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Review

# Clinical value of natriuretic peptides in chronic kidney disease

*Carla Santos-Araújo*[a,*], *Adelino Leite-Moreira*[b], *Manuel Pestana*[c]

[a] *Department of Physiology and Cardiothoracic Surgery, Cardiovascular R&D Center and Nephrology and Infectious Diseases Research and Development Group, INEB (I3S) Faculty of Medicine, University of Porto, Porto, Portugal*
[b] *Department of Physiology and Cardiothoracic Surgery, Cardiovascular R&D Center, Faculty of Medicine, University of Porto, Porto, Portugal*
[c] *Nephrology and Infectious Diseases Research and Development Group, INEB (I3S) and Department of Renal, Urologic and Infectious Diseases, Faculty of Medicine, University of Porto, Porto, Portugal*

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ABSTRACT

According to several lines of evidence, natriuretic peptides (NP) are the main components of a cardiac-renal axis that operate in clinical conditions of decreased cardiac hemodynamic tolerance to regulate sodium homeostasis, blood pressure and vascular function. Even though it is reasonable to assume that NP may exert a relevant role in the adaptive response to renal mass ablation, evidence gathered so far suggest that this contribution is probably complex and dependent on the type and degree of the functional mass loss.

In the last years NP have been increasingly used to diagnose, monitor treatment and define the prognosis of several cardiovascular (CV) diseases. However, in many clinical settings, like chronic kidney disease (CKD), the predictive value of these biomarkers has been questioned. In fact, it is now well established that renal function significantly affects the plasmatic levels of NP and that renal failure is the clinical condition associated with the highest plasmatic levels of these peptides. The complexity of the relation between NP plasmatic levels and CV and renal functions has obvious consequences, as it may limit the predictive value of NP in CV assessment of CKD patients and be a demanding exercise for clinicians involved in the daily management of these patients.

This review describes the role of NP in the regulatory response to renal function loss and addresses the main factors involved in the clinical valorization of the peptides in the context of significant renal failure.

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* *Corresponding author.*
E-mail addresses: csaraujo@med.up.pt, csa0207@gmail.com (C. Santos-Araújo).
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## Utilidad clínica de los péptidos natriuréticos en la enfermedad renal crónica

*Palabras clave:*
Péptido natriurético tipo B
Pro-BNP aminoterminal
Insuficiencia cardiaca
Enfermedad renal crónica (ERC)
Diálisis

RESUMEN

Existen varias líneas de evidencia que indican que los péptidos natriuréticos (PN) son los componentes principales de un eje cardio-renal que actúa en situaciones clínicas de reducción de la tolerancia hemodinámica cardiaca mediante la regulación de la homeostasis del sodio, la presión arterial y la función vascular. A pesar de que parece razonable asumir que los PN puedan desempeñar un papel importante en la respuesta adaptativa a la ablación de masa renal, la evidencia acumulada hasta ahora sugiere que esta contribución es probablemente compleja y depende del tipo y el grado de pérdida de masa funcional.

En los últimos años los PN se han venido utilizando de manera creciente para diagnosticar, realizar un seguimiento del tratamiento y definir el pronóstico de varias enfermedades cardiovasculares (CV). Sin embargo, en varios contextos clínicos, como el de la enfermedad renal crónica (ERC), se ha puesto en duda el valor predictivo de esos biomarcadores. De hecho, actualmente está bien establecido que la función renal influye significativamente en los niveles plasmáticos de PN y que la insuficiencia renal es el estado clínico que se asocia a unos niveles plasmáticos más elevados de estos péptidos. La complejidad de la relación existente entre los niveles plasmáticos de PN y la función CV y renal tiene consecuencias obvias, puesto que puede limitar el valor predictivo de los PN en la evaluación CV de los pacientes con ERC y su uso puede requerir un esfuerzo adicional por parte de los clínicos encargados del manejo cotidiano de esos pacientes.

