictate extra-low pressure goals. Among the co-morbid conditions that contribute to hypertension, complicate its therapy, and yet demand optimal pressure control are obesity and sleep apnea. We present a prototypic case of an obese, resistant hypertensive subject, and discuss some aspects of cause and management with special emphasis on the possible contributions of obstructive sleep apnea and aldosterone.

Case

A 53-year-old white man was seen on referral for difficult-to-control hypertension. The patient reported a 15-year history of hypertension. By his recollection, his blood pressure had been well controlled on monotherapy for the first several years of treatment, but over the subsequent years his blood pressure had remained elevated despite an increasing number of antihypertensive medications. During the past year, his blood pressure had risen progressively, with systolic pressures persistently 160 to 180 mm Hg and diastolic pressures 100 to 110 mm Hg, despite a 5-drug regimen of amlodipine 10 mg, hydrochlorothiazide 25 mg, benazepril 20 mg, irbesartan 300 mg, and atenolol 100 mg daily. The patient reported a 10-pound weight gain in the previous year.

The patient reported feeling well and denied chest pain, dyspnea, or palpitations. He reported only increased fatigue over the past several years, which he attributed to his medications. The patient also had a history of hyperlipidemia and gastroesophageal reflux disease. He gave no history suggestive of renal disease, catecholamine excess, or endocrinopathy. His mother had mild hypertension (controlled with a single agent) in her 60s, but otherwise his family history, which included 4 siblings and 3 adult children, was negative for hypertension or premature cardiovascular disease. On questioning, the patient admitted to daytime drowsiness, including taking regular naps. His wife reported that he snored loudly and she described his episodes of irregular breathing, including probable apneic spells, while he slept.

Physical Examination

The patient's blood pressure was 172/106 mm Hg, with a heart rate of 58. His body weight was 254 pounds, and his body mass index was 34.4 kg/m^2. His waist circumference was 41 inches, and his waist/hip ratio was 1.15. The patient's optic fundi showed arteriolar narrowing but no hemorrhages or exudates. Auscultation of the heart revealed a presystolic third heart sound (S_4). The abdominal examination was negative; no bruits were heard. The remainder of the physical examination was negative.

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Laboratory Values

Urinalysis and blood counts were normal. Chemistries included a creatinine of 1.1 mg/dL, potassium of 3.6 mEq/L, bicarbonate of 28 mEq/L, and fasting glucose of 96 mg/dL. An early morning ambulatory plasma renin activity was 0.9 ng/mL per hour and plasma aldosterone was 15.5 ng/dL, resulting in an aldosterone/renin ratio of 17. Urinary aldosterone excretion was 15 μg/24 hours. These studies were performed while the patient was ingesting his usual diet, and on that diet, his sodium excretion was 286 mEq (6.6 g)/24 hours. The calculated creatinine clearance, based on a 24-hour urine collection, was 171 mL/min. An echocardiogram showed normal systolic function with mild concentric left ventricular hypertrophy. Ambulatory monitoring showed mean daytime pressure of 154/94 mm Hg.

Treatment

Although the aldosterone/renin ratio suggested primary aldosteronism (see later), it was decided by the clinical staff and the patient to treat medically before launching further searches for adrenal pathology. Accordingly, the patient was treated with spironolactone 25 mg daily in addition to his 5 other antihypertensive drugs. Nothing was performed at that time to address his probable sleep apnea. At 6 weeks, his pressure had fallen from 172/106 to 144/86 mm Hg, and his serum potassium had risen to 4.2 meq/L. The dose of spironolactone was increased to 50 mg per day, and 8 weeks later, his pressure was 136/82. The patient then underwent polysomnographic evaluation, which confirmed obstructive sleep apnea with a respiratory distress index (apnea/hypopnea index) of 19 events/hour. He began treatment with nasal continuous positive airway pressure (CPAP), with improvement in his level of energy and alertness. A follow-up examination 6 months later revealed a blood pressure of 128/80.

Case Summary

The case typifies the common combination of obesity and resistant hypertension in an adult with no clear evidence of renovascular hypertension or pheochromocytoma. We present this example to initiate a discussion of the possible roles of aldosterone and obstructive sleep apnea in the hypertension that accompanies obesity and is frequently resistant to first line therapy. It is clear that our patient responded to an aldosterone antagonist, then responded further to an airway assistance device. What is less clear is the relevance of sleep-disordered breathing and excessive aldosterone to the refractoriness of hypertension in the vast bulk of obese patients.

