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EDITORIAL COMMENT

Blood Urea Nitrogen

A Marker for Adverse Effects of Loop Diuretics?*

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Loop diuretics are used in patients with heart failure (HF) to relieve symptoms of systemic and pulmonary venous congestion. Despite their nearly universal use for this indication, loop diuretics have not been shown to improve survival—indeed, a number of recent studies suggest an adverse relationship between the use of loop diuretics and survival (1–3). This is plausible because loop diuretics block sodium chloride absorption at the macula densa in the thick ascending limb of the loop of Henle, activating the renin-angiotensin-aldosterone system (RAAS) and potentially exacerbating HF (4). Few data exist to inform providers how to use loop diuretics to provide the greatest symptomatic benefit with the least adverse effect. In this issue of the *Journal*, Testani et al. (5) have provided insight into this

See page 375

difficult therapeutic dilemma. They analyzed data from the BEST (Beta-Blocker Evaluation of Survival Trial) to determine whether the blood urea nitrogen (BUN), used as a surrogate marker of neurohormonal activation, might identify patients most likely to have adverse effects from high-dose loop diuretics (HDLDs). The BEST was a National Heart, Lung, and Blood Institute–sponsored multicenter, randomized, placebo-controlled trial comparing a beta-adrenergic blocker, bucindolol, with placebo in patients with New York Heart Association functional class III or IV heart failure, a left ventricular ejection fraction of ≤35%, and who were taking an angiotensin-converting enzyme inhibitor for ≥1 month (6). The BEST did not demonstrate a beneficial effect of bucindolol for the primary endpoint of all-cause mortality, so all subjects could be combined for this analysis. Testani et al. (5) showed that HDLDs (defined as a furosemide equivalent of ≥160 mg/day) compared with low-dose loop diuretics (LDLDs) were not associated with an adverse effect on mortality in the overall BEST population. However, with correction for baseline characteristics, HDLDs were associated with an adverse effect on mortality in subjects with a BUN above the median (21 mg/dl), but a beneficial effect on mortality in patients with a lower BUN. The authors postulate that in the HF patients with the higher BUN, neurohormonal activation with an HDLD was greater than the withdrawal of neurohormonal activation resulting from decongestion, thus leading to a poorer survival. In contrast, the balance in neurohormonal activation with HDLDs and neurohormonal withdrawal was favorably altered in the low BUN group, leading to improved survival. This is an intriguing and novel hypothesis. Several important concepts underlie the premise of this study including the relationship of serum creatinine and BUN to the glomerular filtration rate (GFR) and the complex relationship between sodium and water reabsorption, urea reabsorption, and neurohormonal activation in HF patients.

Serum creatinine has generally been used clinically to estimate renal function in HF. Serum creatinine is freely filtered at the glomerulus and not reabsorbed. However, creatinine undergoes tubular secretion, and thus creatinine clearance overestimates inulin clearance, the gold standard for GFR (7). Likewise, because blood urea levels are affected by protein intake, catabolism, and tubular reabsorption, BUN is not as reliable a marker of renal function as the GFR. However, based on the kidney's handling of urea, BUN more closely reflects neurohormonal activation than changes in creatinine or the GFR (8). Urea is freely filtered at the glomerlus and is not secreted, but is reabsorbed in both the proximal and distal renal tubules. Urea reabsorption in the collecting duct is flow dependent so that more urea is reabsorbed as urine flow rates decrease (7) (Fig. 1). Accordingly, an elevation in BUN is a sign of severe HF and has been shown to be a better prognosticator of mortality and rehospitalization than serum creatinine in several recent HF studies (9–13).