En esta revisión se describe el papel que desempeñan los PN en la respuesta reguladora ante la pérdida de función renal, y se abordan los principales factores involucrados en el valor clínico que se asigna a los péptidos en el contexto de una insuficiencia renal significativa.

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## Introduction

Natriuretic peptides (NP) are a family of hormones, sharing similar chemical structure and biological function, with relevant effects in cardiovascular (CV) physiology and pathology. The classical physiological role of NP includes promotion of renal excretion of sodium and water, contributing to blood pressure (BP) regulation. Additionally, NP also exert autocrine and paracrine actions within the circulation, namely vasodilation through the relaxation of vascular muscle cells, anti-fibrotic and anti-proliferative effects and regulation of renin, progesterone, endothelin and vasopressin secretion.[1]

In conditions of acute or chronic volume overload, NP may have an important role as counter-regulatory hormones that compensate the effects of vasoconstrictor-mitogenic-sodium retaining hormones, released by the sympathetic nervous system and the renin–angiotensin–aldosterone system, contributing to the maintenance of circulatory homeostasis.[2] Additionally, NP have been previously implicated as possible mediators of the integrated response to functional renal mass loss, with a distinct contributory role depending both on the degree of renal failure and on the time elapsed from the beginning of renal function decline.

The disease state associated with the highest circulating levels of NP is renal failure.[3] In this setting, increased NP circulating levels cannot linearly be interpreted as an expression of the activation of the NP system, as observed in the context of left ventricle (LV) wall stress associated with heart failure (HF) or volume overload. Indeed, previous evidence from a number of studies have suggested that plasmatic levels of NP may be regulated both by the rate of synthesis/cardiac release of NP and by the rate of removal of the peptides from the circulation.[4,5] As a consequence, NP circulating levels in patients with significant renal failure have to be interpreted in light of the severity of renal dysfunction and a higher cut point is expected as chronic kidney disease (CKD) stage advances.

The aim of the present work is to review the role of the NP system in the adaptive response to renal function loss and to address the clinical utility of NP circulating levels in the CV management of patients with severely impaired renal function.

## Natriuretic peptide system

Natriuretic peptides play a major role in the maintenance of sodium and body volume homeostasis and in the modulation of the proliferative and fibrotic responses.[6,7] Four members of the NP family have been described so far, all sharing a common 17-amino acid ring structure. Atrial NP (ANP) is produced in the cardiac atria and is secreted in response to an increased atrial wall tension.[8] B-type natriuretic peptide (BNP) is synthesized as an amino acid precursor protein (pro-BNP) and released from the ventricles in response to increased ventricular wall stress.[9] On secretion, the pro-BNP hormone is cleaved in a 1:1

equimolar ratio to a 32-amino acid C-terminal fragment (BNP) that is biologically active and a 76-amino acid N-terminal fragment (N-terminal pro-BNP – NT-pro-BNP), which is biologically inactive. Compared with BNP, NT-pro-BNP has the advantage of having a longer plasma half-life and lower biologic variation.[10] There are two types of C-type NP (CNP): a 22-amino acid form, more potent and secreted in the central nervous system and endothelial tissue in response to shear stress; and a 52-amino acid form.[11] All these types of NP can be detected in human plasma. D-type NP (DNP) is found in the venom of green mamba snake and the primary stimulus and main function are still currently unknown in humans.[12]

## B-type natriuretic peptide

B-type natriuretic peptide was originally isolated in extracts from porcine brain in 1988 but was rapidly recognized to be largely synthesized and released from the ventricles in response to LV wall stress.[13] BNP exerts most of its cellular effects through the activation of the transmembrane guanylyl cyclase, natriuretic peptide receptor-A (NPR-A).[14] Another natriuretic peptide receptor, natriuretic peptide receptor-C (NPR-C), is devoid of guanyl cyclase activity and is responsible for NP internalization and degradation.[15] However, NPR-C may not behave exclusively as a clearance receptor but could also illicit physiological functions through the inhibition of adenylyl cyclase signal transduction system, interfering with the cellular mechanisms involved in the regulation of cell growth.[15]

