

Natriuretic peptides in cardiac and renal failure

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Summary

Natriuretic peptides are a family of vasoactive peptides which are involved in the control of water and sodium homeostasis. They are thus part of a regulatory system that is commonly activated in cardiac as well as renal failure.

Formerly the B-type natriuretic peptides BNP and NT-proBNP in particular gained importance as reliable markers for diagnosis and risk stratification in heart failure patients. More recently it has been shown that the plasma concentrations of these cardiac neurohormones are also increasingly elevated in patients with progressively impaired renal function. Nevertheless, the natriuretic peptides were also found to be of diagnostic and prognostic value in this group of patients, who are at enormously elevated risk of cardiovascular disease, though with higher cutoffs. In addition, most recent data indicate that high BNP or NT-proBNP levels are associated with accelerated progression of chronic kidney disease. B-type natriuretic peptides may therefore evolve as markers of the cardiorenal syndrome.

Natriuretic peptides

Natriuretic peptides are a family of naturally occurring polypeptide hormones involved in the regulation of body fluid homeostasis and vascular tone. This family includes three major structurally related but genetically distinct natriuretic peptides: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). The mature peptides share a common 17-amino acid ring structure formed by a disulphide

linkage essential for receptor binding. ANP and BNP are cardiac hormones mainly secreted from the atrium and the ventricle respectively, whereas CNP is of endothelial origin. ANP and BNP bind to the natriuretic peptide A-receptor (NPR-A) and mediate the biological actions of natriuresis, vasodilatation and renin inhibition. In contrast, CNP lacks renal actions but causes vasodilatation via binding to the NPR-B.

Because of their utmost significance as diagnostic and prognostic parameters, this article will focus on B-type natriuretic peptides. The B-type natriuretic peptide is synthesised in cardiac myocytes as a 134 amino acid pre-pro hormone, which is subsequently cleaved to yield a 108 amino acid pro-peptide that is stored in secretory granules within the myocytes. In response to the appropriate stimulus, pro-BNP is proteolytically cleaved into the biologically active mature BNP and the biologically inactive N-terminal (NT)-proBNP (76 amino acids), which are released into the blood stream (Figure 1). Although BNP is also produced in atrial tissue and in right ventricular myocardium, highest concentrations of BNP have been found in the myocardium of the left ventricle.

The mature B-type natriuretic peptide is a 32-amino acid polypeptide hormone which is rapidly released by the ventricles of the heart in response to myocardial stretch. Upon release the neurohormone affects body fluid volume (through natriuresis and diuresis) and vascular tone (Figure 2). Since high ventricular filling pressure is a common feature in congestive heart failure (CHF), plus the fact that body fluid homeostasis and vascular tone play an essential role in the pathophysiology of CHF, BNP has been investigated as a candidate marker for cardiac neurohormonal activation in patients with CHF.

B-type natriuretic peptides as diagnostic and prognostic parameters of heart failure

Dyspnoea is a common but unspecific symptom in heart failure and may therefore be misdiagnosed. A series of studies have investigated the relevance of BNP (and NT-proBNP) in the diagnosis and prognosis of congestive heart failure [1]. First evidence for the value of BNP as a diagnostic marker for heart failure came from the prospective *Breathing Not Properly Multinational Study* (BNPMS) which investigated whether BNP is able to differentiate between dyspnoea due to heart failure and dyspnoea caused by other diseases [2]. 1586 patients who presented to an emergency department with acute dyspnoea underwent blood BNP measurement. BNP plasma concentrations were markedly higher in patients with clinically diagnosed CHF than in those without CHF. A plasma value >100 ng/L diagnosed CHF with a sensitivity of 90% and a specificity of 76% [2]. Moreover, multivariate analysis revealed that BNP was an independent predictor of CHF. BNP increased the diagnostic accuracy of initial clinical judgment from 74 to 81% [3]. In many studies since then both BNP and NT-proBNP have been found to improve the diagnosis of heart failure [1]. Swiss and Canadian studies showed that the use of BNP and NT-proBNP respectively in the acute differential diagnostics of dyspnoea helps to shorten the time to initiating appropriate treatment of heart failure as well as the duration of intensive care and hospitalisation [4, 5], which ultimately translated into a reduction in costs. In consequence, determination of BNP or NT-proBNP has been recommended by many guidelines for the diagnosis of acute heart failure [6, 7]. Figure 3 shows a widely accepted decision tree (8). Plasma concentrations of BNP and NT-proBNP are not only elevated in pa-

