Do Plasma Levels of Brain Natriuretic Peptide (BNP) and N-Terminal proBNP (NT-proBNP) Increase in Diastolic Dysfunction as Well as in Systolic Dysfunction?

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After the structure of atrial natriuretic peptide was established, a Japanese group isolated the brain (also known as B-type) natriuretic peptide (BNP) from porcine brain extracts in 1988 by monitoring the relaxant activity of the chick rectum. Subsequent studies demonstrated that BNP is a cardiac hormone that is mainly expressed in the heart, where its concentration is considerably higher than in the human or rodent brain. It is well known that mechanical stress, such as pressure and volume overload, neurohumoral factors, and cytokines stimulate the gene expression of BNP and levels of myocardial BNP mRNA and circulating BNP and N-terminal proBNP (NT-proBNP) are remarkably increased in patients with congestive heart failure (HF). Clinical studies also showed that BNP levels correlate well with the left ventricular end-diastolic pressure (LVEDP) and ejection fraction (LVEF). Therefore, BNP is considered to function as an emergency defense against ventricular overload in disease states and it has been used as a marker of ventricular function or stress. However, there are few studies that have investigated whether BNP may be used as a marker of LV diastolic dysfunction in patients with coronary artery disease (CAD).

In this issue of the Journal, Sonoda et al report on measuring the NT-proBNP levels in 115 consecutive patients undergoing cardiac catheterization for suspected CAD and compared the NT-proBNP levels with indices of diastolic function. Of the patients, 17 were excluded, so 98 patients with LVEF >50% measured by left ventriculography were enrolled. The authors measured 2 indices of diastolic function: the time constant tau of LV relaxation and inertia force. Patients with impaired LV relaxation had relatively reduced LVEF and higher LV end-diastolic and end-systolic volumes than those with preserved LV relaxation. Plasma NT-proBNP levels were significantly higher in patients with impaired LV relaxation than in those with preserved LV relaxation. Patients without inertia force had a significantly longer LV time constant tau, higher LVEDP, and worse LV systolic function than those with inertia force. Plasma NT-proBNP levels were significantly higher in patients without inertia force than in those with inertia force. Univariate regression analysis revealed that the time constant tau of LV relaxation and inertia force were significantly correlated with logNT-proBNP levels. In addition, multivariate regression analysis showed that logNT-proBNP levels significantly correlated with the time constant tau of LV relaxation and inertia force after adjusting for confounders. Furthermore, the NT-proBNP level that could separate patients with impaired LV relaxation from those with preserved LV relaxation with relatively high sensitivity but low specificity was 56.5 pg/ml, that with moderate sensitivity and specificity was 139.5 pg/ml, and that with low sensitivity but high specificity was 197.0 pg/ml by receiver-operating characteristics curve analysis. NT-proBNP levels to separate patients without inertia force from those with inertia force were shown in a similar manner. Specifically, NT-proBNP levels >56.5 pg/ml had negative predictive value of 100% for identifying LV relaxation impairment. In contrast, NT-proBNP levels ≥44.5 pg/ml had sensitivity of 62.5% and specificity of 93.9% for detecting lack of inertia force.

HF is a growing worldwide epidemic and is associated with substantial morbidity and mortality. HF has been divided into HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). Up to 50% of patients with HF have HFpEF, suggesting that isolated diastolic dysfunction (DD) is the pathophysiological mechanism underlying the clinical syndrome of HF in these patients. A recent study showed that among patients with HF, the 1-year mortality and hospitalization for HF did not differ among those with HFpEF vs. HFrEF. Furthermore, even in the absence of clinical HF, DD is associated with increased rates of future hospitalizations, development of HF, and all-cause mortality. Therefore, accurately diagnosing DD could possibly lead to improved treatment and may have substantial healthcare implications, from both the clinical and resource utilization perspectives. Early identification of DD will allow clinicians to implement management strategies, such as risk factor modification and pharmacotherapies, sooner in order to improve prognosis. Therefore, a simple, reproducible, cheaper and useful biomarker test is desirable. In that sense, Sonoda’s work to detect early DD by NT-proBNP is of importance. In general, Doppler echocardiography is the method of choice to diagnose DD in routine clinical practice. Abnormal diastolic function is subdivided into impaired relaxation, pseudonormal, and restrictive-like filling patterns based on trans-mitral Doppler flow pattern. Recently, Grewal et al classified 181 patients as having a...
normal, impaired relaxation, pseudonormal, or restrictive filling pattern based on transmural Doppler flow patterns and grouped them into normal/mild vs. moderate/severe DD. All patients had normal EFs. Their results were that NT-proBNP >600 pg/ml and BNP >100 pg/ml were the strongest predictors of moderate/severe DD; NT-proBNP >300 pg/ml was found to be less predictive. In Sonoda et al’s study, they showed that NT-proBNP >244.5 pg/ml was able to detect lack of inertia force and may have the potential for specific diagnosis of LV isolated systolic dysfunction. Although the reason for the difference between the 2 studies remains unknown, the patients in Grewal’s study had higher serum creatinine levels than those in Sonoda’s study, which may explain the higher NT-proBNP levels. Another possible explanation is the difference in methods. The former study used the indices of moderate to severe DD by Doppler echocardiography, whereas the latter study used the indices of the time constant tau of LV relaxation and inertia force by cardiac catheterization. Moderate to severe DD by Doppler echocardiography may include more severe DD than is shown by the indices measured by cardiac catheterization.

Taking these findings together, it seems certain that the NT-proBNP and/or BNP level increases with DD. However, because NT-proBNP is influenced by loading conditions and renal function, we need to pay attention to the interpretation of the value. Moreover, the clinical significance of the inertia force is not well investigated either. Furthermore, there is no established drug that improves DD. In addition, a new problem seems to arise in the BNP measurement system. Recent studies showed that not only BNP and NT-proBNP, but also a significant amount of precursor proBNP, circulate in human blood. Moreover, proBNP-108 and NT-proBNP are O-glycosylated in the N-terminal region. Glycosylation of the middle portion of NT-proBNP-76 (Thr44) affects binding of the antibody directed against epitopes proBNP[42–46], potentially leading to underestimation of the actual concentration of circulating NT-proBNP-76 in the current assay system (Roche Elecsys proBNP II). In the present assay system of BNP and NT-proBNP, they also cross-react to proBNP. In the future, which indices of DD best correlate with the patient’s condition and prognosis should be investigated, as well as which BNP molecular form best correlates with the indices of DD. Nevertheless, the study by Sonoda et al raises an important hypothesis: in patients with CAD and LVEF >50, increased NT-proBNP may be a predictor of DD.

References