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Natriuretic peptides in heart failure: Their role in daily practice

Krystyna Łoboz-Grudzień, Joanna Jaroch

Department of Cardiology, T. Marciniak Hospital, Wrocław Medical University, Public Health Faculty, Wrocław, Poland

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Natriuretic peptides (NP) are volume sensitive hormones that have attracted the interest of investigators in the setting of heart failure (HF) during recent years. NP levels may reflect the end-diastolic wall stress which is elevated by both increasing filling pressure and left ventricular dilatation. Brain natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP) have a negative correlation with left ventricular systolic function and have been proposed as diagnostic tools and prognostic markers in HF patients [1, 2]. Cardiovascular guidelines recommend that both peptides should be considered equal [1].

The value of BNP and NT-proBNP in daily diagnostic practice

Many studies have shown that the measurement of BNP and NT-proBNP can distinguish patients with acutely decompensated HF from those who present with other causes of dyspnea. The BNP threshold level of 100 pg/mL was based on studies of patients with acutely decompensated HF rather than chronic HF. However, the NP levels cannot be used to differentiate systolic from diastolic dysfunction; their measurement might be used to find patients with HF in the general community, to quantify symptoms and functional limitations, and to predict the risk of cardiovascular events. In the interpretation of plasma NP levels several factors such as age, sex, renal function, cardiac rhythm, obesity, and drug therapy should be taken into account [3–5]. The clinical application of both NPs exceeds their use as rule-out blood tests for HF.

The value of BNP and NT-proBNP in quantifying functional capacity

During recent years the parameters of cardiopulmonary exercise have provided the more objective assessment of functional capacity in patients with HF than New York Heart Association (NYHA) class. However, there is a limited relation between maximal oxygen consumption and parameters of severity of HF, such as NYHA functional class and left ventricular ejection fraction (LVEF). It has recently been suggested that plasma BNP levels are related to VO_2 at peak of exercise and could be a predictor of impaired exercise capacity in patients with HF [6–8]. In this issue of "Cardiology Journal", Koç et al. [9] present the usefulness of NT-pro BNP for the prediction of low functional capacity (FC), decreased LVEF, and the identification of patients at highest risk of future cardiovascular events. In the assessment of FC, the exercise test has been used, and the cutoff value for NT-proBNP in the prediction of FC < 5 METs was defined [9]. The relationship between NP and the functional capacity may be explained by the fact that patients with an elevated rest left ventricular diastolic pressure are prone to the marked elevation of the capillary wedge pressure during exercise.

What is the role of BNP and NT-proBNP in predicting low LVEF?

Echocardiographic LVEF is an arbitrary and objective marker of cardiac dysfunction and is helpful to identify patients with poor prognosis. Although echocardiography remains a gold standard for the detection of left ventricular dysfunction, NPs are attractive for screening for left ventricular systolic

Address for correspondence: Prof. Krystyna Łoboz-Grudzień, Department of Cardiology, T. Marciniak Hospital, Traugutta 116, 50–420 Wrocław, Poland, e-mail: kloboz@wp.pl

dysfunction in asymptomatic populations with subclinical disease [10]. In the study of Koç et al. [9], a strong negative correlation between NT-proBNP and ejection fraction was found and an NT-proBNP cut-off value was defined for the prediction of LVEF < 30% in a population with a broad spectrum of NYHA classes (I–IV). Hence, it could be supposed that NP might replace ejection fraction in daily practice. Hetmanski et al. [11] measured plasma BNP values and compared them to echocardiographic measurements of left ventricular function in 653 prescribed loop diuretic patients in a large community based population. The study demonstrated a significant correlation between plasma BNP and echocardiographic ejection fraction. However, the area under the ROC curve was 0.587 indicating poor sensitivity and specifity in diagnosis of HF in the general community, which is supported by the wide range of values of BNP. Tang et al. [12] reported that in symptomatic patients up to 21% have levels of BNP below the threshold criteria value < 100 pg/mL. The suggested explanation is that patients with end-stage HF may have very low NP levels because the ability of their ventricles to release NP may have become exhausted; another explanation could be that they respond to the optimal therapy. The intraindividual heterogeneity of plasma BNP value might affect our ability to use a single "cutoff" value as a target to guide therapy. Hence, there is a lack of evidence supporting the concept that NP may replace ejection fraction. The complex evaluation joining BNP and imaging test seems to be a rational approach.

The value of NP in the evaluation of left ventricular diastolic dysfunction

Left ventricular diastolic dysfunction is a common finding in patients with left ventricular systolic dysfunction, and a restrictive filling pattern estimated by Doppler echocardiography is associated with an increased mortality rate. BNP can be considered the most powerful predictor of the restrictive pattern in patients with severe left ventricular dysfunction [13, 14].

The severity of diastolic dysfunction is correlated to the increased levels of both BNP and NT-proBNP. It is interesting that in the study by Koç et al. [9] linear regression analysis showed that left atrial end-diastolic dimension and NT-proBNP are the most significant predictors for left ventricular E/A ratio, reflecting the restrictive filling pattern. The restrictive filling pattern is associated with increasing left ventricular end-diastolic and left atrial pressure. Furtermore Lubien et al. [15] reported that BNP can detect the presence of diastolic abnormalities even in patients with normal systolic function, but they were not able to differentiate the various diastolic filling patterns.

The use of BNP and NT-proBNP as prognostic markers in heart failure

The prognostic value of risk factors such as ejection fraction, complex arrhythmia, and heart failure symptoms is limited [16]. There are several data regarding prognostic implications of different neurohormonal markers, including BNP and NT-proBNP. NT-proBNP was superior to LVEF in predicting mortality and heart failure occurrence in the Australia/New Zealand Heart Failure Study and in the COPERNICUS NT-proBNP substudy [17, 18]. In accordance with those studies, the current paper by Koç et al. [9] indicated that among several variables only NT-proBNP, left ventricular mass index, and resting heart rate were independent predictors of future cardiovascular events, but not LVEF. The authors also defined the cut-off value of NT-proBNP for the prediction of cardiovascular events. However, to define cutoff points for quantifying the severity of HF and for risk stratification, further studies based on large cohorts are required.

Recently, NP levels have been shown to be modulated by medication. The relationship between a drop in NP level and the improvement of symptoms suggests that NP tailored therapy may be an attractive approach in future.

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