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Editorial

Worsening Renal Function during Acute Decompensated Heart Failure: A Bad Signal Never to Ignore

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▸ See the article "Clinical Impact of Worsening Renal Function in Elderly Patients with Acute Decompensated Heart Failure" in volume 3 on page 128.

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Worsening renal function (WRF) is a well-known risk factor associated with adverse clinical outcomes in patients with acute and chronic heart failures.[1-4] Despite the association between renal dysfunction and worse clinical outcomes, it remains unknown whether WRF is a mediator or marker for adverse outcomes. Moreover, it is difficult to diagnose and manage WRF in patients with acute decompensated heart failure (ADHF).

Volume overload is a very common cause of deterioration in heart failure. This is associated with physiological abnormalities in multiple organ systems, including myocardial ischemia, neurohormonal activation, liver dysfunction, and intestine villi ischemia, which enables bacterial endotoxins to enter the circulation, inducing an inflammatory reaction.[5] In addition, the elevation of the central venous pressure increases interstitial and tubular hydrostatic pressures, which decreases net glomerular filtration leading to adverse outcomes.[6] Therefore, reversal of the volume overload, so-called decongestion, is one of the most important treatment goals to improve patients' symptoms and prognoses. However, there is no gold standard to determine the target of decongestion, that is, to evaluate the optimal effective circulatory volume. Thus, it remains challenging to select the optimal strategy for decongestion. Furthermore, a frequent adverse effect of decongestion is over-correction, which is reflected by a rise in creatinine levels. It is noteworthy that, although a creatinine elevation is usually induced by depletion of the effective circulatory volume, this relationship is suitable only when production and removal of creatinine are at a steady state.[7] In the dynamic volume status of ADHF, the distribution and excretion of creatinine are volatile; therefore, creatinine levels cannot exactly reflect the accurate renal function or volume status. Along with these intrinsic limitations in assessing the effective circulatory volume in patients with ADHF, previous studies have shown interesting, although conflicting, results between WRF and adverse outcomes.

The post-hoc study of the Diuretic Optimization Strategies Evaluation (DOSE) trial, which was a prospective, double-blind, randomized trial that investigated the optimal dose and frequency of furosemide, showed that increasing creatinine over 72 hours after admission was associated with low risk for the composite outcome of death, rehospitalization, or emergency room visit within 60 days (hazard ratio [HR], 0.81 per 0.3 mg/dL increase; 95% confidence interval [CI], 0.67–0.98, p=0.026).[8] The Evaluation Study of Congestive Heart

Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, which was originally designed to investigate whether pulmonary artery catheters might lead to clinical outcomes in hospitalized patients with severe heart failure, showed that in-hospital WRF was not significantly associated with 180-day all-cause death in patients who achieved true decongestion at discharge.[9] In this study, volume status was evaluated using hemodynamic pulmonary artery catheterization (right atrial pressure ≤8 mmHg and/or wedge pressure ≤15 mmHg at discharge) as a gold standard and clinical exam (≤1 sign of congestion at discharge) as additional criteria. Moreover, in the Renal Optimization Strategies Evaluation-Acute Heart Failure (ROSE-AHF) trial, aggressive diuresis induced WRF in 21.2% of the population, while other markers of kidney injury, such as the N-acetyl-β-d-glucosaminidase and kidney injury molecule 1, did not deteriorate by diuresis. This implied that WRF was not a good marker of renal function evaluation in patients with ADHF receiving massive volume correction.[10] In the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH) trial, in-hospital WRF, which occurred in 11% of enrolled patients with heart failure, was associated with a high incidence of the composite of heart failure hospitalization and all-cause mortality (HR, 1.63; 95% CI, 1.10–2.40; p=0.014).[4] As was previously mentioned, various methods are tested to evaluate the accurate volume status in patients with ADHF, and the relationship between WRF and clinical outcomes seemed to be conflicting in previous trials.

Collectively, the clinical impact of WRF remains controversial, and no gold standard exists to evaluate "true WRF." Although a rise in creatinine is a widely used definition, probably due to its accessibility, it is well known that creatinine elevation depends on various other factors, such as muscle mass, baseline renal function, etc.[11] However, apart from the validity of creatinine rise as a definition of WRF, it is certain that "renal dysfunction" particularly has a bad effect. Testani and Brisco-Bacik[12] explained that several hypothetical mechanisms, including inflammation, oxidative stress, or induction of apoptosis by uremic toxins, may partially contribute to the adverse effect of renal dysfunction. On the other hand, it is evident that decongestion by diuretics is an essential treatment strategy in patients with ADHF. However, the target of decongestion is usually the abnormal free fluid in the third space (i.e., interstitial edema), while diuretics decongest the patient by initially reducing the intravascular volume. As a natural response, fluid recovery should occur by redistribution from the extravascular space to intravascular space. To prevent renal deterioration by overcorrection, it is important to decongest the patient at an optimal pace to an optimal state.[13] It may be impossible to evaluate this complex, delicate process using only the creatinine level. Much is elucidated in the treatment of patients with ADHF without inducing renal dysfunction.[14][15]

In the issue of the Journal, Sawamura et al.[16] focused on the clinical significance of WRF in vulnerable elderly patients who were admitted and treated for ADHF. While the actual meaning of WRF in ADHF and its relationship with outcomes are being studied, there have been few studies on the clinical impact of WRF in elderly patients. As the population of aging patients with heart failure is rapidly increasing, it has become an important issue to determine how to adequately treat ADHF in elderly patients. Authors divided the patients into four groups according to age (<80 years, n=331 and ≥80 years, n=323) and WRF statuses (WRF, n=137 and non-WRF, n=517). WRF was defined as (1) an increase in serum creatinine (SCr) levels ≥0.3 mg/dL or ≥1.5 times within 48 hours from arrival or (2) urine output ≤0.5 mL/kg/h within 48 hours from arrival. Survival analyses revealed that the WRF group had significantly more cardiac events (defined as all-cause mortality, re-hospitalizations caused

by decompensated heart failure, and lethal arrhythmias) than the non-WRF group in the ≥80 years group (log-rank P = 0.025), although not in the <80 years group (log-rank p=0.50). In the ≥80 years old group, the WRF group had a larger mean blood pressure drop (13 vs. 21 mmHg, p=0.003) and a larger heart rate drop (11 vs. 18 mmHg, p=0.01). Although the results did not prove any causal relationship between WRF and the cardiac events, it confirmed the close association between WRF and hemodynamic instability, which may lead to adverse clinical outcomes, especially in the elderly population.

As elucidated in the literature, WRF occurring during the treatment of patients with ADHF with diuresis might represent the correction of congestion; however, decongestion in these patients is an essential process to improve ADHF. While it is important to balance rapid decongestion and overcorrection, the elderly are more vulnerable to our management. They have less compliant vasculatures, which cannot promptly respond to dynamic circulatory changes, resulting in renal hypoperfusion or other organ damages that might offset decongestion benefits. The surrogate marker of WRF, creatinine level, may be less accurate in elderly patients; therefore, further research is needed to accurately evaluate the true state of intravascular volume. In conclusion, we should be more cautious in treating elderly patients with ADHF, and extreme attention to renal function may never be sufficient to derive the best outcome in these patients.

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