Blood Urea Nitrogen as an Integrated Biomarker for Hospitalized Heart Failure

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Pathophysiological conditions (ie, hemodynamic and neurohormonal conditions), as well as metabolism regarding nitrogen, in hospitalized heart failure (HHF) patients are quite different from those in patients with stable HF. Although HF should be considered as a sequential entity from the acute to the chronic state, it is important to keep in mind that pathophysiological conditions change over time, and therefore, the clinical significance of biomarkers in HF will differ between the acute and chronic phases.

In this issue of the Journal, Chen et al demonstrate that high serum levels of blood urea nitrogen (BUN), a well known renal or metabolic biomarker, are associated with an increase in re-hospitalization and mortality in HHF patients with systolic dysfunction mainly because of dilated cardiomyopathy. Urea is formed in the liver as a major endproduct of the metabolism of ingesting protein and is excreted and partly reabsorbed by the kidneys. Therefore, the BUN level represents the balance between the production and reabsorption of urea and the renal excretion of urea. Activation of the rennin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) because of unstable hemodynamics with cardiovascular dysfunction, diuretic use, and so on, cause renal vasoconstriction and decrease the glomerular filtration rate (GFR), which then reduces the renal excretion of urea. The RAAS increases concentration-dependent urea reabsorption in the proximal tubules and the SNS increases flow-dependent urea absorption in the distal tubules. Furthermore, arterial underfilling secondary to low cardiac output stimulates synthesis and release of arginine vasopressin, which upregulates urea transporters in the inner medullary collecting duct and enhances urea reabsorption. On the other hand, it is known that HHF is a hypercatabolic state, which increases urea production. Thus, the increase in BUN reflects not only decreased GFR but also aberrations in fluid volume and metabolic balances, neurohormonal activities, and hemodynamics in patients with HHF, suggesting that BUN is not only a commonly used biomarker, but also an encompassing biomarker that reflects many pathophysiological interactions in HHF patients. The mechanisms of an increase in BUN regarding these interactions in HHF patients are summarized in the Figure.

In most HHF patients, the BUN level, as well as that of serum creatinine, changes during hospitalization. Subanalysis of the OPTIME-CHF study demonstrated that a higher admission BUN level and increasing BUN during hospitalization, independent of the admission value, were associated with poor outcomes. Based on these findings, BUN-guided therapy may be useful for improving outcome, especially the readmission rate, in HHF patients. This concept should be clarified by prospective studies.

Chen et al also demonstrate that diastolic blood pressure (DBP) is an important factor in predicting cardiovascular events, although other studies have demonstrated systolic blood pressure (SBP) as a strong prognostic marker in HF patients.

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Figure. Mechanisms underlying increased blood urea nitrogen (BUN) levels in hospitalized heart failure (HHF) patients. GFR, glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; IAP, intra-abdominal pressure; SNS, sympathetic nervous system; AVP, arginine vasopressin.
It is interesting but difficult to explain why DBP was a prognostic marker in the study by Chen et al, although they mention that low DBP does impair coronary flow during dias-
tole. It is well known that DBP reflects systemic vascular res-
stance and pulse pressure (ie, SBP−DBP) is correlated to car-
diac output. Therefore, to understand the result regarding DBP
in the present study, it is necessary to encompass the interpre-
tation between systemic vascular function and cardiac func-
ction and also the differences in SBP between both studies (ie,
approximately 110 mmHg in the present study vs. 140 mmHg
in the OPTIMIZE-HF registry), which were the result, in part,
of the differences between both studies in the underlying dis-
eases that led to HHF. In the present study, most of the en-
rolled patients had dilated cardiomyopathy (76.9%), but this
is 13–24% in real-world HHF patients. It should, however,
be kept in mind that DBP may be an important pathophysi-
ological marker in HHF patients, although most studies have
neglected DBP as a prognostic marker. The clinical significance
of DBP should be also examined in HHF patients.

Thus, it is important to clarify the characteristics of the bio-
markers used clinically in HHF patients, as the present study
demonstrates. Using properly integrated biomarkers such as
BUN, as well as specific ones such as brain natriuretic peptide,
might lead to improvement in outcomes, especially the re-
admission rate, of HHF patients.

Disclosures
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