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What does an Elevated N-terminal Pro-brain Natriuretic Peptide (NT-pro-BNP) Mean in my Renal Patient?

Renal Hastamda Artmış bir N-terminal Pro-beyin Natriüretik Peptidi (NT-Pro-BNP) ne Anlama Gelir?

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ABSTRACT

The N-terminal pro-brain natriuretic peptide (NT-pro-BNP) is released in response to volume expansion and/or increased tension on cardiac ventricular myocytes. In non-uremic patients, NT-pro-BNP is a useful diagnostic and prognostic biomarker for diagnosis and risk assessment of patients with heart failure. However, impaired kidney function is associated with elevated circulating levels of NT-pro-BNP. The present review summarizes the literature on NT-pro-BNP in kidney disease, both acute and chronic. We attempt to highlight the importance of estimating kidney function before interpreting an elevated NT-pro-BNP measurement. We also suggest that NT-pro-BNP is not a reliable marker of heart failure in the acute setting, but that longitudinal changes may be of value when tracking volume status in this patient group.

KEY WORDS: Chronic kidney disease, Heart failure, NT-proBNB natriuretic peptides, Cardiac biomakers

ÖZ

N-terminal pro-beyin natriüretik peptidi (NT-pro-BNP) kardiyak ventriküler miyositlerde artmış gerilim ve/veya hacim artmasına cevaben salınır. Üremik olmayan hastalarda NT-pro-BNP kalp yetmezlikli hastaların tanısı ve risk değerlendirmesi için faydalı bir tanısal ve prognostik biyomarkerdir. Ancak, bozulmuş böbrek fonksiyonu artmış dolaşan NT-pro-BNP düzeyleriyle ilişkilidir. Bu derleme hem akut hem kronik böbrek hastalığında NT-pro-BNP ile ilişkili literatürü özetlemektedir. Yükselmiş bir NT-pro-BNP ölçümünü yorumlamadan önce böbrek fonksiyonunu tahmin etmenin önemini vurgulamaya çalışıyoruz. Ayrıca NT-pro-BNP'nin akut durumda kalp yetmezliğinin güvenilir bir markeri olmadığını ama bu hasta grubunda hacim durumunu izlerken longitudinal değişikliklerin önemi olabileceğini belirtiyoruz.

ANAHTAR SÖZCÜKLER: Kronik böbrek hastalığı, Kalp yetmezliği, NT-proBNB natriuretic peptidler, Kardiyak biobelirteçler

INTRODUCTION

Physiologic and pathologic states leading to volume expansion and/or increased tension on left ventricular myocytes engender the release of cardiac natriuretic peptides (1). The most well-studied of these, brain natriuretic peptide (BNP) is a 32 amino acid peptide hormone. Biologically active BNP is the remaining part of a genetically transcribed prohormone, which is cleaved to form BNP and N-terminal (NT)-pro-BNP (76 amino acids) both of which can be measured in the circulation by immunoassay (2). Cardiac myocytes constitute the major source of production of these peptides, and the main stimulus for peptide synthesis and secretion appears to be myocyte stretch. In contrast to the closely related atrial natriuretic peptides (ANP/NT-proANP), which originate mainly from atrial tissue, BNP and NT-pro-BNP are mainly produced by ventricular myocytes (1). Of clinical interest, ventricular (NT-pro)BNP production is upregulated in cardiac failure and following a myocardial infarction, probably due to increased mechanical stretch (1, 2). After secretion, BNP binds

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to the natriuretic peptide receptor type A, causing increased intracellular cGMP production and thus inducing diuresis, vasodilatation, inhibition of renin and aldosterone production as well as cardiac and vascular myocyte growth and leading to decreased cardiac preload (1, 2). In mice, knockout of the BNP gene leads to cardiac fibrosis, while BNP over-expression leads to hypotension and bone malformation (3). BNP is cleared from plasma through binding to the natriuretic peptide clearance receptor type C, and appears relatively resistant to proteolysis by neutral endopeptidases (4). In contrast, NT-pro-BNP is thought to be principally cleared by renal excretion, but these mechanisms await further study (4, 5). Consequently, the half-life of BNP is 20 minutes, whereas the half-life of NT-pro-BNP is 120 minutes (6) leading to approximately six-fold higher concentrations of NT-pro-BNP than BNP despite their equivalent secretion.