Resistant Hypertension

Resistance to standard pharmacologic therapy bedevils management of hypertension and frustrates clinicians and patients who understand the dangers but cannot seem to achieve the ever-lower blood pressure goals. Among all groups of hypertensive subjects, the most difficult challenges are presented by diabetic subjects and the elderly. One common co-morbid condition in both of these groups is obesity. As the population ages and gains weight, resistant hypertension is becoming increasingly common. In the recently completed Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), only 30% of patients had their blood pressure controlled on monotherapy, whereas almost 30% were receiving 3 or more medications at year 5.[1,2] The hypertension-resistant patients were more likely to have obesity or diabetes than the patients with more easily controlled hypertension.[2] Resistance to pressure reduction is also common in patients with other co-morbidities, such as left ventricular hypertrophy. In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study of patients with LVH, less than 50% of patients had their blood pressure reduced to $<$140/90 mm Hg after 5 years of intensive antihypertensive treatment.[3]

Obesity causes hypertension. Of that there can be no doubt, because weight loss is almost always helpful in managing accompanying high blood pressure. Overweight persons are 3-times more likely to have hypertension than normal-weight individuals, and risk estimates from the Framingham Heart Study suggest that 78% of new cases of hypertension in men and 65% in women are related to excess body weight.[4] Every 10-pound weight gain is associated with an estimated 4.5-mm Hg increase in systolic blood pressure.[4,5] Considering the difficulty patients encounter when attempting to lose weight, we owe it to them to ameliorate the sequelae of obesity, including hypertension, whether or not they achieve target weight. We next discuss possible mechanisms that might link excess fat and increased blood pressure and offer some thoughts about therapy based on two of the possible mechanisms.

Pathogenesis Theories

Obesity-Induced Sympathetic Nervous System Hyperactivity

Sympathetic activity is clearly increased in obese subjects compared with non-obese controls. Studies of resting muscle sympathetic nerve activity, norepinephrine spillover from the kidney, and plasma norepinephrine indicate greater sympathetic activation with increasing body weight.[6–8] Sympathetic hyperactivity is associated with increases in blood pressure, heart rate, cardiac output, and renal tubular sodium reabsorption.[9] These changes are a direct consequence of α-receptor and β-receptor stimulation and an indirect effect of sympathetic activation of other vasopressor systems such as the renin-angiotensin-aldosterone system. The mechanism by which obesity stimulates sympathetic activation remains obscure. Although some evidence suggests that leptin from adipocytes increases sympathetic stimulation of the kidney and brown adipose tissue in rats; evidence of the role of leptin in sympathetic activation in humans is less conclusive.[10,11] One way obesity might cause sympathetic activation is by inducing obstructive sleep apnea.[12]

Obesity-Induced Impairment of Renal Function

Guyton showed that subtle impairment of the kidneys' ability to excrete sodium could increase blood pressure. He emphasized the reciprocal relationship between arterial pressure and sodium excretion. This aspect of renal function, called "pressure natriuresis," is abnormal in obese humans, so that

sodium is retained at normal pressures, and higher pressures are required to achieve sodium balance.[13] The mechanism by which obesity shifts the pressure-natriuresis relationship to higher arterial pressures is unknown. One or more of the following mediators could be involved: aldosterone, angiotensin, insulin, sympathetic nerves to the kidneys, fat deposits in the kidney parenchyma, or substances released from adipocytes.[13]

Obesity Effects on Aldosterone, Angiotensin, and Their Regulators

Plasma aldosterone levels are elevated in some obese hypertensives, especially patients with excess fat deposits in their abdomen, so-called upper body obesity or visceral obesity.[14,15] The elevated aldosterone and blood pressures fall when patients successfully lose weight.[15,16] The mechanism by which excess visceral fat increases aldosterone is unknown. Fat cells synthesize angiotensinogen, the substrate that yields angiotensin when cleaved by renin.[17] Angiotensinogen can only increase aldosterone if it contributes to increased renin activity and the generation of angiotensin II, but elevated aldosterone levels in obese subjects appear to be independent of plasma renin activity.[14,15,18] Control of aldosterone secretion is very complex and involves an array of inhibitors and stimuli.[19,20] One inhibitor of aldosterone secretion is atrial natriuretic peptide. Levels of this inhibitor are reported to be decreased in obesity.[21] That difference might suffice to increase aldosterone secretion in the obese. Potential non-classical adrenal stimuli include recently identified oxidized products of linoleic acid.[22] Their role may be particularly important in obese or insulin-resistant subjects whose plasma levels of fatty acids are increased, and in whom oxidative stress might lead to increased production of active oxidized derivatives of fatty acids.[23,24] A recent report describes the existence of as-yet-unidentified macromolecular stimuli of aldosterone production released from cultured human adipocytes.[25]

