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EDITORIAL COMMENT

Renin-Angiotensin-Aldosterone System Activation During Decongestion in Acute Heart Failure

Friend or Foe?*

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In the television game show *"Friend or Foe?"* 3 teams of 2 strangers attempt to persuade their partners to share their accumulated winnings rather than steal it for themselves. In order to win, candidates need the pivotal combination of both knowledge and trust. Much like the television show, the question of whether short-term renin-angiotensin-aldosterone system (RAAS) activation during decongestive treatment in acute heart failure represents an innocent bystander effect (friend) or harmful event (foe) requires a critical look at the available evidence (knowledge) and pathophysiological rationale (trust).

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In this issue of *JACC: Heart Failure*, Mentz et al. (1) offer an intriguing post-hoc subanalysis from the DOSE (Diuretic Optimization Strategies in Acute Heart Failure) and CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) studies, which represent the largest contemporary datasets for RAAS biomarker changes during decongestive treatment for acute heart failure. The authors assessed plasma renin activity (PRA) and plasma aldosterone levels at baseline and after 72 h and 96 h of decongestive treatment. Subsequently, they compared baseline levels and the evolution of both biomarkers between the randomized treatment arms of each trial. Additionally, the impact on worsening renal function (WRF) incidence and the clinical endpoint of death or readmission for heart failure after 60 days was evaluated. They observed that PRA increased significantly more during decongestive therapy in the continuous group than in the bolus furosemide group of DOSE and in the ultrafiltration group compared to the stepped pharmacological care arm of CARRESS-HF. In contrast, there were no significant differences in PRA changes between the high- and the low-dose furosemide group of DOSE. Neither were there any significant differences in plasma aldosterone levels observed among the different treatment arms of either DOSE or CARRESS-HF. Both the increasing PRA and plasma aldosterone were strongly correlated with incident WRF, but neither was predictive of adverse clinical outcome after 60 days.

PHYSIOLOGY OF THE RAAS

To better appreciate these findings, a brief review of the RAAS physiology may be helpful. Renin is an enzyme synthesized by specialized granular cells of the juxtaglomerular apparatus and released by the afferent arteriole in response to 3 main stimuli: 1) decreased arterial blood pressure, sensed by

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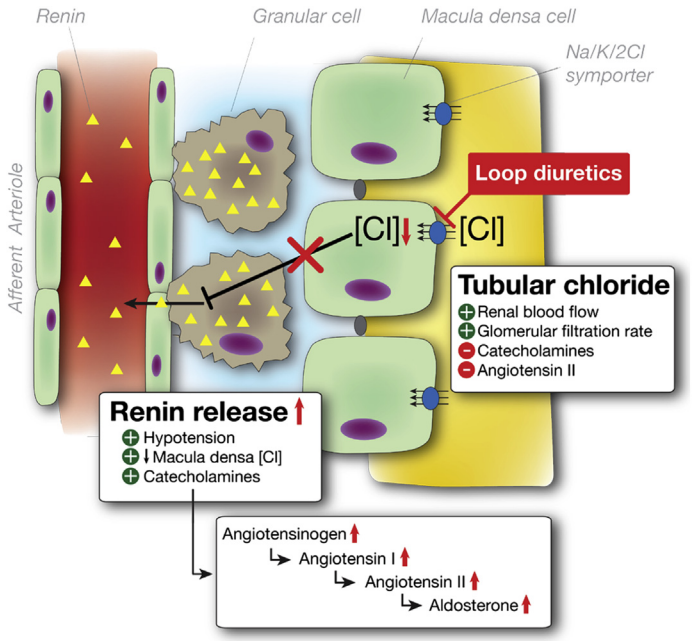
baroreceptor cells in the arteriolar vessel wall; 2) decreased intracellular chloride levels inside macula densa cells lining the renal tubules at the end of Henle's loop, which is potentiated by potassium depletion; and 3) sympathetic activation (**Figure 1**). Renin breaks down circulating angiotensinogen secreted by the liver, forming angiotensin I, which is subsequently converted into angiotensin II by endothelial cells, mainly from the pulmonary vasculature. Angiotensin II is the most potent stimulator of aldosterone release by the adrenal glands. This humoral system has been identified as a pivotal player in the pathophysiology of heart failure (2). Indeed, persistent and excessive RAAS activation causes adverse cardiac remodeling and contributes to fluid retention with signs and symptoms of congestion. For this reason, PRA and plasma aldosterone levels are of potential interest not only as markers of disease severity but as mediators of heart failure progression. Obviously, the inherent assumption is that both neurohormones can be accurately measured and reflect the degree of underlying RAAS activation. However, known confounders as well as biological variables of the measurements may hinder their reliability, especially in a setting where large volume shifts are occurring (3). Moreover, it is well known that PRA and plasma aldosterone levels are notoriously variable unless meticulously collected under uniform settings.

FIGURE 1 The Juxtaglomerular Apparatus



Regulation of renin release and impact of loop diuretic therapy (figure courtesy of Lars Grieten).

RAAS ACTIVATION, HEART FAILURE SEVERITY, AND CLINICAL OUTCOME

Consistent with published reports, Mentz et al. (1) demonstrate that the relationship between RAAS activation and heart failure severity still stands strong, even in the contemporary era of heart failure management with high adherence to neurohumoral blocker therapies including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor antagonists, all of which may differentially influence RAAS activation and RAAS biomarkers. Specifically, baseline PRA and plasma aldosterone levels were higher in patients with more advanced heart failure, illustrated by a lower left ventricular ejection fraction, a higher proportion of New York Heart Association functional class IV patients, more frequent use of implantable cardioverter-defibrillators, lower systolic blood pressures, and higher maintenance doses of loop diuretics. Somewhat surprisingly, these stigmata of more advanced heart failure did not translate into higher 60-day mortality or readmission rates in patients with high RAAS activation. How can we explain this? First, the fact that readmission and/or mortality rates approached 40% at 60 days in both studies points to the fact that patients were at very high risk of adverse outcomes. Such a population may already have reached the ceiling of adverse consequences from RAAS activation, with other factors such as residual congestion being more important. This is further supported by the low proportion of patients in both the DOSE study (15% after 72 h) and CARRESS-HF study (10% after 96 h) that achieved complete clinical decongestion (4,5). Second, the study by Mentz et al. (1) appears to be underpowered to demonstrate an effect of baseline RAAS activation on clinical outcomes. Based on 95% confidence intervals, baseline PRA higher than the median was potentially associated with either a 2% decreased or 13% increased risk of death or readmission for heart failure, with plasma aldosterone levels higher than the median corresponding to either a 1% decrease or 28% increase of the same endpoint. Third, the follow-up time of 60 days might have been too short to capture the detrimental effects of persistent RAAS activation, which may cause slow disease progression over time.

In conclusion, more adequately powered studies are needed to assess the influence of RAAS activation