JACC: HEART FAILURE
VOL. 3, NO. 2, 2015

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jchf.2014.10.005

EDITORIAL COMMENT

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

Friend or Foe?*

Frederik H. Verbrugge, MD,†‡ W.H. Wilson Tang, MD,§ Wilfried Mullens, MD, PhD†‖

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).

SEE PAGE 97

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

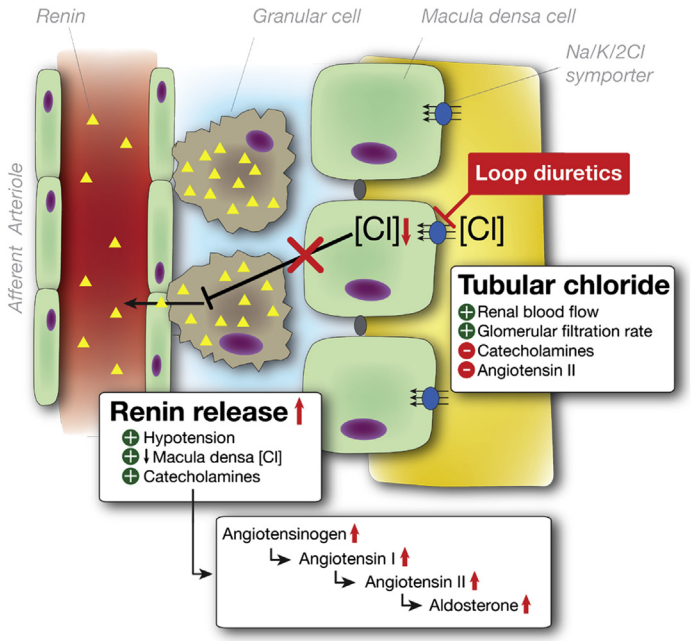
To better appreciate these findings, a brief review of the RAAS physiology may be helpful. Renin is an enzyme synthesized by specialized granular cells of the juxtaglomerular apparatus and released by the afferent arteriole in response to 3 main stimuli: 1) decreased arterial blood pressure, sensed by

*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

From the †Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium; ‡Doctoral School for Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; §Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio; and the ‖Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium. Dr. Verbrugge is supported by a PhD fellowship of the Research Foundation-Flanders. Drs. Mullens and Verbrugge are researchers for the Limburg Clinical Research Program, UHasselt-ZOL-Jessa, which is supported by the Limburg Sterk Merk foundation, Hasselt University, Ziekenhuis Oost-Limburg and Jessa Hospital. Dr. Tang has reported that he has no relationships relevant to the contents of this paper to disclose.

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

on clinical endpoints and it would be interesting to evaluate whether results in chronic versus acute heart failure differ.

RAAS ACTIVATION DURING DECONGESTION

A particularly interesting question is whether acute RAAS activation during decongestive treatment in acute heart failure has any prognostic meaning or association with adverse events. Historically, this phenomenon has been considered unfavorable as an adverse consequence of diuretic therapy (6). In the study by Mentz et al. (1), neither the change in PRA nor plasma aldosterone changes after 72 h or 96 h were associated with mortality or heart failure readmissions after 60 days, with hazard ratios suggesting that any residual effect was unlikely. Whether this means RAAS activation during decongestive treatment is not at all important remains unsure because of the high assay and biological variability of both PRA and plasma aldosterone measurements. In contrast, there was a strong correlation between RAAS activation and incident WRF, which itself has also been associated with worse outcome (7). However, recent evidence has clearly demonstrated that a small increase in serum creatinine concentration is unlikely to portend worse prognosis if thorough decongestion can be achieved and that the same may well hold true for RAAS activation (8). In this respect, it should be noted that in both the DOSE and CARRESS-HF studies, patients were responsive to diuretics, as shown by the strongly negative fluid balance in nearly every patient. In contrast, the ADHERE (Acute Decompensated Heart Failure National Registry) study demonstrated that in real-world practice, approximately one-half of patients experience virtually no net fluid loss during their hospitalization for acute heart failure (9). Interestingly, recent evidence suggests that diuretic efficiency itself (defined as diuresis or natriuresis corrected for loop diuretic dose) rather than diuretic dosing may better reflect therapeutic responses in acute heart failure (10–12). This may partly explain why PRA and aldosterone levels were similar in different dosing groups. Nevertheless, the results by Mentz et al. (1) are reassuring in that RAAS activation during effective decongestion in patients who are responsive to diuretic therapy is probably not harmful.