Hyperaldosteronism is common among patients with resistant hypertension. In a recent study, the prevalence of primary hyperaldosteronism was approximately 20% among patients referred to a hypertension specialty clinic for resistant hypertension.[26] In that cohort, the resistant subjects were generally obese (mean BMI=32.5 kg/m^2) and had a very high prevalence of known and suspected sleep apnea, emphasizing the potential role of the two disorders in contributing to development of hyperaldosteronism, either independently or in combination.[27]

Obesity, Obstructive Sleep Apnea, and Hypertension

Obstructive sleep apnea (OSA) and hypertension are strongly associated. Approximately 50% to 60% of sleep apnea patients are hypertensive, and an estimated 50% of hypertensive patients have sleep apnea.[28] This association is particularly strong in patients with resistant hypertension. In a recent study of patients with resistant hypertension, defined as poorly controlled hypertension despite use of 3 different antihypertensive agents, Logan et al diagnosed previously unsuspected OSA in 34 of 41, or 83%, of evaluated subjects.[29] Further, the more severe the sleep apnea, the more likely the resistance to antihypertensive therapy.[30]

Sleep apnea is associated with obesity, especially with central (visceral, upper-body) obesity. The effects of obesity and sleep apnea on blood pressure are approximately additive. Sleep apnea increases the risk of hypertension independent of body weight. This was demonstrated in the Wisconsin Sleep Cohort Study in which there was a linear relationship between blood pressure and apnea/hypopnea index independent of body mass index.[31]

Mechanisms of sleep apnea-induced hypertension have not been fully elucidated. Vascular stiffening secondary to repeated intermittent arousals, increased levels of circulating vasoconstrictors such as norepinephrine and endothelin, and sympathetic activation have been suggested by animal models of OSA.[32–35] In humans, muscle sympathetic activity is elevated in patients with OSA compared with non-OSA controls, and the high level of nerve activity is decreased by CPAP. This is strong evidence for sympathetic activation as a contributor to the hypertension of sleep apnea.[12,36–38]

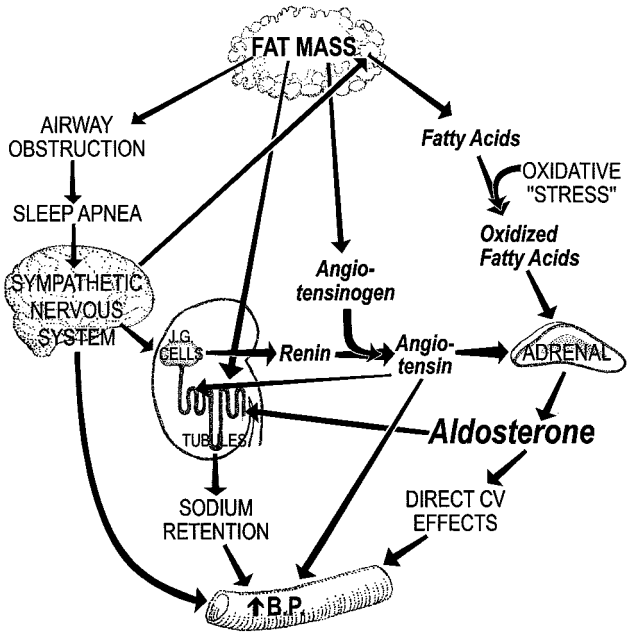
Animal models of OSA suggest activation of the renin–angiotensin system.[39,40] In humans, a recent study reported that plasma angiotensin II and aldosterone levels were higher in hypertensive subjects with OSA compared with healthy controls without OSA or hypertension.[41] This suggests that OSA activates the complete renin-angiotensin-aldosterone axis. In patients referred to us with resistant hypertension, hyperaldosteronism was more likely to be present in patients with confirmed OSA than in those at low-risk for OSA based on the absence of symptoms.[27] In our OSA-positive subjects, 24-hour urinary aldosterone excretion was significantly greater than aldosterone excretion by OSA-negative patients, but renin activity was suppressed. That raises the possibility that OSA, or concomitant obesity in apneic patients, can stimulate aldosterone secretion by an effect on the adrenal independent of plasma renin.

