Diuretic Resistance—A Key to Identifying Clinically Significant Worsening Renal Function in Heart Failure?

Worsening renal function (WRF) in patients hospitalized with acute heart failure (AHF) presents a frequent clinical dilemma that is compounded by the inconsistent results of studies seeking to determine whether WRF in AHF is associated with worse clinical outcomes, such as death or readmission. More recent studies suggest that when serum creatinine concentration rises from a hemodynamic process such as appropriate blood pressure lowering or decongestion, WRF is no longer associated with adverse outcomes.[1-3] Fortunately, this situation occurs most of the time, but still 15% to 30% of patients with WRF do not achieve adequate decongestion and have a significantly higher risk of death or heart failure readmission. Identifying these high-risk patients early during a hospitalization can be a challenge because they are a minority of all AHF patients. Furthermore, although we have refined our understanding of when WRF is clinically significant, identification of the pathophysiologic drivers for inadequate decongestion and adverse outcomes still proves elusive.

In this issue of *Mayo Clinic Proceedings*, He et al[4] confirm the findings of prior studies and advance the field of WRF by approaching the problem with latent class analysis to phenotype subgroups of WRF that give clues to potential pathologic contributors to outcomes. Using 2 established randomized trials of AHF decongestion therapy, Diuretic Optimization Strategies Evaluation (DOSE) and Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF), the authors focused on those participants who developed WRF (defined as an increase of >0.3 mg/dL in serum creatinine concentration) within the first 72 hours of hospitalization. They included the 113 patients with WRF into a latent class analysis model that yielded 2 optimal subgroups of WRF.

The key feature defining these 2 populations was their response to diuretic therapy, defined as either minimally responsive to diuretics (MRD) or responsive to diuretics (RD), based on their urine output during the first 3 days of hospitalization. This is consistent with prior findings that congestion status discriminates WRF outcomes as the RD group had greater decongestion evidenced by greater fluid loss, greater weight loss, and a higher percentage achieving a decline of 30% or more in N-terminal pro—B-type natriuretic peptide. Significantly, distinguishing WRF by response to diuretics provides an actionable "stress test" that can trigger additional investigations and management, as opposed to a retrospective change in congestion markers.[5]

Indeed, this was seen here as WRF-MRD patients had WRF and a poor diuretic response much earlier (often within 24 hours) than WRF-RD patients. Focusing on diuretic response or conversely diuretic resistance has advantages: therapy can be escalated to potentially change the disease trajectory in this high-risk group; future observational studies can focus on this higher risk population to better understand drivers of adverse outcomes with WRF in AHF; and an appropriate population of WRF patients can be enrolled in clinical trials to ensure that new therapies are focused on the highest risk subgroup.

Diuretic responsiveness has often been evaluated by urine output per milligram of furosemide. The furosemide stress test (urine output per a 1- or 1.5-mg/kg dose of furosemide) has been used in critical care to

identify patients with acute kidney injury who are more likely to progress to severe acute kidney injury or death.[5] However, using urine output as a measure presents challenges, given potential inaccuracies with urine collection outside of a critical care or clinical trial setting. Furthermore, it does not necessarily reflect the goal of diuresis, which is natriuresis rather than aquaresis. Studies have reported that measuring a spot urine sodium level 2 hours after loop diuretic administration provides a stronger correlation with urinary sodium excretion.[6] Following spot urine sodium levels rather than urine output has been found to be prognostic with the furosemide stress test in AHF, and a small trial reported that a natriuresis-driven diuretic protocol better predicts diuretic response and can improve decongestion.[7,8] The findings of He et al reinforce this change in focus from WRF alone to WRF with diuretic resistance.

Other key findings from He at al include the comorbidities associated with an increased odds of WRF-MRD: diabetes and chronic obstructive pulmonary disease (COPD). Diabetes is a recognized cause of type 5 cardiorenal syndrome (a systemic condition leading to cardiac and kidney disease), and thus it is unsurprising that diabetic patients were more likely to experience WRF. However, diabetic patients specifically had more WRF-MDR, probably from preexisting diabetic kidney disease. Pathophysiologic processes potentially contributing to diuretic resistance in diabetic chronic kidney disease with decreased glomerular filtration rate and albuminuria include reduced loop diuretic delivery from reduced proximal tubular diuretic secretion, albuminuria binding loop diuretics in the tubule, and intrinsic tubulointerstitial fibrosis at the loop of Henle.

Chronic obstructive pulmonary disease would seem an unlikely contributor to WRF, but studies have reported a pulmonary-renal connection with lung disease promoting acute kidney injury.[9] In addition, patients with COPD may have group 3 pulmonary hypertension leading to increased right ventricular failure and renal venous pressure, promoting diuretic resistance. Thus, lung disease and not AHF may be the driver of worse outcomes of WRF in AHF patients with concomitant lung disease. These findings require validation in larger studies, and the exact processes contributing to diuretic resistance in diabetes and COPD require further research as they may have implications for other populations.

Whereas the findings of He et al have helped further direct us toward clinically significant WRF in AHF, they are largely hypothesis generating, need validation in larger studies, and prompt many more questions. The most important question is how we might make these findings actionable so we can improve our patients' outcomes. Does diuretic resistance result from underdosing of loop diuretic, or is augmentation with another diuretic necessary as suggested?[10] Either of these scenarios may be appropriate for some WRF-MRD patients, but others may experience WRF-MRD from other pathophysiologic causes, such as intrinsic renal damage, a noncardiorenal process like infection or hypotension, or a comorbidity (like COPD) causing kidney injury or dysfunction. Could a standardized furosemide stress test with a spot urine sodium level be more informative for discriminating pathophysiologic drivers of WRF-MRD? This may be a more rapid way to discriminate WRF as RD or MRD and potentially point to contributing processes within or outside the kidney.

Although He et al were able to phenotype WRF patients into 2 groups, the overall sample size of 113 patients is small and limited the ability to perform an algorithm-based variable selection for latent class analysis, potentially excluding key distinguishing variables from the model. Indeed, there may be a need for further discrimination to identify the different pathophysiologic drivers of WRF-MRD and to identify features earlier than when WRF has occurred or diuretic resistance is noticed. This is an area in which biomarkers reflecting different pathophysiologic processes hold promise. Although prior studies of kidney injury biomarkers in AHF, including one done in the ROSE-AHF study, have largely been negative, this is likely because cardiorenal biomarkers were applied broadly to all AHF patients rather than focusing on the

minority of patients with clinically significant WRF.[11] The findings of this study suggest that there is a rationale to evaluate cardiorenal biomarkers in a focused population of patients with WRF-MRD. This may finally reveal the promise of cardiorenal biomarkers and elucidate the pathophysiologic drivers of adverse outcomes. Such a personalized approach might finally be able to deliver the promise of early identification of high-risk patients and intervention based on the specific driver of WRF, thus improving our patients' outcomes.

POTENTIAL COMPETING INTERESTS

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