The complex relationship between sodium and water reabsorption, neurohormonal activation, and BUN in patients with HF is outlined in Figure 2. Initially, HF causes low cardiac output and arterial underfilling, which unloads the arterial baroreceptors and results in activation of both the sympathetic nervous system (SNS) and the RAAS (14). RAAS activation increases sodium and water reabsorption throughout the nephron by activation of the proximal tubular sodium-hydrogen exchanger and sodium-bicarbonate cotransporter and in the distal tubule and collecting ducts through the sodium-chloride cotransporter and sodium epithelial channels, respectively (15). Increased SNS activity increases proximal tubular sodium transport by stimulation of α-adrenergic receptors, an effect independent of the GFR (16). There is significant crosstalk between these systems. Angiotensin II stimulates SNS activity, which activates the

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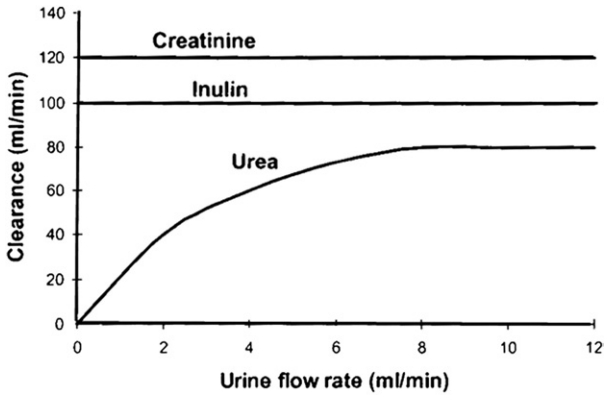

Figure 1 **Tubular Urea Reabsorption and Flow Dependence of Urea Clearance**

Inulin is freely filtered at the glomerulus and is neither secreted nor reabsorbed; thus, inulin clearance is the gold standard for the glomerular filtration rate. Creatinine is also freely filtered and not reabsorbed, but creatinine is secreted in the distal nephron, so creatinine clearance exceeds inulin clearance. Urea is freely filtered and not secreted but undergoes reabsorption in the distal nephron. Reabsorption of urea is flow dependent, so that more urea is reabsorbed at lower urine flow rates. Thus, high blood urea nitrogen is a marker for more severe heart failure. Reprinted, with permission, from Berl et al. (7).

RAAS by a direct effect on β-adrenergic receptors in the juxtaglomerular apparatus (15,17). Moreover, arterial underfilling stimulates arterial baroreceptor-mediated nonosmotic arginine vasopressin (AVP) release, which causes further solute-free water retention (17,18). Increased tubular reabsorption of sodium and water may elevate right atrial pressure with an increase in renal venous and interstitial pressures and further activation of the RAAS that, in turn, activates the SNS (19–21).

As with sodium and water reabsorption, increased reabsorption of urea in HF patients results from several different mechanisms. Reabsorption of sodium and water in the proximal tubule leads to an increase in urea concentration, promoting the passive reabsorption of urea. AVP secretion increases urea reabsorption via the urea transporter in the inner medullary collecting duct (18). As HF progresses, AVP-mediated up-regulation of the renal urea transporters serves to increase urea reabsorption in excess of any decrement in the GFR (18). Proximal tubular sodium and water reabsorption and AVP-stimulated water absorption in the distal tubule slow urine flow, further increasing the reabsorption of urea (19). Thus, it is reasonable to suggest that HF patients with an elevated BUN have a higher level of neurohormonal activation than those with a lower BUN. Certainly if HDLD are detrimental in patients with a high BUN and more neurohormonal activation, this high-risk group might be targeted for alternative methods of sodium and water removal such as ultrafiltration that may not lead to additional neurohormonal activation (22,23).