Increased circulating levels of BNP can be observed in several disease states and are generally interpreted as an expression of the activation of the NP system. However, plasma concentration of BNP is regulated simultaneously both by the rate of synthesis and release of NP and by the rate of removal of the peptides from the circulation.[16] The clearance of BNP involves two pathways: enzymatic degradation by neutral endopeptidase and receptor-mediated endocytosis followed by lysosomal degradation via the NPR-C.[6] Despite the fact that the relative importance of these two mechanisms in the removal of NP from the circulation is still controversial, it has been previously demonstrated in NPR-C knockout mice that the absence of this clearance mechanism is associated with significant prolonged plasmatic half-life of exogenous BNP.[17] Additionally, the modulation of target organ receptor expression may be determinant for the local bioavailability of NP and, by that mechanism, play an important role in the regional control of the NP system activity. Therefore, the local actions of NP can be limited both by increased NPR-C renal expression and/or by NPRA downregulation. In accordance to this, several lines of evidence have suggested that resistance to NP related to changes in the renal expression of NPR-A may explain in part the maintenance of volume expansion (VE) in edema formation conditions, namely in congestive HF.[18,19]

In normal subjects NT-pro-BNP is continuously released from the heart and can be measured in plasma, in equivalent concentrations with BNP. However, in patients with LV dysfunction, by mechanisms not yet clarified, NT-pro-BNP concentration is systematically higher than that of BNP. Based on this, some authors advocate that NT-proBNP plasmatic levels may be a better marker of HF progression.[20]

## BNP and adaptation to functional renal mass loss

### *Uninephrectomy*

The removal of a single kidney immediately stimulates the growth and function of the remnant renal mass. This acute compensatory response is recognized during the first days after unilateral nephrectomy (Unx) and is characterized by an increase in electrolyte excretion, a mild decrease in cardiac output and a transient rise in BP.[21] Some weeks later, a time-dependent increase in both systolic and diastolic BP is observed, together with a sustained reduction in the natriuretic response to VE, suggesting that the relative role of the natriuretic systems in the control of sodium balance may differ overtime.[22]

Atrial natriuretic peptide has been previously implicated as a possible mediator of the acute renal response to contralateral renal ablation. Indeed, previous studies have documented a suppressed natriuretic response to Unx in a rat model of diminished ANP release obtained by right atrial appendectomy.[23] The importance of the NP system in the regulation of sodium balance in response to unilateral renal ablation was also reinforced by the observation of an impaired renal sodium excretion response after the blockade of circulating ANP by monoclonal antibodies in an animal model of Unx.[24] The role of BNP, the selective renal modulation of both the effector (NPR-A) and the clearance (NPR-C) NPR and, more importantly, the time course of these changes after Unx were recently described in a rat model of uninephrectomy.[25] In this study, the renal up-regulation of NPR-A combined with the down-regulation of NPR-C suggested that the renal NP system may be an important mediator of the long-term regulation of salt and water balance, extracellular fluid volume and BP after Unx, partially counteracting the blunted activity documented in other neuro-humoral natriuretic systems.[26] Additionally, it was suggested that the local changes in NPR-C expression in the renal medulla of Unx rats, resulting in a decreased expression of this receptor, could operate as a contributing factor for the compensatory growth observed after unilateral renal ablation, supporting an important role of the NP in the compensatory response observed after Unx. Nevertheless, the exact function of the NP system in the regulation of the adaptive response to unilateral renal mass ablation remains to be fully clarified.

