GERIATRICS AND GERONTOLOGY SPECIAL SECTION
EDITORIAL
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THE AMERICAN JOURNAL of MEDICINE®

Does Aldosterone Blockade Improve Physical Performance in Older Individuals?

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The impact of the renin-angiotensin-aldosterone system on muscle function and physical performance in aging and several chronic conditions—notably heart failure—has been demonstrated in a number of recent studies. In the Health, Aging, and Body Composition study, subjects receiving angiotensin-converting enzyme inhibitors had significantly greater lower-extremity muscle mass compared with subjects receiving other antihypertensive drug classes.[1] Angiotensin-converting enzyme inhibitor use may improve the response to exercise training, and there seem to be angiotensin-converting enzyme genotype influences on these responses.[2-4] These angiotensin-converting enzyme inhibitor effects are likely important with respect to functional decline, sarcopenia, and perhaps frailty. The persistence of angiotensin-converting enzyme activity despite angiotensin-converting enzyme inhibitor therapy—referred to as "angiotensin-converting enzyme escape"—forms the basis for investigations that have examined the effect of aldosterone on physical performance and provides the rationale for the hypothesis that spironolactone blockade would lead to improved physical performance tested in the well-designed randomized controlled clinical trial reported by Burton et al.[5] This trial failed to provide evidence that 20 weeks of therapy with low-dose (25 mg) spironolactone improved performance in the 6-minute walk test—the study's primary outcome. There was modest improvement in one quality of life measure—a secondary outcome—in the spironolactone-treated group.

There are several important cautions to cite before accepting a conclusion that aldosterone—and its inhibition—does not have an effect on physical performance. First, it is possible that the older subjects included in this study did not have a high enough level of physical impairment. The selection criteria relied solely on self-reported limitations in performing activities of daily living that are not quantified with respect to the number or severity of these limitations. The baseline 6-minute walk test distance is not provided, so it is not possible to assess the group's overall level of physical impairment at the study's outset. Selecting a subject group with a higher level of impairment based on a threshold of 6-minute walk test or perhaps gait speed would address this concern. As cited in the article in the context of the noted improvement in a secondary study outcome, the EQ-5D survey measure of health-related quality of life and its pain score domain, aldosterone blockade may have anti-inflammatory effects. To this end, selecting a study population with high levels of interleukin-6 or other cytokines may have merit. Another selection criterion to consider would be to target individuals with the highest tertile of baseline aldosterone levels (while still in the normal range) who may benefit most from aldosterone blockade. Second, although acknowledged as a potential limitation, the aldosterone antagonist used in the study, spironolactone, is a nonspecific mineralocorticoid antagonist with pharmacologic effects that extend beyond blocking aldosterone. Studying a more specific aldosterone antagonist, such as eplerenone, would mitigate this concern. In addition, despite the group difference noted in the change in aldosterone levels from baseline to 20 weeks, the low-dose spironolactone chosen for this investigation may not have been sufficient to produce complete aldosterone blockade. Third, the study's primary physical performance outcome, the 6-minute walk test distance, is a complex measure of functional status and endurance. Many factors in addition to improved muscle function will influence the 6-minute walk test distance, including cardiac and pulmonary function, musculoskeletal limitations and pain, and effort level. More specific measures of muscle performance would address this concern. Usual gait speed assessed in a 4-m walk test is emerging as a physical performance measure that is highly clinically relevant, including its strong association with mortality risk.[6]

The negative result from this randomized trial poses a significant challenge to but does not entirely refute the hypothesis that aldosterone blockade will improve physical performance among older individuals. Additional investigations in older subjects selected for physical impairment or

Funding: None.
Conflict of Interest: None.
Authorship: The author is solely responsible for the content of this manuscript.

0002-9343/$ -see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.amjmed.2013.03.010

inflammation using a selective aldosterone antagonist seem to be an important next step.

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