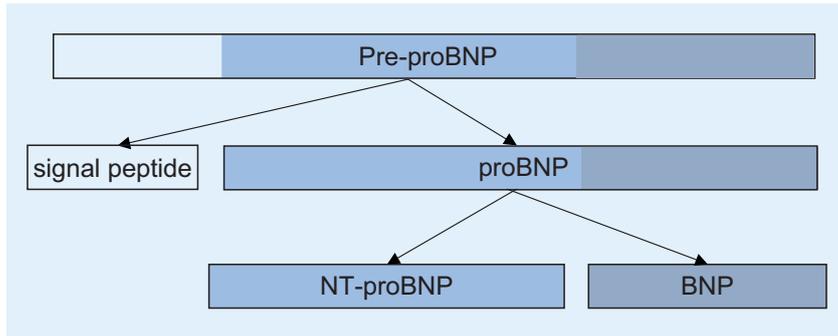


Figure 1. Biosynthetic pathway of human BNP.

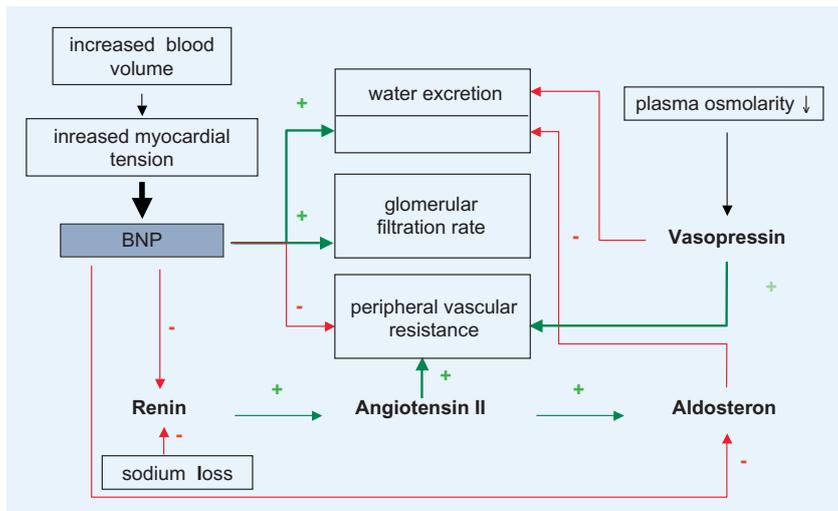


Figure 2. Physiological actions of BNP.

tients with decompensated heart failure (HF) but correlate with the severity of HF as stratified by the New York Heart Association (NYHA) functional classification [1, 6, 7, 8]. Further, BNP levels are elevated in the plasma of patients with diminished left ventricular ejection fraction (LVEF) with a clear association between the increase in BNP concentration and reduction of LVEF [1, 6, 7, 8].

Besides being a valuable diagnostic tool in heart failure, plasma levels of BNP and NT-proBNP also yield prognostic information for patients with CHF as well as for those with acute coronary syndromes. High plasma levels of either BNP or NT-proBNP, either at baseline or after initiation of treatment, have been found to be independent predictors of mortality in those patients [1, 9, 10]. In addition, BNP and NT-proBNP were also found to be a prognostic marker in patients who underwent cardiac surgery for coronary revascularisation, correction of valve defects or inborn dysplasias of the heart [11, 12]

Both BNP and NT-proBNP show similar diagnostic and prognostic quality in heart failure patients [1]. This is not surprising, as NT-proBNP and BNP are derived from a common precursor and are both released after cleavage into the blood stream. However, despite this common origin blood levels of the two molecular species differ significantly, mainly due to the different clearance characteristics. BNP, the smaller peptide, is the biologically active compound and is cleared via specific natriuretic peptide receptors as well as neutral endopeptidases in the blood. In contrast, NT-proBNP, the larger and biologically inactive peptide, is thus far assumed to be cleared solely by renal excretion. The half-life of BNP is much shorter than that of NT-proBNP (22 minutes vs. approximately 120 minutes). Thus NT-proBNP is more stable and exhibits less fluctuation over time. NT-proBNP can be determined in all kinds of plasma and serum specimens, whereas BNP requires EDTA plasma or EDTA blood. In addition, upon storage NT-proBNP is more stable than BNP.