Chronic kidney disease (CKD) and congestive heart failure (CHF) are both common diseases associated with elevated NT-pro-BNP in epidemiological studies. While the prevalence of CKD is estimated at 20% in the whole population (7), and as high as 37.8% of the Western population above 70 years old (8), CHF is thought to be present in more than 5% of the general population (9). There is also a significant overlap, with more than 70% of CKD patients are thought to suffer from CHF (10). As there are significant interactions between the heart and kidneys in both health and disease, this significant comorbidity deserves special attention. An especially important aspect is the marked dysregulation of multiple central physiological axes that occur with CKD and that have important implications for both the detection of and the risk of developing CHF, as well as its' therapy. We will here attempt to review one such aspect, namely the marked importance of knowing kidney function when interpreting an elevated NT-pro-BNP measurement obtained in order to diagnose or stage CHF.

NT-pro-BNP and the confounder of renal function

Given the large overlap between patients with CKD and CHF, it is of interest to note that NT-pro-BNP is uniformly reported to be elevated in patients with significantly reduced glomerular filtration rate (GFR) (11-15). While CKD patients are also at high risk of CHF, as well as other inducers of myocardial stress such as fluid overload and arterial stiffness, it is noteworthy that the kidney tubulus is an important target for NT-pro-BNP action while the kidney also plays a role in its' clearance (16, 17).

The interpretation of an elevated NT-pro-BNP in conjunction with a low GFR is further complicated by the greatly increased risk of CVD observed with declining GFR. Indeed, while the 3-years cardiovascular-event risk in an individual with a glomerular filtration rate (GFR) of 90 ml/min is 15%, it rose to 40% in those with a GFR of 30 ml/min (18). Also, declining GFR and increasing albuminuria independently predicts the amount of calcified atherosclerotic plaques in the coronary arteries (19) as well as the risk of clinical CVD events (20). However, it should be noted that the reverse association is also true; prevalent CVD is associated with a higher incidence of CKD. About one-quarter of patients with coronary artery disease, one-third of patients with acute myocardial infarction and almost half of patients with congestive heart failure have an estimated GFR of less than 60 ml/min (21-23).

NT-pro-BNP and cardiac dysfunction

Clinically, circulating BNP and NT-pro-BNP are routinely used to diagnose heart failure, as well as for prognosticating heart failure and acute coronary syndromes (24). Both BNP and NT-pro-BNP have been shown to be strong predictors of morbidity, mortality and recurrent cardiovascular events independent of other risk factors, including conventional (25) factors and biomarkers representing the acute-phase reaction and endothelial activation, and even from left ventricular (LV) systolic function estimated by clinical methods (i.e. by echocardiography or contrast ventriculography). Moreover, NT-pro-BNP appears to have a better prognostic ability than BNP (12). For example, in a substudy of COPERNICUS (26), consisting of 1011 patients with symptomatic chronic CHF and EF<25%, subjects with a NT-pro-BNP above the median (1,767 pg/ml) showed a 2.7-fold increased risk of death as compared to those below the median (27, 28). Also, Masson et al. (28) report in a direct comparison of BNP and NT-pro-BNP in 3916 patients with chronic and symptomatic heart failure that NT-pro-BNP was superior to BNP as a predictor of both morbidity and mortality, as well as a better marker of the risk of hospitalizations for heart failure. Interestingly, an elevated NT-pro-BNP is a strong predictor of mortality even in stable patients at least 6 months after an acute coronary event, even in the absence of any clinically apparent heart failure (29). Population-based studies also suggest that plasma levels of BNP and NT-pro-BNP are useful screening tests for heart failure (30, 31) and asymptomatic LV dysfunction (5).

While BNP and NT-pro-BNP are thus useful markers of prognosis in CHF, the exact reasons are unclear. First, while myocyte stretch may be the major driver of BNP and NT-pro-BNP production, many other factors also contribute (32). Thus, elevated BNP and NT-pro-BNP concentrations occur with the presence of LV dysfunction (33), abnormalities in heart diastolic function (34), right ventricular dysfunction (35), valvular heart disease (36), abnormalities in heart rhythm (37), an elevated pulmonary artery pressure (36), and the presence and severity of ischemic heart disease (38).