Obesity-Induced Hyperinsulinemia and Insulin Resistance

Obesity is almost always accompanied by insulin resistance, if not diabetes. This linkage is strongest when the excess fat is visceral.[42] Hypertension is, in turn, associated with insulin resistance.[43] The mechanisms that link these 3 conditions are not clear. A prominent hypothesis stems from the observation that insulin can exert subtle sodium-reabsorbing effects on the kidney.[44] If this renal effect of insulin were superimposed on other salt-regulating influences, then it might suffice to raise blood pressure.[13]

Common Themes Among Pathogenesis Theories

Among the several hypothetical mechanisms linking obesity to hypertension, there are two recurring themes. One is the role of excessive sodium retention, mediated by sympathetic nerve traffic to the kidneys, fat-induced alterations in renal function, increased production of aldosterone, and/or the renal effects of increased insulin. A second common theme is sympathetic nervous system activation mediated by fat itself, or by repeated episodes of hypoxemia during sleep apnea. There is no reason to assume that the same mechanisms apply



Real and theoretical links connecting obesity to hypertension. From left to right, the arrows indicate the effect of excess fat on the upper airway to cause obstructive sleep apnea, with consequent stimulation of sympathetic impulses that cause renin release and vasoconstriction; a poorly understood effect of excess fat on the kidney to cause sodium retention; production of angiotensinogen by adipocytes; and production of nonesterified fatty acids by adipocytes leading to generation of putative adrenal stimuli. Fatty acid release is stimulated by the sympathetic discharge that follows apnea. Aldosterone secretion is postulated to be increased by the activated renin–angiotensin cascade and by oxidized derivatives of fatty acids. Hypertension and vascular pathology is viewed as a result of direct sympathetic stimulation, sodium retention, and the direct and indirect effects of angiotensin and aldosterone, all increased by obesity to levels inappropriately high for a given subject's fluid volume status.

to all patients, but we see aldosterone as a potential point of convergence of these themes, a hypothesis that is discussed more fully later. The Figure depicts possible interrelationships among fat depots, the sympathetic nervous system, the renin-angiotensin-aldosterone axis, and the kidney, all conspiring to elevate blood pressure and damage the cardiovascular system.

Diagnostic Approach to the Resistant Obese Hypertensive Subject

It is not difficult to diagnose obesity and hypertension, and a simple measurement of waist circumference adds an approximation of visceral distribution of excess fat. It would also be useful to diagnose the likely mechanism by which obesity raises blood pressure in individual patients to provide some rationale for specific therapy. However, 3 of the proposed mechanisms are beyond the scope of standard clinical measurements: excess sympathetic activation, sodium retention, and insulin resistance. Only the renin-angiotensin-aldosterone axis is subject to reasonably accurate laboratory testing.

Aldosterone, Angiotensin, and Their Regulators

The principal regulators of aldosterone secretion are angiotensin II, usually measured as its surrogate, plasma renin activity, and circulating potassium. Plasma renin activity, in the absence of renal disease, reflects the adequacy of plasma volume and the effectiveness of renal perfusion. For purposes of this discussion, the most useful test of renin-angiotensin-aldosterone status is measurement of both plasma aldosterone concentration and plasma renin activity. The ratio of aldosterone to renin is useful in uncovering patients in whom aldosterone is inappropriately high, ie, above the range needed to maintain adequate plasma volume and renal perfusion. In the presence of normal serum potassium, and while the subject is ingesting at least 200 mEq of sodium per day, with the renin activity below 1.0 ng/mL per hour, an aldosterone/renin ratio (plasma aldosterone concentration/plasma renin activity) above 20 implies excessive aldosterone secretion.[45]

