Parathyroid Hormone in Heart Failure – Candidacy for a Biomarker or Therapeutic Target? –

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Although parathyroid hormone (PTH) is a major regulator of bone and mineral metabolism, there is a growing body of evidence suggesting that hyperparathyroidism is associated with adverse outcomes in patients with cardiovascular diseases.¹ In patients with advanced heart failure (HF), urinary and fecal excretion of calcium induced by hyperaldosteronism, together with calcium excretion caused by high dosages of loop diuretics, results in secondary hyperparathyroidism.² In experimental studies, PTH has been shown to have direct actions of hypertrophy and arrhythmogenicity on myocardial cells and tissues partly through cytoplasmic calcium overloading and triggered oxidative stress (Figure).³

It remains to be confirmed in clinical situations, however, whether high serum levels of PTH are only an epiphenomenon in patients with more severe disease, or whether there is any possibility that excess PTH levels directly contribute to the pathogenesis or deterioration of HF. Nonetheless, PTH is an independent predictor of all-cause and cardiovascular mortality, as well as of functional capacity and hospitalization, in patients with HF.^{4,5} Among such studies, Sugimoto et al demonstrated that high serum levels of intact PTH can predict hospitalization for stabilizing of HF in the outpatient setting.⁶ Multivariate analysis showed that a PTH level ≥ 47 pg/ml (elevated) is the independent and strongest predictor of HF hospitalization

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compared with plasma B-type natriuretic peptide (BNP). These studies have thus led to evaluation of PTH as a biomarker in HF.

Article p2704

Biomarker-based management is widely used in clinical practice because of its advantages, including high reproducibility, simplicity in handling, and in the interpretation of results, even by non-specialists. BNP is an established representative biomarker in the field of HF, indicating the effectiveness of diagnosis and risk stratification, together with screening for cardiac dysfunction and guidance on optimal treatment,⁷ but PTH testing may provide additional value for better risk stratification through a multimarker strategy on the basis of the identification of the subphenotype related to hyperparathyroidism. For example, PTH measurement in patients with HF could help monitor the efficacy of treatments in patients with chronic kidney disease etc.⁸ In addition, PTH measurement may lead to personalized therapy such as vitamin D supplementation or preferential aldosterone blocker usage on the basis of the interaction between PTH and the relevant hormones.⁹

However, there are several limitations to utilizing PTH as a biomarker in HF management. As reported in this issue of the Journal, Sugimoto et al¹⁰ are the first to demonstrate a relationship between mortality and serum PTH levels in patients with acute decompensated HF (ADHF). An association between higher PTH levels and decreased mortality was observed in their study, which is inconsistent with previous observations of community and outpatient HF. It remains a challenge to predict the risk in individual patients with ADHF, because the risk is associated with complex variables and comorbidity.¹¹ The critical issue of using PTH as a biomarker in patients with HF is the association of PTH with outcomes independent of confounders. PTH levels need to be adapted on the basis of interactions with the kidney and vitamin D levels. These interactions are derived from previous reports of HF.¹² In addition, neurohumoral activation in patients with HF may exhibit opposite pathophysiological effects depending on the clinical condition: acute or chronic HF. PTH release is unaffected by sudden changes in ventricular volume,¹³ and the trigger and clinical significance of PTH in patients with ADHF have not been well clarified. Furthermore, PTH levels may continuously

alter in patients with ADHF, depending on the sampling time points. Therefore, future studies are warranted to not only assess baseline PTH in stable HF but also to measure PTH over time from acute to chronic disease, for determining the benefit of PTH transition in predicting outcomes and guiding the management of HF.

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