JACC: HEART FAILURE
VOL. 3, NO. 10, 2015

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jchf.2015.06.004

EDITORIAL COMMENT

Verdict In

Congestion Guilty!*

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The study by Salah et al (1) published in this issue of *JACC: Heart Failure* analyzed the same patients' cohorts used by the authors to develop a discharge risk model for acute decompensated heart failure (ADHF) named the ELAN-HF (European CoLlaboration on Acute decompeNsated Heart Failure) score (2). After identifying independent predictors of 180-day all-cause mortality, the authors assigned weights to individual risk markers proportional to their regression coefficients. Notably, 5 of the 8 predictors of all-cause 180-day mortality (62%) are measures of congestion: reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≤30%, elevated NT-proBNP levels at discharge, peripheral edema, admission sodium level <135 mmol/l, and discharge serum urea levels ≥15 mmol/l (42 mg/dl).

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The close correlation between natriuretic peptide (NP) levels and cardiac filling pressures has been unequivocally proven, and NP measurements have been used for nearly 2 decades to estimate severity of fluid overload (3). In heart failure (HF), hyponatremia occurs in the setting of heightened renal sodium avidity as a result of increased free water reabsorption mediated by neurohormonally induced release of arginine vasopressin (AVP) (4). This hormone also regulates the action of the urea transporter in the collecting duct. Therefore, a rise in blood-urea-nitrogen levels may be a marker of neurohormonal activation independent of changes in glomerular filtration rate (GFR), rather than an indicator of hypovolemia (5).

Building upon the foundations of their previous findings, Salah et al. (1) have now evaluated the impact of the dynamic changes occurring in NP levels and renal function during ADHF on 180-day all-cause mortality (2). Finding of the current study, that a reduction in NT-proBNP ≥30% is the strongest predictor of favorable outcomes, regardless of changes in renal function, bolsters the notion that the key goal in ADHF patients should be to achieve optimal decongestion even at the cost of worsening renal function (WRF) (6). Persistent congestion has been consistently shown to worsen HF outcomes, regardless of age and underlying renal function (6). This observation is not surprising in light of the detrimental effects in multiple organ systems of fluid accumulation, regardless of whether it is due to rapid fluid shifts from regional vascular beds to the systemic circulation triggered by neurohormonal activation or to an actual increase in plasma volume from excess sodium and water retention by the kidney (7). Nevertheless the reasons why unresolved congestion may trump WRF as a predictor of prognosis in ADHF patients are very complex and incompletely understood. A study in an isolated heart preparation showed that progressive increase in myocardial water decreased contractility and coronary flow reserve (8). These findings indicate that myocardial congestion actually leads to ischemia. Indeed, the combination of congestion, ischemic HF, and inotrope administration has been described as the "perfect storm" leading to myocardial changes similar to those of an acute myocardial infarction (9). Recent data show that in HF the kidney itself contributes to congestion very early, before any detectable intervention of the neurohormonal system. A recent landmark study compared natriuresis in response to volume expansion in patients with pre-clinical HF with reduced or preserved EF versus controls (10). Compared to normal subjects, asymptomatic HF patients had a significantly decreased sodium excretion in response to volume expansion. This remarkable observation implies that the kidney itself may play a

*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

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key role in the development and progression of congestion in HF. Often overlooked are many other critically important changes that occur in the kidney in the setting of cardiac dysfunction. When renal plasma flow decreases, the kidney strives to maintain GFR by increasing filtration fraction. Various transporters actively transfer sodium across the luminal side of proximal tubular cells. However, due to the permeability of the proximal tubular epithelium, sodium freely returns to the lumen, and net sodium reabsorption depends predominantly upon passive Starling forces between peritubular capillaries and renal interstitium, independent of neurohormonal activity. Due to the increased filtration fraction in HF, the higher oncotic pressure in the peritubular capillaries facilitates sodium and water reabsorption. This is further enhanced by the decline in interstitial oncotic pressure due to the removal of interstitial proteins by lymphatic flow. The increased reabsorption of sodium chloride in the proximal tubule reduces its availability to the macula densa. Decreased intracellular chloride causes NOS I and COX-2 activation and release of NO and PGE2, which, in turn, mediate renin release by the granulosa cells of the afferent arteriole, a process which further enhances neurohormonal activation (7). Increased sodium reabsorption in the proximal tubules coupled with a decreased GFR in individual nephrons results in decreased distal tubular flow, which enhances response to aldosterone and resistance to the action of NPs (7). In HF, all these processes are magnified by neurohormonal activation that causes not only further sodium and water retention but also profound changes in the splanchnic, gut, hepatic, and splenic circulations, all of which produce both organ dysfunction and intra-abdominal edema accumulation (7). It is not surprising, therefore, that increased central venous pressure (CVP) in itself has been repeatedly shown to decrease GFR. An elevated CVP is rapidly transmitted to the kidney's venous circulation, causing renal venous hypertension. Elevated renal venous pressure increases interstitial hydrostatic pressure. If this exceeds tubular hydrostatic pressure, the tubules collapse. Consequently, increasing intratubular pressure opposes filtration and therefore decreases net glomerular filtration (6). This mechanism is supported by experimental data showing a linear decrease in GFR upon increases in renal venous pressure, especially during volume expansion (11). One important caveat is that the CVP can vary dramatically based on venous tone without an actual increase in plasma volume (12). Regardless of its cause, however, venous congestion itself has been shown to produce endothelial activation, up-regulation of inflammatory cytokines, hepatic dysfunction, and intestinal villi ischemia. The last effect produces abnormalities of the epithelial cells and loss of their intestinal barrier function. As a result, lipopolysaccharide or endotoxins produced by gram-negative bacteria residing in the gut lumen enter the circulation, further escalating the inflammatory milieu already established by venous congestion and neurohormonal activity (13). All these facts clearly point to congestion as the culprit for HF disease progression and end-organ damage.

