Editorial

A Balancing Act: Preserving Renal Function and the Need for Decongestion

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Acute and chronic management of cardiovascular congestion is one of the central challenges of today's heart failure (HF) care. Patients presenting with HF decompensation to the hospital nearly universally express signs and symptoms of congestion[1] and in response, providers reflexively initiate decongestive therapies. Diuretics are by far the most common first-line agent used to treat patients with acute HF. This approach is firmly rooted in the concept that cardiovascular decompensation is driven by salt and water retention, with resultant intravascular and extravascular expansion. Yet, there is a growing body of evidence to suggest that internal blood volume redistribution might contribute to acute or chronic decompensation.[2] Neurohormonal activation and decreased compliance of the venous reservoir (ie, vasculature within the abdominal compartment) are central to this concept. Thus, it is increasingly recognized that processes that lead to cardiac decompensation are not uniform and more importantly the management strategies of acute HF need to be individualized based on the underlying pathophysiology. This is particularly true for HF with preserved ejection fraction (HFpEF), which is a heterogeneous syndrome.[3]

Furthermore, the process of HF decompensation and the process of therapeutic decongestion are tightly linked to the status of renal function. Worsening renal function (WRF), irrespective of the way it is clinically defined, is a common "complication" of HF-related hospitalizations and occurs in up to 60% of acute HF hospitalizations.[4,5] The majority of the work to date has focused on the characterization of patients with heart failure and reduced ejection fraction (HFrEF).[6,7] We know that temporary WRF, in the setting of active inpatient treatment, is not associated with a worse prognosis but is rather a marker of appropriate decongestion/hemoconcentration[6] and temporary WRF does not appear to be a marker of true renal tubular damage.[8] In contrast, persistent WRF, defined as an ongoing elevation of creatinine at discharge or during outpatient follow-up is commonly a marker of sicker patients, and is more likely to be associated with true kidney injury and worse clinical outcomes.[9] Whether the same findings extend to patients with HFpEF has been under investigation.[4] Because key parameters of a patient's volume status such as total body volume extent, intravascular volume content, vascular tone, etc, in general differ between HFrEF and HFpEF, there is reason to believe that in HFpEF the development of WRF in the setting of a HF hospitalization presents a different phenotype with a different prognosis.

In this issue of the Journal, Sato et al. (REFERENCE) analyzed a prospective Japanese registry (JASPER) of patients hospitalized with HFpEF in an attempt 1) to understand which patients with HFpEF develop WRF, and 2) to evaluate the prognosis of WRF after discharge. Some important facts about the analysis and the population under investigation need to be underscored. First, only two measurements of creatinine were available, on admission and at discharge. The authors defined WRF as an increase in creatinine of >0.3 mg/dL or a decrease in estimated glomerular filtration rate of at least 20% during hospitalization. Second, the average duration of hospitalization was 15 days,[10] because Japanese patients routinely undergo educational/rehabilitation programs prior to discharge. Thus, the WRF in this analysis is likely a reflection of persistent WRF.

The key findings are:

- In a cohort of over 500 patients with HFpEF, about 1 in 5 developed persistent WRF in the setting of their HF hospitalization.
- Patients who developed persistent WRF had a higher burden of cardiovascular comorbid disease and had worse baseline renal function. Further, patients with higher baseline systolic blood pressure who are

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Manuscript received June 21, 2019; revised manuscript accepted June 21, 2019.

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1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2019.06.007

prescribed loop diuretics were at increased risk of developing WRF.
- Patients with WRF experienced greater changes in sodium and greater reduction in systolic blood pressures than seen in patients without WRF.
- Patients with WRF on discharge had significantly worse clinical outcomes in the long-term.

Many of the findings here mirror the experience in patients with HFrEF.[4,7] The incidence of temporary or persistent WRF between HFrEF and HFpEF appear to be comparable. Similarly, risk factors for the development of persistent WRF are similar to prior reports in HFrEF.[4] Whether the physiology of WRF in HFpEF differs from HFrEF remains to be shown. Patients with HFpEF tend to have lower blood volumes than HFrEF and it is arguably more of a vascular phenotype, in which volume redistribution rather than volume overload drives cardiac decompensation.[2,11] Thus, hypothetically, patients with HFpEF are at greater risk of decreased renal blood flow. This hypothesis is however yet to be confirmed and the present results do not provide further clarity.

Key limitations of the JASPER registry include the inability of the investigators to further characterize the temporary nature of the WRF, and discharge congestion status. By the virtue of its design, the registry does not allow a direct comparison to patients with HFrEF. It cannot be emphasized enough: it is not only important to evaluate the chronicity of WRF but place it in the context of the individual patient's congestion status. Adequate decongestion remains of highest importance and is associated with better outcomes, regardless of changes in renal function.[6,12–14] However, the "benign" nature of WRF has only been suggested for temporary WRF in the setting of clinical decongestion. There is now plenty of evidence to suggest that either persistent vascular congestion (no matter how it is clinically measured) or the persistence of renal dysfunction are predictors of unfavorable outcomes in acute HF. Future efforts need to: 1) clarify whether persistent WRF is simply an inevitable result of more severe disease or is truly a function of the underlying physiology paired with decongestion, and 2) identify biomarkers that can be used clinically to differentiate whether an event of WRF is "benign" and temporary, or an indicator of renal tubular injury and likely to persist. Some candidate biomarkers are neutrophil gelatinase-associated lipocalin (NGAL), *N*-acetyl-b-D- glucosaminidase (NAG), and kidney injury molecule 1 (KIM-1). Given the high incidence of WRF, the anxiety it provokes, and the potential prognostic implications, concerted efforts to further study WRF are required.

Disclosures

The authors report no relevant disclosures.

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