Since the prognostic value of natriuretic peptides has usually been investigated in stored plasma samples, this may explain why NT-proBNP was a somewhat more efficient prognostic marker than BNP.

B-type natriuretic peptides in renal disease

BNP and NT-proBNP plasma levels have not only been found to rise in heart failure (Figure 4). Markedly elevated plasma levels of BNP and NT-proBNP can be found in pulmonary embolism, as the response of the accompanying pulmonary hypertension and right heart failure, as well as in sepsis [8, 13, 14]. Moderately elevated plasma levels of BNP and NT-proBNP are found in several conditions that interfere with cardiac function, such as ventricular dysfunction, coronary heart disease, pulmonary hypertension and hyperthyroidism, and also in sepsis, subarachnoidal haemorrhage, liver cirrhosis and renal failure [8, 13–17].

Since patients with chronic kidney disease (CKD) are at extremely high cardiovascular risk and frequently experience coronary events and heart failure, this increase of BNP and NT-proBNP levels has initially been considered an unwanted confounder in the diagnosis of CHF. However most recent studies have shown that both BNP and NT-proBNP are also suitable diagnostic and prognostic biomarkers of heart failure in patients with chronic kidney diseases [18–22], requiring, however, higher diagnostic cutoffs (Figure 3c).

However, it is as yet unknown how renal disease affects plasma concentrations of BNP or NT-proBNP. To unravel the underlying mechanism we investigated the relevance of BNP and NT-proBNP in patients with mild to moderate renal failure, and their prognostic value with respect to renal function [17].

Like others we found that BNP and NT-proBNP plasma concentrations rise in parallel with decreasing renal function: both BNP and NT-proBNP were progressively higher in patients with progressively declining measured and estimated glomerular filtration rate (GFR) respectively [17, 23].