Although this use of BUN is a novel and intriguing concept, this study is a first step that will require prospective validation. HDLDs may cause more neurohormonal acti-

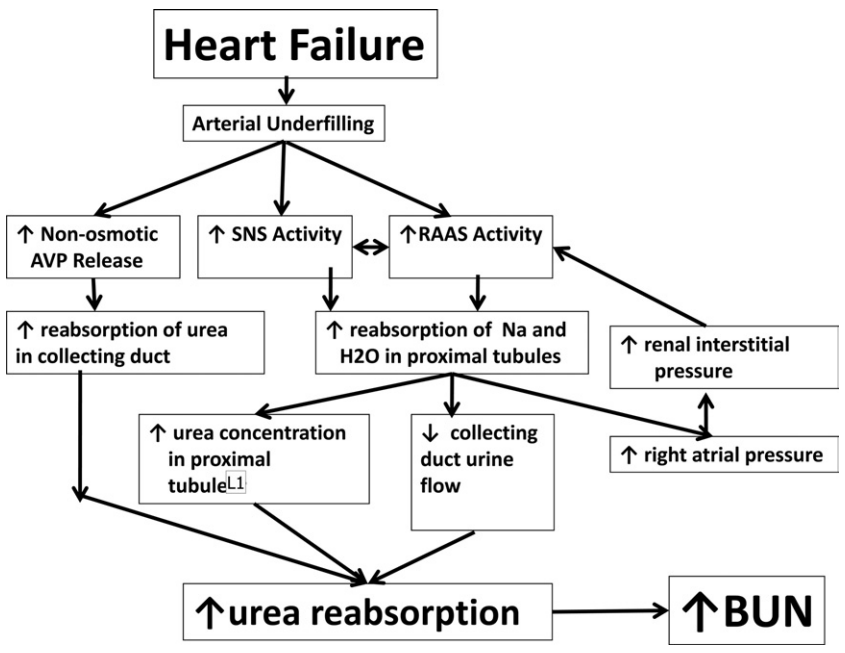

Figure 2 **Interactions Between Neurohormonal Activation, Renal Function, and Absorption of Urea**

Heart failure causes arterial underfilling, which results in neurohormonal activation including activation of the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS), and nonosmotic arginine vasopressin (AVP) release. SNS and RAAS activation cause increased reabsorption of sodium and water in the proximal tubule, leading to increased proximal tubular urea concentration and decreased urine flow in the collecting duct with both resulting in increased urea reabsorption. AVP also stimulates urea reabsorption in the collecting duct. The increased reabsorption of sodium and water leads to increased right atrial pressure and renal interstitial pressure, which further activates the RAAS. BUN = blood urea nitrogen.

vation than LDLDs. However, even LDLDs would be expected to block sodium chloride transport in the ascending loop of Henle and the macula densa, resulting in neurohormonal activation. The requirement for HDLDs versus LDLDs is dependent on intrinsic renal function as well as neurohormonal activation (24). Although the analysis corrected for baseline creatinine, it is possible that serum creatinine might have been as discriminative as BUN. If so, it would suggest that the underlying degree of renal dysfunction, not neurohormonal activation, is the critical predictive factor in the adverse effects of HDLDs. On the other hand, those HF patients with the highest neurohormonal activation may also have the most renal vasoconstriction and thus renal functional impairment. Plasma norepinephrine concentration, the only direct marker of neurohormonal activation in this study, was significantly higher in the HDLD compared with the LDLD group and in the high BUN compared with the low BUN group. However, the levels of plasma norepinephrine in this study did not indicate a high level of neurohormonal activation and were closest to those reported in the SOLVD (Studies of Left Ventricular Dysfunction) prevention rather than treatment cohort (25). The plasma norepinephrine differences in the low and high BUN groups and in the HDLD and LDLD groups are also less than the difference between each of the quartiles in the VAL-HeFT (Valsartan in Heart Failure Trial), suggesting that these high and low BUN groups and HDLD and LDLD groups both have very modest differences in neurohormonal activation (26). Finally, this study evaluated only baseline levels of BUN and not the changes in BUN with increasing doses of diuretics.

Despite these issues, Testani et al. (5) are to be congratulated for this novel study suggesting that higher levels of neurohormonal activation estimated by BUN might predict potential adverse effects of loop diuretics. Future studies establishing the value of BUN in predicting neurohormonal activation and prospectively testing the hypothesis set out by Testani et al. are eagerly anticipated.

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