Treating Resistant Hypertension With a Neglected Old Drug

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“Be Not Too Fast to Cast the Old Aside”*

Hypertensive patients are said to be resistant to therapy when their pressures exceed goal despite treatment with 3 antihypertensive drugs. The tendency of most clinicians is to treat resistant patients with stronger and stronger agents in higher and higher doses. By contrast, a few reports in the literature suggest surprising usefulness of spironolactone, a relatively weak diuretic, in resistant hypertension.1-6 In this issue of Hypertension, Chapman et al7 describe the largest reported cohort of resistant hypertensive subjects who responded to spironolactone. The average fall in blood pressure was approximately 22/10 mm Hg on 25 mg per day, quite a noteworthy effect for a low dose of a reputedly feeble old agent, especially when added to 3 newer drugs with better reputations! What’s more, the resistant patients who responded to spironolactone included older subjects with predominantly systolic hypertension, many of whom were diabetic, a notoriously recalcitrant group.

Spironolactone antagonizes aldosterone and other salt-retaining steroids by competing for the mineralocorticoid receptor. This action is the simplest but not the only plausible explanation for the efficacy of spironolactone, and it implies that aldosterone plays an unusually prominent role in supporting the pressure of resistant patients. If aldosterone caused resistance, one might assume that those patients were producing a lot of it, but it is unlikely that a dose of 25 mg of spironolactone could have had dramatic effects as an aldosterone antagonist if the endogenous steroid levels were very high. Clinical experiments teach that it requires as much as a 1000-fold excess of spironolactone to antagonize a given amount of aldosterone.8 If that ratio holds for essential hypertensive subjects, 25 mg of spironolactone could have antagonized only 25 μg of aldosterone, a relatively low daily rate of secretion. In other cohorts where aldosterone was measured and spironolactone was effective, aldosterone in blood or urine was only slightly elevated.4 Although Chapman et al7 did not measure aldosterone in their subjects, there was suggestive evidence for its influence: serum potassium levels were slightly lower at baseline and rose higher on treatment in patients who responded best to spironolactone. Body weight fell by an average of 1 lb in responding patients. Perhaps aldosterone levels in resistant subjects were only slightly elevated above the amounts needed for sodium and potassium homeostasis, and spironolactone was just the “last straw” of diuresis needed to break the back of resistant sodium retention. However, there was much more of a drop in pressure than might be expected from such a small fall in body weight. The large number of responders and the small average change in weight mean that many patients must have enjoyed a drop of pressure with no diuresis. Previous advocates of spironolactone were also skeptical that its efficacy could be explained entirely by a diuretic effect.1 Might aldosterone support resistant hypertension by a nonrenal mechanism?

Aldosterone has been shown to induce cardiovascular fibrosis and hypertrophy. Customary wisdom has it that these changes result from a combination of hypertension and direct, genomic effects of aldosterone on cells in the heart and blood vessels. This might be part of a vicious cycle where structural changes, such as arterial fibrosis, contribute to elevated pressure. Maybe the remarkable pressure drop with spironolactone was partly attributable to reversal of the hypertrophic effects of aldosterone. Similar reasoning was mentioned by authors reporting on aldosterone antagonists in heart failure, where the benefits seemed out of proportion to the diuretic effect, and there was biochemical evidence of structural remodeling.9,10

Aldosterone can stimulate contraction of vascular smooth muscle directly by a “nongenomic” mechanism distinct from the hormone’s effects on sodium reabsorption. Reversal of this action might explain some of the antihypertensive efficacy of spironolactone, but those direct effects of aldosterone on vascular smooth muscle are relatively resistant to receptor antagonists.11

If aldosterone levels were relatively high in spironolactone responders, one might ask what elevated them. Aldosterone secretion is regulated by a complex array of hormones and simpler chemicals, prominent among them being angiotensin. It is possible that the treatments that preceded spironolactone in resistant hypertensive subjects shrank vascular volume, stimulated renin release, and shifted a large part of pressure support to aldosterone. In opposition to that idea is the equal effectiveness of spironolactone in patients who were receiving diuretics and those who were not and in those receiving angiotensin-converting enzyme inhibitors compared with those who were not. In further opposition is the large proportion of diabetics and the elderly among the responders reported by Chapman et al7; both conditions tend to lower activity of the renin/angiotensin/aldosterone axis. Might nonclassical regulators stimulate aldosterone production inappropriately?
Visceral obesity and obstructive sleep apnea are each associated with increased aldosterone, and both conditions contribute to resistance to antihypertensive therapy. It is possible that the response to spironolactone reflected the presence of visceral obesity and/or sleep apnea, which stimulated aldosterone secretion. Visceral fat itself was not assessed, but there was no association of body mass index with spironolactone responsiveness in the Chapman et al. cohort, and the usual predisposing factors for sleep apnea were not evident. We cannot explain the efficacy of spironolactone by invoking either classical or nonclassical stimuli of aldosterone secretion, although we cannot exclude those mechanisms until they are measured.

Some of the past studies of aldosterone in obesity and sleep apnea suggested gender specificity of the association. In the large Anglo-Scandinavian Cardiac Outcomes Trial cohort reported by Chapman et al., where obesity and sleep apnea were apparently unimportant, both men and women responded to spironolactone, although there was a tendency for greater efficacy in women.

Perhaps it is inappropriate to focus exclusively on antagonism of aldosterone or some other mineralocorticoid. One of spironolactone’s primary metabolites, canrenone, is a partial agonist/antagonist of membrane sodium-potassium ATPase and competes with ouabain for binding to that enzyme. In some rat models of hypertension, canrenone exerted a rapid hypertensive effect, possibly by displacing an endogenous ouabain-like pressor. If this action is important in resistant essential hypertension, aldosterone antagonists that lack an effect on ATPase will not be as effective as spironolactone. The only other aldosterone antagonist approved in the United States is eplerenone, a sibling of spironolactone. The only other aldosterone antagonist marketed, every practitioner would have heard by now that 25 mg of spironolactone can display astounding efficacy in difficult hypertension. If spironolactone could talk, it would say what an elderly Mark Twain said of himself: “Reports of my death are greatly exaggerated.”

Sources of Funding
This work was supported in part by grants from the Department of Veterans Affairs and the National Institutes of Health.

Disclosures
None.

References
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Hypertension. 2007;49:763-764; originally published online February 19, 2007; doi: 10.1161/01.HYP.0000259806.91169.01

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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