Editorial Commentary

Can a Cardiac Peptide Predict Mortality in Human Hypertension?

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See related article, pp 702–709

Since 1981, with the seminal work by de Bold and coworkers, the function of the heart as an endocrine organ has been increasingly appreciated.1 In response to myocardial stretch and volume overload, atrial and ventricular myocytes synthesize and secrete the biologically active atrial (ANP) and B-type (BNP) natriuretic peptides, which are generated from their prohormones by the proconvertases corin and furin. Importantly, ANP and BNP are generated together with their inactive amino-terminal fragments NT-proANP and NT-proBNP. Both ANP and BNP play key roles in the regulation of electrolytes and water balance in the overall control of blood pressure and intravascular volume. This key role in blood pressure homeostasis was predicted based on the cardiorenal response to their infusion in animals and humans, as well as from studies in novel murine models in which their genes (NPPA and NPPB) or common receptor (GC-A) were genetically disrupted. Indeed, most recently, genetic variants of the ANP and BNP genes that lie in tandem on chromosome 1 have translated into increases in circulating ANP and BNP with lower blood pressure and reduced risk for hypertension.2

Most importantly, studies have revealed the pleiotropic properties of ANP and BNP that go beyond salt and water homeostasis and include properties of renin-angiotensin-aldosterone system inhibition, sympatho-inhibiting activity, suppression of cardiac fibrosis and hypertrophy, enhancement of lusitropic function, and metabolic protective properties.1,3

Again, these actions are mediated by GC-A and the second messenger cGMP.

Circulating BNP, and, most importantly, NT-proBNP, have emerged worldwide as useful biomarkers that aid in the diagnosis of heart failure (HF). Recently, studies in the general population, as well as in the elderly in the general community, have demonstrated that NT-proBNP in the absence of HF is a powerful prognostic biomarker for increased mortality and for future HF.4 Specifically, in the general community, those with risk factors alone (stage A HF) or structural abnormalities of the heart without symptoms of HF (stage B HF) who had an NT-proBNP above the 80 percentile but with values below that seen in symptomatic HF were at high risk for future HF. Importantly, an additional key finding was that the prognostic power of NT-proBNP for mortality and future HF was absent in humans without cardiovascular risk factors or structural abnormalities.

In the current issue, Paget et al5 take the prognostic use of NT-proBNP into an important clinical population. Specifically, they sought to address the prognostic value of NT-proBNP in predicting all-cause mortality in hypertensive patients. The predictive value of NT-proBNP was assessed on top of traditional risk factors, ambulatory blood pressure, renal function, and 2 of the most widespread ECG indexes of left ventricular hypertrophy (LVH), the Sokolov-Lyon index and the R-wave amplitude in lead aVL. A total of 684 hypertensive patients with no history or symptoms of HF were followed for a mean period of 5.7 years. In this cohort, LVH prevalence assessed through ECG was 14%, revealing that the cohort in analysis was comparable to a common primary care sample of hypertensive patients.6 The cohort was divided into tertiles according to NT-proBNP plasma levels: (1) group 1, NT-ProBNP <50.8 pg/mL; (2) group 2, 50.8 pg/mL ≤ NT-ProBNP <133 pg/mL; and (3) group 3, NT-proBNP ≥133 pg/mL. Importantly, the mortality risk increased with NT-proBNP levels. Indeed, the group characterized by the highest levels of NT-proBNP and below levels observed with overt HF showed a 3.3-fold increased risk of all-cause mortality when compared with group 1. Moreover, the prognostic value of NT-proBNP was independent of traditional cardiovascular risk factors, including age, systolic blood pressure, sex, hyperlipidemic status, diabetic status, smoking, body mass index, history of cardiovascular disease, renal disease, and ECG LVH.

To exclude any possible modulating effect of LVH on the association between plasma NT-proBNP and all-cause mortality, they performed a further analysis in a subgroup of patients with no ECG evidence of LVH. This analysis confirmed the results obtained for the whole cohort, because NT-proBNP remained a significant predictor of mortality even in patients free from LVH. Thus, the interesting study by Paget et al5 confirmed once more the prognostic value of NT-proBNP as a reliable biomarker for predicting mortality risk in a cohort of hypertensive patients with and without LVH. Importantly, the predictive value of NT-proBNP is independent of traditional risk factors, including systolic blood pressure, renal disease, or ECG indexes of LVH in human hypertension.

The study underscores several points of interest. The large sample allows confirmation of what has already been observed in smaller cohorts of previous studies: NT-proBNP is a powerful biomarker in the assessment of mortality risk in...
hypertension. The NT-proBNP plasma levels of 133 pg/mL used as a cutoff to identify an increased risk of mortality is consistent with the values reported previously by McKie et al\textsuperscript{4} in a random sample of the US general population and by Rutten et al in the Rotterdam Study.\textsuperscript{7} It should be noted that a slightly higher threshold of 170 pg/mL plasma levels of NT-proBNP was proposed by Olsen et al\textsuperscript{8} as an indicator of increased risk for hypertensive subjects in the Losartan Intervention for Endpoint Reduction in Hypertension sub-study. Furthermore, the present study analyzed not only high-risk hypertensive patients but also a hypertension cohort representative of that seen in the primary care setting, including low-risk hypertensive patients with no ECG evidence of LVH. Unfortunately, no information is provided with regard to diastolic dysfunction, filling pressures, and echocardiographic parameters. However, we do not consider this lack of data as a major limitation. The exclusion of hypertensive subjects affected by HF or presenting HF-related symptoms has probably reduced the prevalence of diastolic dysfunction in the study cohort to a small number. Moreover, NT-proBNP, already recognized as a reliable biomarker of preclinical ventricular diastolic dysfunction in the general community,\textsuperscript{9} would have identified those patients as high-risk subjects.

Where do we go from here based on the findings reported by Paget et al?\textsuperscript{5} First, we need to understand the mechanisms by which hypertension, even in the absence of LVH, increases circulating BNP and NT-proBNP. Are there local myocardial humoral factors that are activated in hypertension that increase production of BNP in cardiomyocytes? What are they and how are they regulated? Second, we need clinical trials with more aggressive antihypertensive medications in high-risk subjects with the highest levels of circulating NT-proBNP to verify whether we can reduce the stress on the heart and decrease circulating BNP to see whether NT-proBNP reduction is associated with a decrease in mortality in hypertension.

In summary, evidence has clearly demonstrated that NT-proBNP is a reliable predictor of mortality and cardiovascular risk in the context of human hypertension independent of traditional risk factors, including ambulatory systolic blood pressure, renal disease, and ECG indexes of LVH. This suggests the importance of NT-proBNP in the assessment of hypertensive patients in order to perform a more accurate risk evaluation and in the future leading to a possible NT-proBNP guided therapy able to achieve a more favorable clinical outcome.

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Disclosures
None.

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