Relative Aldosterone Excess

Relative to What?

John W. Funder

There is clear evidence that the vessel wall is an aldosterone target tissue, and that aldosterone at physiological levels produces vasoconstriction by genomic and rapid nongenomic actions. Similarly, in clinical studies cited by Duffy et al, patients with primary aldosteronism show impaired flow-mediated dilatation among other indices of endothelial dysfunction; in addition, mineralocorticoid receptor blockade reverses endothelial dysfunction in patients with hypertension or heart failure. In this issue of the journal Duffy et al explore vasodilator responses to methacholine, nitroprusside, and verapamil over a wide dose range in good-sized cohorts of hypertensive and normotensive subjects, to establish possible correlations with renin-angiotensin-aldosterone status. This is clearly a worthwhile undertaking, although the authors candidly admit they had expected to find elevated renin in hypertensives to be correlated with most marked impairment in vasodilatation and, in fact, found the opposite.

That said, there are several issues of interpretation and analysis that need to be raised. First is the usage “relative aldosterone excess” in the title and throughout the article. No differences between hypertensives and normotensives were segregated into quartiles on the basis of aldosterone levels nor in either group divided into quartiles, with the exception of the highest renin quartile among normotensives: the significantly higher aldosterone-aldosterone status. This is clearly a worthwhile undertaking, although the authors candidly admit they had expected to find elevated renin in hypertensives to be correlated with most marked impairment in vasodilatation and, in fact, found the opposite.

The second major reservation that needs to be applied to the findings is the implications of the major discrepancy between the bottom panels of Figures 1 and 4: This discrepancy is among the findings that are baldly presented but not further discussed. The authors show a very muted vasodilator response to nitroprusside in the lowest renin quartile but a very brisk response to the same stimulus in the highest aldosterone to renin quartile. Put simply, the most likely explanation of this remarkable difference is that of a mistake. It may be that the group of 10 low renins (values 0.1 to 0.3 ng/mL per hour) is not exactly the same as the highest quartile in terms of aldosterone to renin ratio; a glance at Table 1 shows that it would be surprising if there were not 8 or 9 patients common to both groups. Despite the high variances, the mean values for the ratio in quartile 1 is 3-fold that in quartile 2, 7-fold that in quartile 3, and 12-fold that in quartile 4 (mirroring the plasma renin values), not unexpectedly given the flat, normal aldosterone levels.

The probability that the 2 groups (lowest plasma renin quartile, highest aldosterone-renin ratio quartile) very largely overlap is underscored by the near identical profiles shown in the top panels of Figures 1 and 4. Even if, as the authors note, “not all participants had all agonists” the populations shown in Figures 1 and 4 are identical, merely segregated into quartiles by different (but highly related) indices. If Figures 1 and 4, on revisiting, are both correct, then the authors have a fascinating and possibly very illuminating finding on their hands. Before a dehiscence between stimulating NO production (methacholine) and acting as an NO donor (nitroprusside) is attributed to aldosterone/renin ratio, net of plasma renin per se, it would be useful to know the overlap between the 2 quartiles, and the vasodilator responses when patients are segregated into quartiles on the basis of aldosterone levels.

It would also be useful to see some analysis of the clear differences between normotensive and hypertensive subjects, which similarly may shed light on what is a complex and sometimes conflicted area. Much of the complexity stems from the lack of distinction between physiological stimuli of...
the renin-angiotensin-aldosterone system (eg, sodium deficiency) and exogenous, nonphysiological inputs (eg, angiotensin infusion), in which the normal homeostatic negative feedback mechanisms cannot operate. Much of the conflict is also in a sense artifactual and might be, in part at least, resolved by acknowledging that most mineralocorticoid receptors are occupied by normal circulating levels of glucocorticoids. Under normal conditions, physiological glucocorticoids act as mineralocorticoid receptor antagonists, but when the protective enzyme 11β-hydroxysteroid dehydrogenase is blocked or deficient (in epithelia, or the vessel wall), cortisol becomes a mineralocorticoid receptor agonist; the same antagonist-to-agonist change is seen when intracellular redox state is altered by generation of reactive oxygen species.

The focus on aldosterone, rather than mineralocorticoid receptor status, is thus less likely to yield unequivocal results than studies using receptor antagonists, which block the effect of whatever agonist. If, on the other hand, the data in Figures 1 and 4 can be validated, the present article may make a much more important contribution than the authors, who set out to prove the opposite, ever dreamed of.

References
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Hypertension. 2005;46:643-644; originally published online September 19, 2005; doi: 10.1161/01.HYP.0000184227.75221.6e

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:
http://hyper.ahajournals.org/content/46/4/643

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