DECONGESTION STRATEGIES AND RAAS ACTIVATION

Although an effect of different decongestion strategies in the DOSE and CARRESS-HF studies on RAAS activation might be suggested during decongestion (only 10% to 15% were effectively decongested at follow-up), these findings should be interpreted with some caution. Treatment arms of the studies were indeed randomized, yet 12% of patients were excluded from the current analysis because of missing data, and there were some differences in baseline characteristics between this cohort and the study population, most notably left ventricular ejection fraction and renal function. Moreover, PRA follow-up values were missing in another 13% of patients, resulting in one-fourth of the original population being excluded from the current analysis. More important, the second PRA and plasma aldosterone assessment occurred at a single time point well after the initiation of the randomized treatment (72 h in DOSE versus 96 h in CARRESS-HF). Hence, the decongestion strategy randomized was modified substantially at follow-up. For instance, even after 48 h in the DOSE study, 31% of patients in the high-dose group had switched to oral therapy versus 17% in the low-dose group. Moreover, although patients in the former versus the latter group received a dose that was 2.5 times higher at the beginning of the trial, it remained only 1.7 times higher upon the moment of follow-up RAAS biomarker assessment. Similarly in CARRESS-HF, less than one-quarter of patients were receiving ultrafiltration treatment after 67 h, and fewer than one-half the patients of the stepped pharmacological care arm were still on the regimen specified by the protocol after 96 h. Consequently, the analysis by Mentz et al. (1) demonstrates the impact of different decongestion strategies on RAAS activation at a single time point after initiation of a decongestive strategy, rather than peak RAAS activation, which is expected to occur together with intravascular volume depletion or diuretic resistance, and results should be interpreted in this particular context.

PERSISTENT RAAS ACTIVATION

The finding that increased and persistent PRA was more frequently observed with continuous rather than with bolus furosemide treatment deserves some discussion, especially because continuous furosemide treatment did not result in higher diuretic efficiency in the main DOSE study (2). It has been recognized for some time that maintaining adequate arterial blood pressure may preserve renal function, whereas persistently aggressive intravascular volume depletion may drive up PRA (6,13,14). Importantly, the latter may not be sufficiently captured by weight loss and urine output. This may also explain the observation that individually

titrated, stepwise pharmacological care clearly outperformed ultrafiltration in CARRESS-HF study, in which the constant initial ultrafiltration rate of 200 ml/h may have generated consistent intravascular volume removal similar to a continuous furosemide infusion, relying heavily on the plasma refill rate. Therefore, any difficulty in mobilizing excess interstitial fluid into the circulation may have led directly to impaired renal perfusion and WRF, resulting in pronounced PRA increases as observed in this study. Thus, the optimal diuretic strategy should depend not only on the initial dosage choice or mode of therapy but also on what should be the evolving therapeutic target (i.e., the timeframe and amount of decongestion). Unfortunately, the latter remains largely empirical and likely requires meticulous considerations of different drug combinations for different situations (15).

CONCLUSIONS

Although extensive evidence from the field of heart failure has conditioned us to treat RAAS activation as a foe, the current study by Mentz et al. (1) confirms that in the setting of acute heart failure, baseline or persistent RAAS activation is a marker of more advanced disease with overall worse prognosis. However, whether one can still trust transient RAAS activation during decongestive treatment as a friend remains insufficiently elucidated. Nevertheless, we can be reassured from these data that a higher dosing strategy of loop diuretics in the context of low diuretic resistance in patients who were clearly volume-overloaded was not associated with persistent RAAS activation or more adverse consequences. This should make clinicians confident about not tolerating residual congestion and allow judicious use of high-dose loop diuretics to achieve a net negative fluid balance.

ACKNOWLEDGMENT The authors thank Lars Grieten for the illustration.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Wilfried Mullens, Department of Cardiology, Ziekenhuis Oost-Limburg, Schiepse Bos 6, 3600 Genk, Belgium. E-mail: wilfried.mullens@zol.be.

REFERENCES

1. Mentz RJ, Stevens SR, DeVore AD, et al. Decongestion strategies and renin-angiotensin-aldosterone system activation in acute heart failure. J Am Coll Cardiol HF 2015;3:97–107.

2. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med 1999;341:577–85.

3. Kerstens MN, Kobold AC, Volmer M, Koerts J, Sluiter WJ, Dullaart RP. Reference values for aldosterone-renin ratios in normotensive individuals and effect of changes in dietary sodium consumption. Clin Chem 2011;57:1607–11.

4. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797–805.

5. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012;367:2296–304.

6. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. Br Heart J 1987;57:17–22.

7. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol 2004;43:61–7.

8. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation 2010;122:265–72.

9. Gheorghiade M, Filippatos G. Reassessing treatment of acute heart failure syndromes: the ADHERE registry. Eur Heart J Suppl 2005;7 Suppl B:B13–9.

10. Testani JM, Brisco MA, Turner JM, et al. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. Circ Heart Fail 2014;7:261–70.

11. Verbrugge FH, Nijst P, Dupont M, et al. Prognostic value of glomerular filtration changes versus natriuretic response in decompensated heart failure with reduced ejection. J Card Fail 2014;20:817–24.

12. Singh D, Shrestha K, Testani JM, et al. Insufficient natriuretic response to continuous intravenous furosemide is associated with poor long-term outcomes in acute decompensated heart failure. J Card Fail 2014;20:392–9.

13. Dupont M, Mullens W, Finucan M, Taylor DO, Starling RC, Tang WH. Determinants of dynamic changes in serum creatinine in acute decompensated heart failure: the importance of blood pressure reduction during treatment. Eur J Heart Fail 2013;15:433–40.

14. Testani JM, Coca SG, McCauley BD, Shannon RP, Kimmel SE. Impact of changes in blood pressure during the treatment of acute decompensated heart failure on renal and clinical outcomes. Eur J Heart Fail 2011;13:877–84.

15. Verbrugge FH, Grieten L, Mullens W. New insights into combinational drug therapy to manage congestion in heart failure. Curr Heart Fail Rep 2014;11:1–9.

KEY WORDS acute heart failure, aldosterone, diuretics, renin, ultrafiltration