A high aldosterone/renin ratio by itself would suggest that a search for adrenal pathology should be launched and/or therapy with an aldosterone antagonist initiated. Some caveats are appropriate. First, a single determination on a single sample is not adequate. The aldosterone/renin ratio should be measured on several different days. Second, it is possible to find a high plasma aldosterone concentration/plasma renin activity ratio in patients with low aldosterone levels if the plasma renin activity is suppressed to extremely low levels, by beta-blockers for example. Under those circumstances, a high aldosterone/renin ratio would not be meaningful in pathogenic terms, because the aldosterone levels would not be high enough to do harm. In general, a high ratio is meaningful only when plasma aldosterone exceeds 15 ng/dL (416 pmol/L).[45]

Another potential problem in interpreting aldosterone/renin ratios is the variation among laboratory measurements of aldosterone and renin. Confusion can arise because aldosterone and renin are not always reported in the same units. If, for example, aldosterone is reported in pmol, then a "high" ratio is one that exceeds 555.

The aldosterone/renin ratio can be useful even when drawn during therapy with some antihypertensive drugs, but not all. Spironolactone or amiloride will invalidate the test because they interfere directly with aldosterone action, and spironolactone interferes with aldosterone biosynthesis.[46] As mentioned, beta-blockers can decrease renin release to very low levels, which can result in a false-positive ratio. The ratio is not completely invalidated by drugs that interfere with the renin-angiotensin axis, like angiotensin-converting enzyme inhibitors and angiotensin receptor-blockers. These drugs would tend to increase plasma renin activity and decrease the ratio, so a high aldosterone/renin ratio in the presence of these drugs becomes even more alarming. The drugs presenting the least interference with the aldosterone/renin ratio are calcium channel blockers and alpha-adrenergic antagonists.

Obesity Versus Adrenal Adenoma or Hyperplasia

Although a high aldosterone/renin ratio may signal a search for aldosterone-producing tumors, we suggest that some resistant hypertensive subjects with obesity and/or obstructive sleep apnea will have high ratios for reasons apart from intrinsic adrenal pathology. In these patients, something about excess fat and/or sleep-disordered breathing may stim-

ulate the adrenal independent of renin and angiotensin. We found that plasma aldosterone levels correlated approximately with the amount of visceral fat in two cohorts, and the correlation with fat persisted after the influence of renin was excluded by statistical analysis.[14,15] Other investigators have shown a relationship between obesity and activation of the renin-angiotensin-aldosterone axis.[16,47,48] Hiramatsu et al found that the most obese subjects had the greatest discrepancy between aldosterone and renin, suggesting that obesity stimulated the adrenal directly.[18] We are pursuing possible humoral mechanisms by which visceral fat can stimulate the adrenal to produce inappropriately large amounts of aldosterone and have found evidence for the participation of oxidized polyunsaturated fatty acids.[22]

If our hypothesis is validated, then there will be inevitable confusion between patients secreting excess aldosterone because of their obesity, and those with abnormalities of the adrenal cortex such as adrenal adenomas or hyperplasia, entities subsumed under the term "primary aldosteronism." In subjects being treated for resistant hypertension, a high aldosterone/renin ratio has a high sensitivity (approximately 90%) for identifying primary aldosteronism, but its specificity is considerably lower (approximately 70%).[26] We propose that the false-positives include patients with obesity whose aldosterone production is stimulated by factors arising in adipocytes or is stimulated by sleep-disordered breathing. Another confusing entity is so-called low-renin essential hypertension (LREH). This group of hypertensive subjects has never been delineated with respect to cause and diagnosis, and there may be a large overlap of LREH with patients with obstructive sleep apnea or adipocyte-stimulated adrenals.

In subjects with high aldosterone/renin ratios, before commencing a search for tumors, one might consider a therapeutic trial of an aldosterone antagonist such as spironolactone or eplerenone. Obese subjects with aldosterone excess frequently respond to doses as low as 25 mg/d, as did the patient described. It is also reasonable to consider the diagnosis of obstructive sleep apnea before searching for adrenal disease in patients with elevated aldosterone/renin ratios. We do not know how obese subjects with mild hyperaldosteronism react to tests that are commonly used to detect primary aldosteronism, such as the fludrocortisone suppression test, saline infusion, or upright posture. Based on the subjects we have examined, some of whom were studied while on high-salt and low-salt diets, we would anticipate that saline infusion and fludrocortisone would partially suppress plasma aldosterone levels in obese subjects with mild hyperaldosteronism. Suppression would argue against the presence of an adenoma; however, our subjects still demonstrated a correlation between body fat and aldosterone during a high-salt diet, so we would expect that obese patients with elevated plasma aldosterone levels would have levels higher than lean patients undergoing the same test.

