Significance of B-Type Natriuretic Peptide Measurement in Patients With Chronic Kidney Disease

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It is well established that patients with renal dysfunction have an increased frequency of cardiovascular events. This concept of cardiorenal association has come to be widely acknowledged after relevant cases were found not only abroad but also in Japan, as described in the Hisayama Study. The practical definition of renal dysfunction as “chronic kidney disease” (CKD), which is clinically applicable, has contributed much to the spread of this knowledge on cardiorenal association. But even though it is essential to include glomerular filtration rate (GFR) in the definition of CKD, urinary findings are not always used in many studies for CKD patients.

In this issue of the Journal, Sakuma et al sought a method of choosing CKD patients with higher risk. As a result, they focused attention on plasma B-type natriuretic peptide (BNP) level in stage 3 CKD patients, because BNP has been found to be a predictor of cardiovascular prognosis not only in patients with cardiac diseases but also in the general population. The authors in their cohort study selected CKD patients according to two types of criteria for CKD: decreased GFR and/or proteinuria. Follow up of the subsequent onset of cardiovascular events among these subjects was performed. When the subjects were divided into 4 groups according to plasma BNP concentration, the BNP concentration in the highest-level group was approximately ≥40 pg/ml. Compared with the lowest BNP group, the incidence of cardiovascular events was significantly higher in the highest BNP group, with a hazard ratio of approximately 5. This difference was observed regardless of the definition of CKD. Based on these results, the authors concluded that plasma BNP level was useful for predicting future cardiovascular events in subjects with CKD in the general population.

This study is valuable in the following 3 respects. It was necessary in this study to check whether background factors in the highest BNP group differed from those in the other groups. Although there was little difference in GFR, anemia, or other risk factors among the groups, age, prevalence of hypertension, and prevalence of atrial fibrillation were higher than those in the other groups. In particular, the morbidity of atrial fibrillation reached approximately 10% in this group, with an incidence 10-fold that in the other groups. The presence of atrial fibrillation increases plasma BNP as well as the incidence of cardiovascular events. Even after statistical adjustment for these factors, however, the difference between the highest BNP group and the others did not change, indicating the existence of latent cardiac overload in the group with highest BNP. BNP was thus sensitive enough to detect this latent cardiac overload. The threshold BNP level suggestive of cardiovascular risk in CKD patients may be approximately 40 pg/ml.

Another significant feature of this study was its clear finding of relatively little difference between the groups when they were classified according to the two CKD definitions. According to the current definition of CKD, CKD patients can be classified into 3 groups: those with GFR ≤60 ml · min⁻¹ · 1.73 m⁻² and proteinuria, those with GFR ≤60 ml · min⁻¹ · 1.73 m⁻² but without proteinuria, and those with GFR ≥60 ml · min⁻¹ · 1.73 m⁻² and proteinuria. In cohort studies, use of the spot urine technique may lead to incorrect findings. In fact, in many large-scale clinical trials the definition of CKD has been based on GFR alone. In contrast, aggravation of prognosis was indicated by the presence of proteinuria alone in studies such as the Framingham Study. Similarly, the presence of microalbuminuria affects prognosis. This study demonstrated a high incidence of events when both of these two factors, that is, lower GFR and proteinuria, were present. Detailed results, however, for example plasma BNP levels and prognosis in those who were only proteinuria positive, were not provided.

The third significant feature of this study is its demonstration of the importance of BNP measurement in CKD. It is known that factors other than secretion of BNP from myocardial cells also influence BNP concentration in the blood (Table). In general, plasma BNP levels increase as renal function decreases. It is therefore widely believed that plasma BNP level does not reflect cardiac overload if renal function is already decreased. Because measurement of NT-proBNP was begun prior to that of BNP in some parts of Europe and

| Table. Extra Myocardial Effects on Plasma BNP Level |
|-----------------|-----------------|
| Relative increase | Relative decrease |
| Aging            | Obesity         |
| Female           | Cardiac tamponade |
| Renal dysfunction | Constrictive pericarditis |

BNP, B-type natriuretic peptide.
In the USA, there is much evidence from large-scale studies with regard to the importance of NT-proBNP determination as an index of heart disease. NT-proBNP is secreted with BNP in equimolar ratios after the converting enzyme, furin, acts on proBNP in myocardial cells (Figure). Because NT-proBNP is cleared mostly from the kidneys, blood concentration increases with decrease in renal function. Degradation of BNP, however, occurs largely through its binding to biological receptors and clearance receptors, as well as decomposition by neutral endopeptidase (NEP). Because of the large number of receptors and high concentration of NEP in the kidney, it is possible that renal dysfunction also inhibits the metabolism of BNP. Among studies that compared the clearance of NT-proBNP with that of BNP, some reported that the two were similarly influenced by renal function, while others reported that the influence of renal function on plasma BNP was less pronounced; these findings suggest that a clear conclusion regarding this has yet to be reached.8,9 Furthermore, proBNP is secreted into the blood without processing in conditions such as heart failure, in which BNP synthesis is enhanced. Plasma levels of the precursor of BNP, which has a higher molecular weight, are influenced by renal function. Because the currently available method of BNP measurement recognizes proBNP to approximately the same extent as BNP, increased BNP concentration may be found in conditions of decreased renal function due to increased proBNP. It is known, however, that BNP concentration does not increase until close to end-stage renal failure as long as cardiac function is preserved.10 Accordingly, it can be concluded that in cases of decreased renal function a high BNP level reflects abnormal cardiac function to an exaggerated manner. Thus, determination of renal function as well as plasma BNP concentration is useful for the identification of a high-risk group in the general population.

References