Blood Urea Nitrogen and Serum Creatinine
Not Married in Heart Failure

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Klein and colleagues have retrospectively analyzed results derived from the prospective, randomized Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study and contribute an interesting article to this inaugural issue of Circulation: Heart Failure. Their analysis provides further evidence that the level of renal function in patients with worsening heart failure and impaired systolic function is an important predictor of rehospitalization for cardiovascular events and death within 60 days of discharge. Renal function was assessed at admission. Change during hospitalization was recorded for blood urea nitrogen (BUN) and estimated glomerular filtration rate (GFR). Estimated GFR was calculated with the 4-variable equation of the Modification of Diet in Renal Disease study, which depends on serum creatinine, age, and sex. Of interest, the BUN on admission and change in Renal Disease study, which depends on serum creatinine, was assessed at admission. Change during hospitalization was recorded for blood urea nitrogen (BUN) and estimated glomerular filtration rate (GFR). Estimated GFR was calculated with the 4-variable equation of the Modification of Diet in Renal Disease study, which depends on serum creatinine, age, and sex. Of interest, the BUN on admission and change in BUN during the hospital stay (independent of the admission value) was a statistically better predictor of the 60-day death rate and days of rehospitalization than was estimated GFR. Because BUN is affected by protein intake, catabolism, and tubular reabsorption of urea, it is not as reliable an index of renal function as GFR. Thus, this observation by Klein et al is of particular interest and deserves explanation.

Serum creatinine is freely filtered at the glomerulus, not reabsorbed, but undergoes tubular secretion. Thus, creatinine clearance exceeds inulin clearance, the gold standard for GFR. In contrast, urea is freely filtered, not secreted, but is reabsorbed by the renal tubules. This reabsorption of urea is flow dependent so that more urea is reabsorbed at lower urine flow rates (Figure 1). Most importantly, the reabsorption of urea in the collecting duct is mediated by the effect of arginine vasopressin (AVP) on the urea transporter in the collecting duct. With low-output cardiac failure, activation of the neurohumoral axis maintains arterial perfusion, including the nonosmotic release of AVP. This nonosmotic release of AVP is mediated by arterial baroreceptors. In the OPTIME-CHF study in the present issue, in which serum BUN was analyzed by quartiles, both systolic (110 versus 126 mm Hg) arterial blood pressure and diastolic (64 versus 76 mm Hg) arterial blood pressure were lower in the fourth quartile than in the first quartile. Thus, the higher fourth BUN quartile would be expected to have higher baroreceptor-mediated nonosmotic AVP release. Moreover, these proposed higher plasma AVP concentrations would be expected to increase urea reabsorption in the collecting duct, thereby increasing BUN. In this regard, plasma vasopressin concentrations and vasopressin-dependent urinary aquaporin-2 water channels have been shown to progressively increase as heart failure worsens according to cardiac index and New York Heart Association classification. Moreover, V2-vasopressin receptor antagonists have been shown to increase solute-free water excretion in heart failure patients and experimental animals with heart failure. In the study by Klein et al, the plasma sodium concentration was significantly decreased in the fourth BUN quartile, although the change was small. However, hyponatremia in cardiac failure patients is determined not only by the nonosmotic plasma AVP but also by the water intake. Thirst is increased in heart failure patients, and hyponatremia has been shown to be a risk factor for increased risk of death in advanced heart failure.

The neurohumoral response to arterial underfilling secondary to decreased cardiac output involves not only AVP but also stimulation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system (Figure 2). The renal effects of increased angiotensin and adrenergic stimulation exert both vascular and tubular effects on the kidney. Specifically, angiotensin and adrenergic stimulation cause renal vasoconstriction and decrease GFR and renal blood flow, but they also increase proximal tubular sodium and water reabsorption. As a consequence, the resultant decreased distal fluid delivery will slow tubular flow in the collecting duct and enhance the flow-dependent urea reabsorption. Thus, although the humoral components of the enhanced neurohumoral axis are not routinely measured clinically in heart failure patients, the rise in BUN may serve as an index of neurohumoral activation over and above any fall in GFR. The increased 60-day death rate as the BUN quartiles rise is compatible with this interpretation. In this regard, higher plasma concentrations of plasma renin activity and norepinephrine are associated with increased risk of death in cardiac failure, as occurred with the higher admission BUN values and changes in BUN values during hospitalization.