### *Chronic kidney disease*

In CKD, an increase in NP circulating levels was observed and implicated in the compensatory increase in glomerular filtration rate (GFR) and in the decrease in sodium reabsorption, both under normal and salt-replete conditions.[27] Although CKD is frequently associated with disturbances in CV hemodynamics, the mechanisms responsible for the increase of NP circulating levels in this condition still remain to be elucidated. Indeed, an elevation of BNP circulating levels was previously described in normal aged subjects in the absence of cardiac dysfunction and this was attributed to a decrease in the renal clearance of NP.[28,29] Additionally, renal failure per se has also

been shown to affect the plasmatic levels of BNP, a condition not significantly altered by renal replacement therapy, namely peritoneal dialysis (PD).[30,31]

It is not completely clarified if the elevation in NP plasmatic levels in CKD reflects an activation of the system and effectively results in target organ stimulation. This is a matter of considerable importance given that substantial increments of plasma NP in patients with CKD lead to a modest natriuretic response when compared to normal controls or to glomerulonephritic patients with well-preserved renal function.[32] Additionally, the effects of NP on glomerular hemodynamics were suggested to occur independently from those related to the decrease of sodium reabsorption in renal tubules,[33] implying a prominent role for target organ receptor expression in the control of system activity.

Evidence that the modulation of target organ receptor expression may be determinant for the local bioavailability of NP in CKD and, by that mechanism, play an important role in the regional control of the NP system activity was reinforced in a rat experimental model of renal insufficiency induced by ¾ nephrectomy (¾nx). In this study, BP elevation and compromised natriuretic response to VE in ¾nx rats was associated with a precocious and time-dependent increase in circulating BNP levels, in the absence of cardiac dysfunction. These changes were accompanied by an early, selective and sustained impaired expression of NPR-A in the renal medulla along with an upregulation of NPR-C in the renal cortex, suggesting a distinct modulation of NPRs in the remnant kidney that could define a possible mechanism for NP resistance in CKD.[34] This could help to explain some of the disappointing results observed both with NP infusion in the renal protection against toxin-induced renal failure and in renal function preservation of patients with decompensated HF[35,36] and limit the clinical use of NP in the treatment of cardio-renal dysfunction.

## Clinical utility of BNP and NT-pro-BNP in chronic kidney disease

Several studies in patients with HF showed that BNP secretion from ventricular myocytes increases in relation to the degree of dysfunction and substantiated the use of these peptides in the diagnosis, screening, prognosis and monitoring of therapy of patients with CV conditions.[37,38] Indeed, therapies aiming to reduce the clinical manifestations of HF seem to act primarily through mechanisms that are linked to changes in NP levels, allowing the clinician to guide therapy and adjust the treatment in order to achieve a plasmatic level of these agents below a critical value. In renal failure, however, the role of NP as hemodynamic biomarkers is not straightforward.

### *NP plasmatic levels and renal function*

Renal function affects the plasmatic levels of both BNP and NT-pro-BNP. The factors responsible for elevated levels of NP in CKD are not fully clarified, but the reduced renal clearance of these peptides may not be the main operating mechanism.[39] Alternative explanations include the possibility of decreased renal responsiveness attributed to the reduction in functional renal mass, reduced second messenger production and decreased removal of NP by the clearance receptor in the renal tissue.[40] Some evidence supporting some of these mechanisms has already been addressed in this paper. Despite this, the weight of evidence gathered so far suggests that the elevations in NP observed in severe renal dysfunction may be mainly related to a counter-regulatory response directed from the heart to the kidney, supporting the use of these agents as potential markers of LV remodeling in CKD patients.[41]

