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EDITORIAL COMMENT

Time to Revisit the Value of Urine Collections in Heart Failure*

Jozine M. ter Maaten, MD, PhD, Adriaan A. Voors, MD, PhD

Treatment of acute heart failure is primarily aimed at relieving congestion and achieving euvolemia by administering loop diuretics. Loop diuretic agents inhibit the sodium-potassium cotransporter in the loop of Henle and as such stimulate natriuresis and diuresis (1). During a hospital admission for acute heart failure, response to diuretic agents is most frequently monitored using either weight loss or net fluid balance. However, from a pathophysiological perspective, it might be better to use urinary sodium excretion to monitor effectiveness of diuretics. In heart failure, congestion is a symptom of the kidneys’ inability to adequately regulate sodium homeostasis, which is caused by a cascade that is set in motion by a decrease in cardiac function resulting in activation of the renin-angiotensin-aldosterone activation and sympathetic nervous system (1). Together with a decrease in renal blood flow and renal venous congestion, this causes an increase in fractional sodium reabsorption and consequently diminished response to loop diuretics. Indeed, an impaired natriuretic response to furosemide was associated with worsening renal function and adverse clinical outcomes in patients with acute heart failure (2). Additionally, a single-center study of patients with acute heart failure found that with progressive decongestion, urinary composition changed and was characterized by a drop in urinary sodium concentration, providing a possible metric to titrate diuretic therapy (3). However, despite their potential clinical use, cardiologists often consider urine assessments to be cumbersome, unreliable, and difficult. Additionally, reliable data on variability of sodium excretion during decongestive therapy as well as its association with fluid loss, weight loss, diuretic doses, or outcome is still limited.

In this issue of JACC: Heart Failure, Hodson et al. (4) aimed to: 1) investigate natriuresis as a derivative to assess effectiveness of decongestive therapy; and 2) compare the prognostic value of natriuresis with fluid loss in patients with acute heart failure. In a retrospective analysis of the ROSE-AFH (Renal Optimization Strategies Evaluation in Acute Heart Failure) trial, natriuresis was assessed during the first 4 days of decongestive treatment in 316 patients with acute heart failure. A poor natriuretic response was defined as sodium excretion of <2 g/day, an intermediate natriuretic response as 2 to 4 g/day, and an excellent response as >4 g/day. Overall, interpatient and day-by-day natriuretic response was highly variable. After 24 h, 28.5% of patients were identified as poor responders based on natriuresis, and a poor response was independently associated with an increased risk of all-cause mortality. Importantly, fluid loss or changes in body weight were not associated with outcomes. An interesting finding was that a poor natriuretic response was even associated with poor outcomes in patients with a negative fluid balance. Based on these findings, Hodson et al. (4) suggest that assessment of natriuresis might be a better marker of response to diuretic therapy in acute heart failure than net weight loss and urinary output/ fluid balance.

Hodson et al. (4) are to be congratulated on this well-performed study that provides additional insight in the underlying pathophysiology of sodium handling in response to loop diuretic agents in

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patients hospitalized for acute heart failure. In daily clinical practice, heart failure specialists are frequently confronted with patients with insufficient diuretic response, resulting in residual congestion, which is thought to be one of the main drivers for the high rehospitalization rates following a hospitalization for acute heart failure. Over the last years, a great number of studies have shown that a poor diuretic response (using metrics involving weight or fluid loss) is associated with residual congestion and poor outcome. Residual congestion, assessed by clinical signs of congestion or biomarkers, was also associated with poor outcomes. The authors provides valuable additional information as it shows that natriuresis might be a better marker than weight or fluid loss to guide decongestive therapy. Two minor limitations of this study should be noted. First, patients with a poor natriuretic response had higher natriuretic peptides at baseline and poorer renal function, all indicative for a higher risk of poor diuretic responsiveness. Even though Hodson et al. (4) mention there was no difference between diuretic doses during day 1 over different natriuretic responsiveness profiles, this might not have been the case for weight or fluid loss. To overcome the consequences of these differences at baseline, that is, administering higher doses of diuretics, it might have been informative to additionally provide those parameters indexed for the amount of diuretic agents that were used. In comparison, studies using weight loss without taking difference in loop diuretic doses into account reported conflicting findings, whereas studies using indexed diuretic response metrics consistently showed an increased risk of poor outcome with a poor diuretic response. Second, Hodson et al. (4) only report on all-cause mortality, whereas the association between natriuresis and early hospital readmission would have been of particular interest, because residual congestion is thought to be a main driver for this event. From a pathophysiological point of view, increased sodium avidity, reflected by a poor natriuretic response would most likely lead to more heart failure (re)hospitalizations. Future studies will hopefully shed more light on this.

To provide more evidence for the benefits of urinary measurements, several studies are currently ongoing. One of those studies is aimed at determining whether full 24-h urine collections are better than collecting spot urine samples. Other studies are assessing the potential clinical value of congestion biomarkers (such as bio-adrenomedullin, sCD146, and CA-125), congestion scores, and lung/jugular venous pressure ultrasound to better identify patients with residual congestion who are at higher risk for early rehospitalization (5).

In conclusion, the findings by Hodson et al. (4) support the collection of urine samples and measurement of urinary sodium excretion on a daily basis during an acute heart failure hospital admission to assess response to loop diuretics. Implementation of urinalysis in clinical practice will provide greater insight in the effectiveness of loop diuretic agents and will lead to more individualized treatment strategies, ultimately aimed at improving outcomes for acute heart failure patients.

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