The use of angiotensin-converting enzyme (ACE) inhibitors decreased significantly as the admission BUN rose in the OPTIME-CHF study. In settings of increased circulating angiotensin, as occurs in heart failure, ACE may block the...
selective action of angiotensin to constrict the efferent arteriole of the glomerulus and thereby lower glomerular hydrostatic pressure and decrease GFR unless a sufficient rise in cardiac output occurs to compensate. A paradox occurs, however, because these patients with the higher BUN values may most need the cardioprotective effect of ACE inhibitors. This cardioprotective effect of ACE inhibitors has been shown to occur across a spectrum of BUN values. Nevertheless, in the OPTIME-CHF study, the higher admission BUN and lower GFR in the fourth quartile could not be explained by more use of ACE inhibitors, and apparently the use did not change during the hospitalization.

The observation that during the hospitalization the increase in BUN across the 4 quartiles, independent of admission BUN, also correlated with increasing 60-day death rate is somewhat more difficult to interpret. Although changes in diuretic dose and body weight were not reported in the OPTIME-CHF study, treatment of pulmonary congestion with diuretics may improve breathing but at the same time decrease cardiac index and increase BUN (Figure 3). It is important also to note that loop diuretics act in the thick ascending limb of the Henle’s loop where the macula densa is located. Therefore, independent of any effect on sodium and water balance, loop diuretics block sodium chloride reabsorption in the macula densa and thereby stimulate the RAAS. Although activation of the RAAS contributes to maintaining arterial blood pressure in the presence of low cardiac output, angiotensin and aldosterone do have negative effects on cardiac remodeling.

Another interesting observation in the OPTIME-CHF study is the significant rise in jugular venous pressure as quartile BUN values rose. The associated increase in renal venous pressure would increase renal interstitial pressure and activate the RAAS. Moreover, an increase in cardiac preload and cardiac dilatation are known to be important risk factors for increased death rate in heart failure patients. In some heart failure patients, fluid removal by diuretics or ultrafiltration may not only improve pulmonary congestion but also improve cardiac function (Figure 4). This occurrence may relate to a decrease in ventricular wall stress and to less functional mitral insufficiency. There are potential theoretical, but yet to be proven, advantages of ultrafiltration over loop diuretics for fluid removal in decompensated heart failure patients. Interstitial fluid mobilization into the intravascular compartment has been estimated to occur at 14 to 15 mL/min in fluid-overloaded patients. Thus, in heart failure
patients, if judicious fluid removal with ultrafiltration does not exceed this rate, the RAAS may not be further stimulated, and, if cardiac function improves, activation could actually diminish. Also, for the same volume of fluid, more sodium chloride is removed by isotonic ultrafiltration than by the hypotonic diuresis that occurs with loop diuretics. Moreover, ultrafiltration avoids the potassium and magnesium losses that occur with loop diuretics, but obviously ultrafiltration is more invasive. As is well established, sodium chloride, not water removal, is the primary determinant of change in extracellular fluid volume. Because an estimated 50% of hospitalized patients with decompensated heart failure are discharged with little or no change in body weight, fluid removal in these patients must be somewhat inconsistent.

Nevertheless, clinical improvement with bed rest alone may improve these heart failure patients in the absence of fluid removal, but decompensation may recur upon discharge and restoration of normal activity. Thus, there is much to be learned about fluid removal and the cardiorenal syndrome in patients with decompensated heart failure and impaired systolic function, particularly because the rise in BUN during hospitalization has been shown to correlate with increased 60-day death rate.

Disclosures

None.

References


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