Therefore, effective decongestion may be essential to protect the kidney in the long term, even when fluid removal causes transient WRF. Indeed assessment of the correlation between hemodynamics, renal function, and mortality in 2,557 patients undergoing right heart catheterization for various chronic cardiovascular disorders showed that increased CVP was independently associated with renal dysfunction and unfavorable outcomes (14). In that study, the detrimental effects of CVP were greatest in patients with preserved cardiac index, challenging the belief that in HF WRF is caused solely by intravascular volume depletion resulting from overzealous diuresis (14). One of the key findings of the study by Salah et al. (1) is that severe WRF (defined as an absolute increase in serum creatinine level >0.5 mg/dl in combination with $>25\%$ increase in this measurement) did predict higher 180-day mortality rates, but neither NT-proBNP levels at admission nor the magnitude of NT-proBNP level reduction during hospitalization was correlated with the occurrence of severe WRF (2). In fact serious renal dysfunction was found in some patients whose NT-proBNP level did not change significantly during treatment for ADHF. This strongly supports the notion that in HF, WRF has multiple causes and cannot be attributed solely to decongestive therapies. A major clinical challenge facing clinicians is to discern whether WRF that occurs during the treatment of acutely ill patients is due predominantly to hemoconcentration or to the development of acute kidney injury (AKI), which may or may not result in the development and progression of chronic kidney disease (15). An ideal definition of AKI should have limited complexity, close correlation between its stages and outcomes, high sensitivity and specificity to detect the occurrence of actual acute renal damage, and low cost of use in real time. Such ideal characterization of AKI currently does not exist. In 2004, the Acute Dialysis Quality Initiative group published a landmark consensus definition of AKI in adults, the Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE) classification. In RIFLE, AKI was defined as the rise in creatinine of $\geq 50\%$ from its baseline value and/or a fall in GFR by $\geq 25\%$ and/or a decrease in urine output

below 0.5 ml/kg/h for 6 h or more. The "acute" element of the definition of AKI requires that creatinine levels rise within 48 h (15). Other AKI classifications have been proposed and their performance in AKI prediction is similar to that of RIFLE. Although standardization of definitions has improved early detection of possible AKI, important areas of uncertainty remain. Many factors can cause an acute increase (dietary creatine intake, rhabdomyolysis, drug-induced inhibition of tubular secretion, assay-related false elevations) or decrease (sepsis, muscle wasting, malnutrition) in creatinine levels, often making a definitive diagnosis of AKI difficult. In addition the prognostic value of AKI stages was evaluated in retrospective rather than prospective studies (15). Biomarkers for AKI are broadly divided into functional or structural indicators (injury or damage). Despite enthusiasm for the incorporation of these novel biomarkers into definitions of AKI usable in clinical practice, various obstacles exist to their routine utilization. These include poor performance when the timing of renal insult(s) is unknown or in the presence of confounding comorbidities (especially chronic kidney disease and sepsis), inability to reliably detect AKI in individual patients, failure to identify the specific etiology of AKI and absence of measurable improvements in outcomes and costs (15). As the search for the ideal tool to diagnose AKI continues, effective decongestion must remain the principal target in the treatment of ADHF patients. In fact an increasing number of studies support the conclusion by Salah et al. (1) that during hospitalization for ADHF kidney function should not limit efforts to achieve euvolemia (16).

Ultimately the most effective approach to congestion is to prevent it altogether, as clearly shown by results of the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in Class III Heart Failure) trial: adjustment of medical therapy according to pulmonary artery pressures before the onset of signs and symptoms of congestion significantly decreases HF-related hospitalizations and mortality (17,18).

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KEY WORDS acute decompensated heart failure, acute kidney injury, NT-proBNP, worsening renal function