

Aldosterone Antagonism and Arterial Stiffness

To the Editor:

We wish to congratulate White et al.1 for their evaluation of the effects of the comparative aldosterone blocker eplerenone versus the calcium antagonist amlodipine in old subjects with systolic hypertension. Until recently, eplerenone was presented as a standard antihypertensive agent, acting mainly on diastolic blood pressure, but with limited affinity for the progesterone and androgen receptors as the main interest. Nevertheless, based on previously published data in animal and human hypertension, there were several lines of direct evidence that eplerenone might act more selectively on systolic and pulse pressures through specific effects on the large artery wall. First, in hypertensive rats, spironolactone is known to prevent aortic collagen accumulation and reduce aortic stiffness.2 Second, in rats on a high-sodium diet, chronic aldosterone administration increases the stiffness of the aortic wall material, independently of mechanical stress, a process completely reversed by eplerenone.3 Finally, in hypertensive subjects, increased plasma aldosterone and increased arterial stiffness are positively correlated independent of blood pressure level.4

In the study of White et al.,1 several particularities of the protocol may have minimized the effects of eplerenone on hypertensive conduit arteries. Effectively, although the 2 drugs caused the same systolic blood pressure reduction, amlodipine reduced more diastolic blood pressure than eplerenone. This difference may be due either to a higher vasodilating effect of amlodipine on small arteries or to a more pronounced effect of eplerenone on large artery elasticity. In other words, it is important to verify in each group of the trial whether the diastolic blood pressure reduction was influenced by baseline pulse wave velocity. Indeed, in the Ephesus study,5 subjects who had the more important reduction of cardiovascular mortality under eplerenone were those with the higher baseline pulse pressure. In the work by White et al.,1 it is noteworthy that baseline carotid-femoral pulse wave velocity was the “gold standard” to evaluate arterial stiffness. Indeed, the baseline values of carotid-radial pulse wave velocity is not known. In any event, other studies have shown that aldosterone plays a major role in arterial stiffness, independent of the level of systemic BP in both arterial hypertension. Furthermore, they were both associated with significant changes from baseline in pulse wave velocity. The authors noted that amlodipine induced slightly larger changes from baseline in clinic diastolic BP compared with eplerenone. However, the difference in ambulatory diastolic BP reductions between these 2 agents was just 3 mm Hg, which did not reach statistical significance. Thus, the clinical and physiologic significance of this small reduction in diastolic BP in relation to pulse wave velocity is not known. In any event, other studies have shown that aldosterone plays a major role in arterial stiffness, independent of the level of systemic BP in both arterial hypertension as well as in congestive heart failure.5,6

In regard to the pulse wave velocity substudy, there were no baseline differences for either the carotid-femoral or the carotid-radial pulse wave velocity given by the authors were below those of carotid-femoral pulse wave velocity. Indeed, the baseline values of carotid-radial pulse wave velocity measurements in a sample of the population and needs also determinations of wave reflections and central blood pressure.6,7

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References


Response

We appreciate the comments by Drs Safar and Avolio regarding our publication from earlier this year.1 As noted, both eplerenone and amlodipine were highly effective agents in reducing systolic blood pressure (BP) in older patients with hypertension. Furthermore, they were both associated with significant changes from baseline in pulse wave velocity. The authors noted that amlodipine induced slightly larger changes from baseline in clinic diastolic BP compared with eplerenone. However, the difference in ambulatory diastolic BP reductions between these 2 agents was just 3 mm Hg, which did not reach statistical significance. Thus, the clinical and physiologic significance of this small reduction in diastolic BP in relation to pulse wave velocity is not known. In any event, other studies have shown that aldosterone plays a major role in arterial stiffness, independent of the level of systemic BP in both arterial hypertension as well as in congestive heart failure.5,6

In the study by White et al.,1 there are several other reasons that the effects of eplerenone on large arteries had been minimized. First, because, based on the literature, the effects of eplerenone seem to predominate on structural (aortic collagen accumulation) rather functional arterial changes, it is possible that the duration of follow-up (24 weeks) was too short to compare eplerenone and amlodipine on the basis of systolic blood pressure reduction. In the Reason project, the selective effect of the perindopril-indapamide combination on systolic blood pressure was achieved only after a 1-year follow-up.7 Second, the evaluation of the changes in conduit arteries under eplerenone involved only pulse wave velocity measurements in a sample of the population and needs also determinations of wave reflections and central blood pressure.6,7


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