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Editorial

Cardiorenal Interactions, Diuretic Resistance, and Acute Heart Failure: Renal Response vs Renal Function

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See article by Greene et al., pages 1097–1105 of this issue.

The cornerstone of treatment for acute heart failure, irrespective of left ventricular ejection fraction, is diuresis to relieve pulmonary or peripheral edema ("decongestive therapy"). Intravenous loop diuretics are the standard of care in this situation, with clinical trials of novel therapies failing to demonstrate a meaningful benefit as adjunctive treatment strategies.[1-4] Ultrafiltration can improve congestive symptoms more quickly, but there is limited evidence to support its use as first-line therapy over diuretics.[5,6] The **D**iuretic **O**ptimization **S**trategies **E**valuation (DOSE) trial taught us that continuous loop diuretic infusions are not superior to intermittent intravenous bolus administration for the initial management of acute heart failure.[7]

One consistent finding from real-world and clinical trial data is that persistent congestion portends worse outcomes. The Achilles heel in management of acute heart failure is the lack of effective treatments for patients who do not respond to initial decongestive therapy once all contributing factors have been identified and addressed. In such patients, renal function is often a factor. It is crucial to differentiate cardiorenal syndrome from diuretic resistance; however, the 2 commonly occur hand-in-hand. Cardiorenal syndrome, as it pertains to heart failure, describes the physiology underpinning renal deterioration in either acute or chronic heart failure. Renal perturbations are common in patients with heart failure, and it is not unusual for renal function to deteriorate in the acute decompensated state. Diuretic resistance is an ill-defined entity, describing the patient with a phenotype of minimal or slow clinical and objective response to diuretics. It commonly occurs in the setting of cardiorenal syndrome.

How do we define diuretic resistance? Several definitions have been proposed; however, there is no universally agreed-upon definition. Measures of urine output, net fluid loss per day, weight loss per day, fractional sodium excretion, and urinary sodium-to-furosemide concentrations have been evaluated, with consistently higher all-cause mortality and readmissions for heart failure in patients classified as diuretic resistant.[8-12] An emerging marker of loop diuretic efficiency, Na^+ output/loop diuretic dose, is emerging as one of the best markers assessing the cardiorenal interaction, given its functional tubular and filtration representation.[8,10,13]

It is these diuretic-resistant patients who pose a significant therapeutic challenge in management of acute heart failure. Equally challenging in the treatment of these patients is the range of complex contributors to diuretic resistance that include altered drug pharmacokinetics, renal perfusion and effective circulatory volume, neurohormonal activation, and altered renal sodium handling. Randomized clinical trials are generally lacking, and it is difficult to interpret nonrandomized studies of adjunctive strategies in diuretic resistance because of the varying definitions used and the varying heart failure phenotypes in which diuretic resistance can occur.

It is important to note, however, that improving decongestion, even when sacrificing renal function (GFR), is associated with improved hospital-free survival.[14] Therefore, it appears to be the renal *response* to diuretics in the subjective and objective indicators of effective diuresis, not absolute renal *function* (ie, GFR), that is a prime determinant of outcomes in acute heart failure.

In the current issue of the *Canadian Journal of Cardiology*, Greene et al. present a *post hoc* analysis of the **Al**dosterone **T**argeted Neuro**h**ormonal Combin**e**d with **Na**triuresis Therapy in **H**eart **F**ailure (ATHENA-HF) trial, evaluating high-dose spironolactone (100 mg daily) vs standard of care (25 mg spironolactone or placebo) in acute decompensated heart failure. The primary endpoint of the ATHENA-HF trial was the proportional change in log NT-proBNP from baseline to 96 hours or hospital discharge. Outcomes were analyzed according to categories of renal function and risk factors for diuretic resistance.[15] Their results demonstrated no benefit of high-dose spironolactone on changes in log NT-proBNP over the study period or any secondary congestion endpoints (clinical congestion score, Likert and VAS scale for dyspnea, urine output, and weight) across all 3 tertiles of renal function examined. The authors also report no incremental benefit of high-dose spironolactone in patients with risk factors for

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diuretic resistance (other than GFR), which they defined as blood pressure less than the mean blood pressure of the study cohort, presence of diabetes, and baseline diuretic dose. Worsening heart failure, 30-day worsening heart failure, and 60-day all-cause mortality showed no differential effect between patients treated with high-dose spironolactone vs standard of care.