Clinical relevance of an elevated NT-pro-BNP in a kidney patient

BNP and NT-pro-BNP are highly elevated in patients with chronic kidney disease (CKD) (25, 39, 40). Thus, in a survey of asymptomatic patients with CKD who did not yet require

dialysis, more than half had NT-pro-BNP levels above normal (12). Meanwhile, in patients who had ESRD and received hemodialysis (HD) or peritoneal dialysis (PD), BNP and NT-pro-BNP levels were uniformly increased compared with normal values (13-15). The exact reasons for this elevation remain to be elucidated, but one of the major contributing factors is likely the very high prevalence of LV structural and functional abnormalities. However, as NT-pro-BNP is known to be cleared by the kidneys (16, 17), a gradual increase in circulating levels due to decreased renal metabolism may be expected with progressive loss of kidney function. Furthermore, the kidney is the major organ for excretion of sodium ions and water, both very much implicated in circulating fluid volume and thus cardiac load. It is thus likely that part of the elevation in NT-pro-BNP observed in CKD patients is driven by an actual cardiac stress caused by hypervolemia and impaired fluid balance. As their name implies, the natriuretic peptides strive to increase the excretion of sodium in the kidneys, leading to a greater loss also of water due to tubular secretion, and subsequently to an amelioration of hypervolemia (17, 41).

Clinically, both BNP and NT-pro-BNP levels are strongly correlated with LV hypertrophy and systolic dysfunction in patients with CKD (42) suggesting a physiological link between hypervolemia, cardiac hypertrophy and the release of natriuretic peptides. For example, in a recent study by Takami *et al*. (40), plasma BNP was a reliable marker of LV overload and a powerful predictor of heart failure in nondialyzed patients with CKD.

The elevation of BNP and NT-pro-BNP has also been shown to reflect the presence of myocardial ischemia in asymptomatic patients with CKD (39). Indeed, when a recent study by Satyan et al. (14) compared the prognostic value of NT-pro-BNP with cardiac troponin T (cTnT) in asymptomatic HD patients, NT-pro-BNP was more strongly correlated with LV systolic dysfunction and both all-cause and cardiovascular mortality. Also, in another study of PD patients, NT-pro-BNP emerged as a more powerful predictor of mortality, cardiovascular death and events, as well as congestive heart failure than hsCRP. Finally, Zoccali et al. (42) found that BNP, but not ANP, was an independent predictor of mortality in CKD patients also after adjusting for LV mass and ejection fraction.

Despite the previously described differences in clearance, no studies have compared the prognostic value of BNP and NT-pro-BNP in the dialyzed ESRD population. A head-to-head comparison in nondialysis patients with CKD somewhat surprisingly showed similar correlations between BNP and NT-pro-BNP with renal dysfunction, LV hypertrophy, and coronary artery disease (43).

Presented with an elevated NT-pro-BNP in a patient, several factors must be considered. Patient history is of the utmost importance, as it may reveal previously diagnosed kidney or heart disease. Declining kidney function with age is likely to contribute to an elevation in NT-pro-BNP in an elderly patient, and recent studies have also reported a decrease in the clearance of natriuretic peptides from plasma in older patients, even in the absence of renal dysfunction (44). Also, impairment of non-renal clearance mechanisms, such as clearance through natriuretic peptide receptors in human platelets likely contributes to elevated concentrations of NT-pro-BNP (45). Because of these effects, age specific cut-offs are needed to correctly interpret an elevated level of NT-pro-BNP or BNP. However, hese cut-offs must also take into account the estimated GFR of the patient. For example, recently published cut-off values for the measurement of NT-pro-BNP using a commercial electrochemiluminescence kit (Elecsys proBNP; Roche Diagnostics Corp, Indianapolis, IN, USA) to rule out structural heart disease suggested the cut-off of 125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years and older. From available data (11-15), it is evident that very few (if any) patients with significantly reduced GFR will ever have values as low as these, and all will thus be classified as having CHF even in the absence of objective signs such as those from pulse-wave Doppler or tissue velocity imaging of the heart. Clearly, large studies measuring NT-pro-BNP and eGFR concurrently with objective CHF need to be conducted to develop useful guidelines for our patients. In the mean time, we urge caution when interpreting an NT-pro-BNP value in any patient with a eGFR below 60 mL/min/1.73 m^2, and do not recommend it as a risk-marker of CHF in this population. Future studies will also have to evaluate the usefulness of intra-patient longitudinal variability of NT-pro-BNP as a marker of fluid status in these patients.

In summary, when utilizing NT-proBNP measurements as a marker of cardiovascular disease and volume status, kidney function is an important confounder and must be taken into account when interpreting the results.

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