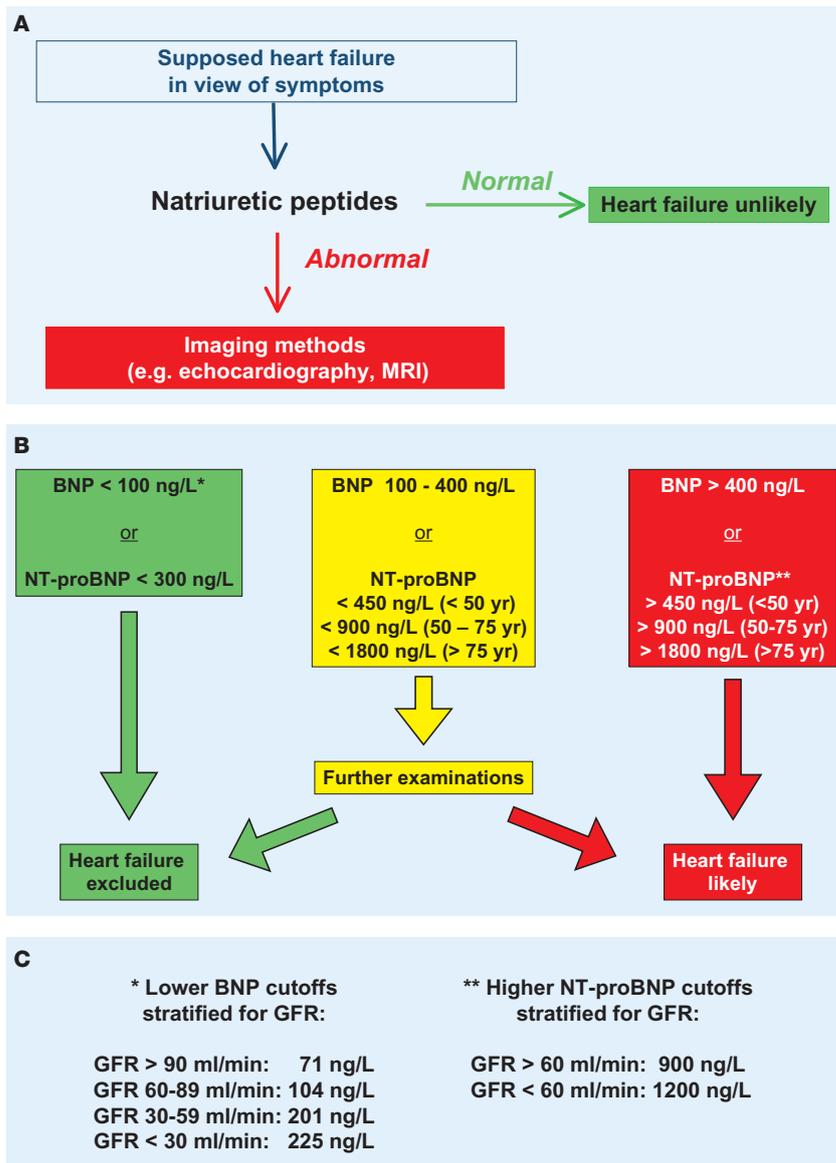


Figure 3. Algorithms for the use of BNP and NTproBNP in the diagnosis of heart failure. A) General algorithm [7]. B) Suggested cutoffs for BNP and NT-proBNP [8]. C) Suggested lower and higher cutoffs for BNP [18] and NT-proBNP [20] respectively according to glomerular filtration rate.

<u>Markedly increased levels</u> (BNP > 500 pg/mL; NT-ProBNP > 1000 pg/mL)	<u>Moderately increased levels</u> (BNP 100 - 500 pg/mL; NT-ProBNP 250 - 1000 pg/mL)
<ul style="list-style-type: none"> • Decompensated heart failure • Pulmonary hypertension • Acute pulmonary embolism • Septic shock 	<ul style="list-style-type: none"> • Ventricular dysfunction • Coronary heart disease • Pulmonary hypertension • Acute pulmonary embolism • Cor pulmonale • Septic shock • Renal insufficiency • Liver cirrhosis • Subarachnoidal haemorrhage • Hyperthyroidism

Figure 4. Major causes of severe or moderate increases in BNP or NT-proBNP.

In 227 predialysis patients stratified into groups according to baseline stages of GFR, as defined by the Classification of the National Kidney Foundation, median BNP levels increased from 34 ng/L (GFR ≥ 90 ml/min/1.73m²) to 57 ng/L (GFR < 30 ml/min/1.73m²). For NT-proBNP this effect was much more pronounced where the median NT-proBNP level increased from 39 ng/L in patients with GFR ≥ 90 ml/min/1.73m² to 456 ng/L in patients with GFR < 30 ml/min/1.73m² [17].

Furthermore, BNP and NT-proBNP also correlate with the progression of renal impairment. In 177 patients followed over a period of up to 7 years, patients with high BNP and NT-proBNP baseline values were more likely to progress to renal endpoints defined as doubling of plasma creatinine or end stage renal disease [17]. Thus, both increased BNP and NT-proBNP plasma concentrations are associated with accelerated progression of mild and moderate primary chronic kidney disease (CKD) to renal endpoints. However, after adjustment for other factors known to be related to progression of chronic kidney disease, NT-proBNP but not BNP was found to be an independent predictor of accelerated chronic kidney disease progression. NT-proBNP therefore provides additional prognostic information to the established risk markers of CKD progression.