Obstructive Sleep Apnea

OSA should be suspected in patients with a history of excessive daytime sleepiness, loud snoring, and witnessed obstructive events during sleep. The latter is a particularly strong predictor of clinically important sleep apnea. Preliminary direct evidence of OSA can be obtained with nocturnal measurements of oxygen saturation using ear oximetry. Definitive diagnosis requires polysomnographic evaluation

Therapy

The most obvious therapeutic modality for obese, resistant hypertensive subjects is weight loss. It has proven efficacious repeatedly in clinical trials, but the problems are as obvious as the logic. Even the most successful regimens have limited durations of success. Noticeable decreases in weight, waist circumference, and blood pressure can serve as powerful positive reinforcements to patients. Needless to say, the invention of safe appetite suppressants would change the face of hypertension therapeutics.

Considering the probable role of sodium retention as an essential element in the linkage between excess fat and hypertension, dietary sodium should be restricted. Our patient was ingesting 3 times as much salt as he should have been. A "no salt added" diet is a reasonable first step. Education about the salt in various foods and condiments should be a routine part of hypertension management.

CPAP treatment facilitates blood pressure reduction in patients with OSA, but on an individual basis, the absolute benefit may be limited. With respect to pharmacologic therapy, given the common occurrence of inappropriate sodium retention in these subjects, diuretics are the mainstay of therapy. Still, many patients will require combinations of 3 or more drugs. A combination of α-adrenergic and β-adrenergic antagonists has been shown to reduce blood pressure better in obese hypertensive patients than in lean subjects, consistent with increased sympathetic activation.[49]

Several authors have lauded the benefits of spironolactone in resistant hypertension, and we concur.[50–52] Recently, we have reported that spironolactone in doses of 25 to 50 mg/d provided significant additional antihypertensive benefit in resistant, obese patients. This benefit was observed despite concurrent therapy with an ACE inhibitor or ARB, calcium channel blocker, and thiazide diuretic.[53] The success of aldosterone blockade, especially when added to other renin system-blockers, clearly suggests that the adrenal in those patients secretes aldosterone independent of the renin-angiotensin axis, and in amounts that exert pressor effects.

Discussion and Speculations

The patient we described in this review is typical of a large proportion of difficult-to-control hypertensive subjects in developed countries where obesity and its sequelae are rampant. Our intent is to point out the possibility that many of these patients have obstructive sleep apnea, hyperaldosteronism, or both. Although one might be tempted to add more powerful drugs to the regimen for resistant hypertension, we suggest considering the possibility that sleep apnea and/or inappropriate aldosterone secretion are contributing to the problem. If so, nasal CPAP and/or an aldosterone antagonist might be efficacious and well tolerated.

Apart from its role in blood pressure and electrolyte homeostasis, aldosterone has direct deleterious effects on the cardiovascular system and kidneys. In animal models, the steroid causes or contributes to hypertrophy, remodeling, and

inflammation of the heart, vessels, and renal parenchyma.[54–57] These deleterious effects are reflected in the response of humans to aldosterone antagonists. Two aldosterone receptor antagonists, spironolactone and eplerenone, have proven beneficial in patients with heart failure, and the benefits exceeded those predicted from blood pressure alone.[58,59] These observations encourage the search for patients secreting more aldosterone than they need. We suggest that hypertensive patients with visceral obesity and/or obstructive sleep apnea should be studied in this regard. They might benefit in more than one way from aldosterone antagonists.

Among the mysteries waiting to be solved are the mechanisms by which obesity and obstructive sleep apnea increase aldosterone secretion and raise blood pressure, and the factors that cause visceral fat to be more damaging than subcutaneous fat. Another mystery is the mechanism by which aldosterone raises blood pressure in patients with obesity or sleep apnea without exerting its other classical effects such as hypokalemia and alkalosis. Fortunately, we need not wait for these answers to help patients achieve normal blood pressure, nor do we need to wait for a safe appetite suppressant. We already know how to ameliorate sleep-disordered breathing and excessive aldosterone, so we may be able to de-fang obesity before we understand it or conquer it completely.

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