There are several important aspects of this study that are particularly noteworthy, and the authors outline these very nicely. Most importantly, this not a study of patients with established diuretic-resistant heart failure. Metrics of diuretic response in this study were urine output and clinical improvement of symptoms. Although there was a clear gradation in urine output based on renal function, the patients in the low-dose or no spironolactone groups had improvements in their clinical congestion and quite acceptable urine output over the 96 hour study duration; 4018 mL in the GFR $\leq$ 50 mL/min/1.73^2 group, 5101 mL in the GFR 51 to 71 mL/min/1.73^2 group, and 6745 mL in the GFR $\geq$ 72 mL/min/1.73^2 group. In addition, all patients had acceptable blood pressure with adequate median systolic blood pressure in all 3 tertiles of renal function: 119 mm Hg, 123 mm Hg, and 123 mm Hg, respectively (given ATHENA-HF excluded systolic blood pressure $\leq$ 90 mm Hg).

In this study, renal function was based on modification of diet in renal disease (MDRD) calculation of GFR on admission, and baseline renal function was not collected. Estimating GFR is complex, particularly in patients with heart failure who can have rapid fluctuations in renal function during decompensations. The prevalence of worsening renal function, traditionally defined as an $\geq$ 0.3 mg/dL (26.5 μmol/L) increase in serum creatinine or $>$ 15% reduction in GFR, ranges from 20% to 40% in acute heart failure patients.[16] GFR is a good marker for chronic kidney disease and a good risk marker for chronic heart failure, but it is a reflection of filtration function only. It says nothing about the important determinants of fluid equilibrium: namely, renal tubular sodium and water avidity. Studies have reported that renal tubular damage is actually quite low in patients with acute heart failure with an abrupt elevation in creatinine, and we know tubular function is important in acute heart failure.[10,17] Ultimately, diuretic resistance performs better than absolute renal function (GFR) for prognostic stratification in acute heart failure.[18]

The relatively small sample size of the ATHENA-HF trial (n = 360 with $<$ 70 patients in each renal tertile) and study duration (96 hours) may have limited the ability to detect a treatment effect; since spironolactone is a prodrug with onset of action 48-72 hours after oral intake, which could account for the nil effect.

On the plus side, the current analysis by Greene et al. demonstrates that the use of high-dose spironolactone did not result in hyperkalemia or significant worsening renal function in the short term. It is noteworthy that, in the lowest GFR tertile, high-dose spironolactone resulted in $>$ 1.5L net urine output and 1.2 kg more weight lost than the standard-of-care group vs a 0.3-kg weight difference between high-dose spironolactone and standard group in the highest GFR tertile, suggesting a trend to better diuresis with high-dose spironolactone in the lower GFR groups. Thus, high-dose spironolactone may have a basis for further evaluation in hospital-based treatment of acute heart failure.

The light at the end of this diuretic tunnel is the revival of clinical trials in search for optimal diuretic strategies in acute heart failure. A multicentre randomized, double-blind phase IV clinical trial of the diuretic effects of **A**cetazolamide in **D**ecompensated Heart Failure With **V**olume **O**ver**l**oad (ADVOR; ClinicalTrials.gov NCT03505788) will investigate if combination therapy with acetazolamide, an inhibitor of proximal tubule sodium resorption, improves loop diuretic response to increase diuresis in patients with decompensated heart failure.[19] Whether improved diuretic efficacy with acetazolamide in patients with heart failure and cardiorenal syndrome translates into better outcomes is currently being tested in another clinical trial (ClinicalTrials.gov NCT01973335). The new diabetic drug class of sodium glucose-linked transporter-2 (SGLT2 inhibitors) also inhibit proximal sodium absorption. Several trials are ongoing, evaluating the effect of SGLT2 inhibitors in the setting of both chronic and acute heart failure. The vasopressin antagonist tolvaptan in patients with diuretic resistance, renal dysfunction, or hyponatramia resulted in more weight loss but no significant improvement in symptomatic improvement over standard diuretic therapy.[20,21] Further studies evaluating tolvaptan in acute heart failure with diuretic resistance and cardiorenal syndrome are ongoing (Tolvaptan for the management of acute decompensated heart failure in patients with advanced or refractory heart failure; ClinicalTrials.gov NCT02959411). There is also an ongoing study comparing metolazone vs chlorothiazide for acute decompensated heart failure with diuretic resistance (ClinicalTrials.gov NCT03574857).

Identifying patients with acute heart failure who fail to respond—or who are at risk of failing to respond—to initial diuretic management is more complex than assessment of GFR. A standardized definition of diuretic resistance that incorporates more accurate, measurable, and physiologic variables of the kidney's ability to respond to diuretic therapies is needed. Further studies evaluating effective strategies for diuretic resistance must first include patients with established diuretic resistance, be of sufficient study duration to identify a treatment effect, and expand outcomes to include clinically relevant endpoints. Requirements of reduced renal response in the form of oliguria and abnormal sodium handling may more accurately define this population for future studies in the medical management of this problematic patient population.

Disclosures

Dr Clarke has participated in consultation/speaking engagements for Novartis Pharmaceuticals, Abbott, Servier Laboratories, and BI. He has participated in research studies for Merck, Otsuka Pharmaceutical, Abbott, and BI.

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