The mechanisms leading to the increase in the concentrations of B-type natriuretic peptides in CKD have not been totally clarified. Since NT-proBNP levels rise much more than BNP levels, renal retention is the most frequently offered explanation of this phenomenon. However, the results of published studies contradict this hypothesis: in patients with renal impairment increased rather than decreased urinary concentrations of BNP have been found compared to healthy controls. In the latter, it has also been found that urinary NT-proBNP correlates significantly with plasma NT-proBNP concentrations and plasma creatinine levels. These inverse correlations between urinary BNP or NT-proBNP levels and renal function suggest that renal retention is not the

only mechanism for elevated B-type natriuretic peptide levels in patients with renal impairment. Rather, elevated BNP and NT-proBNP levels may arise from increased cardiac release in those patients.

Since B-type natriuretic peptides are released from cardiomyocytes, it has been suggested that elevations in BNP and NT-proBNP reflect an underlying heart problem.

However, despite the heart being the main source of B-type natriuretic peptides, a close correlation has been found between BNP, or particularly NT-proBNP, and renal function represented by GFR. In the multivariate regression analysis NT-proBNP remained a significant predictor of accelerated progression of CKD to the combined as well as to the isolated endpoints even after adjustment for GFR and further parameters associated with progression of CKD. In addition, the estimated GFR (eGFR) and left ventricular mass have been found to be independent confounders of BNP and NT-proBNP plasma concentrations in CKD patients. For patients with CKD it therefore seems likely that the progressive elevation of BNP and NT-proBNP with decreasing renal function reflects cardiac involvement in the form of a cardiorenal syndrome. Also, the frequent coincidence of CKD with left ventricular hypertrophy (LVH) and CHF, as well as the correlation of severity of renal impairment with left ventricular dysfunction and CHF, point to a mutual relationship between renal and cardiac impairment.

As CKD progresses, the salt- and volume-regulating capabilities of the kidney are progressively impaired. In consequence, extracellular fluid volume expands as GFR is reduced. We therefore suggested that the inverse

relationship between GFR and plasma BNP, as well as NT-proBNP concentrations, reflect increased volume load of the heart, resulting from the volume expansion due to restricted GFR. Additional influence on BNP and NT-proBNP plasma concentrations may derive from the increased activity of the renin-angiotensin-aldosterone-system (RAAS) in CKD and even in very early and not yet clinically overt stages of cardiac failure. As angiotensin II has been found to induce BNP in cardiac myocytes, increased plasma concentrations of BNP and NT-proBNP in renal failure, and their association with a poor renal prognosis, may reflect activation of RAAS in its supposed role as promoter of CKD. A (patho-) physiological concept has therefore emerged in which increased plasma concentrations of either BNP or NT-proBNP in renal failure not only reflect impaired glomerular filtration but a counter-regulatory response of the heart to pathophysiological changes in haemodynamics and water homeostasis in renal dysfunction. BNP and NT-proBNP in particular may thus be considered markers of the cardiorenal syndrome, a pathophysiological condition which amplifies the progression of both cardiac and renal failure, leading to end stage renal disease and congestive heart failure.

Conclusion and outlook

Elevated plasma concentrations of BNP and in particular NT-proBNP indicate increased risk of accelerated progression of mild or moderate chronic renal failure, ultimately leading to end stage renal disease. Moreover, NT-proBNP provides additional prognostic information beyond that given by factors known to be related

to CKD progression. Therefore, and because increased B-type natriuretic peptide concentrations were previously found to indicate increased risk of cardiovascular events in CKD patients, these patients will benefit from determination of NT-proBNP plasma concentrations with respect to cardiovascular and renal risk stratification. Although NT-proBNP is not the biologically active peptide, it appears to be the more suitable prognostic parameter for monitoring the progression of the cardiorenal syndrome than active BNP itself. There may be several reasons for this: because of its longer half-life compared with BNP, NT-proBNP more stably reflects changes in haemodynamics. Also, the close relationship of NT-proBNP to renal function and the high sensitivity of NT-proBNP in identifying even a slight progression of renal dysfunction make NT-proBNP the more useful parameter for predicting the progression of renal failure.

It is intriguing to postulate that in CKD patients with elevated plasma levels of BNP or NT-proBNP therapeutic interventions aimed at improving cardiac function could slow down the progression of CKD. Intervention studies, which are needed to underpin this concept, could also provide evidence for the causal relationship between cardiac malfunction, increased B-type natriuretic peptide concentrations and CKD progression.

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