### *NP circulating levels and cardiac dysfunction in renal failure*

Recent evidence suggests that circulating BNP levels strongly reflects the LV end-diastolic wall stress both in patients with systolic and diastolic heart failure, a correlation maintained even in the presence of significant renal failure.[42] Indeed, studies performed with both hemodialysis (HD) and PD patients demonstrated that BNP circulating levels maintained a significant potential value in detecting LV hypertrophy and in ruling out systolic dysfunction in this population.[43,44] Despite this, renal function is systematically identified as a major confounding factor in the interpretation of elevated BNP and NT-pro-BNP and a potential limitation in the current utility of NP in the CKD population.[45] In fact, an increase of BNP plasmatic levels reaching about 200 pg/ml has been previously reported in patients with reduced creatinine clearance in the absence of cardiac dysfunction[30] whereas NT-pro-BNP reference values of 1200 pg/ml have been recommended in this population.[39] Consequently, as CKD stage advances a higher cutpoint of these NP is implied. NT-pro-BNP plasmatic levels seem to have a stronger relation with GFR and be more influenced by the normal age-related decline in renal function than circulating BNP levels.[40] For that reason, some authors advocate that below a GFR of 60 ml/min/1,73 $m^2$ and in the elderly, NT-pro-BNP plasmatic levels should be used carefully.

### *NP plasmatic levels in end stage renal disease on dialysis*

The effect of HD on both BNP and NT-pro-BNP plasmatic levels is not entirely clarified and some conflicting results have been reported. Several studies document a predictable elevation of BNP and NT-pro-BNP in end-stage renal disease patients before dialysis and a significant drop in BNP plasmatic levels of about 20–40% after a HD session.[46] This reduction in BNP and NT-pro-BNP levels after the dialysis treatment may be explained by the increased dialytic clearance or by the improved volume control resulting in decreased LV wall stress and reduced secretion of these peptides from the ventricular myocardium.[47] Elevated levels of BNP and NT-pro-BNP have been repeatedly documented in PD patients but, unlike what is observed in HD, PD does not seem to alter significantly the plasmatic levels of these peptides.[48]

### *NP plasmatic levels and volume status on dialysis*

Given that both BNP and NT-pro-BNP circulating levels rise in response to increased ventricular wall stress and decrease after a HD session, it is tempting to hypothesize that BNP and NT-pro-BNP circulating levels may be useful markers

of volume status. Numerous studies have evaluated the potential role of BNP and NT-pro-BNP in volemia assessment and dry weight determination of HD patients, but the results remain inconclusive. In fact, whereas some authors have demonstrated a relation between body fluid distribution assessed by bioimpedance and circulating BNP and NT-pro-BNP levels,[49,50] others failed to establish significant correlations at this level.[51] Ultimately, the lack of a consistent association between BNP and NT-pro-BNP and changes in fluid volume during HD indicates that BNP and NT-pro-BNP are not pure markers of volume status in these patients. Instead, circulating levels of NP in CKD patients most likely reflect increased wall stress resulting simultaneously from LV hypertrophy, systolic dysfunction and volume overload.

The usefulness of NP in the diagnosis of volume status in patients on PD is still widely debated. Some studies failed to show a positive association between clinical volume assessment and BNP or NT-pro-BNP levels in chronic PD patients, leading to the conclusion that NP are inadequate volume assessment tools in this subgroup of patients.[52,53] In agreement with prior studies performed on HD patients, higher levels of serum BNP and NT-pro-BNP were also found in PD patients when compared to normal subjects, in strong correlation with LV hypertrophy and LV ejection fraction.[53,54] On the contrary, other authors demonstrated a significant positive correlation between BNP circulating levels and fluid overload in stable PD patients, particularly during the first months of treatment, suggesting that BNP measurements may be a useful tool in clinical circumstances where the volume status is difficult to define.[55]

### *NP plasmatic levels in different dialysis modalities*

In PD patients, significantly lower plasmatic BNP levels have been described, when compared to HD patients, supporting the hypothesis that cardiac load in PD patients may be lower than that of HD patients.[56,50] In fact, it is recurrently attributed to PD improved stable hemodynamic conditions, lower incidence of systemic hypertension, higher urine output and slower rate of ultrafiltration.[57] Despite the lower levels of BNP in PD, it remains inconclusive whether PD is associated with better volume and BP control when compared to HD and the true significance of this finding remains to be clarified. Differences in BNP circulating levels were also reported when we consider the two available PD modalities: automated PD (APD) and continuous ambulatory PD (CAPD). According to some authors, treatment with APD seems to be associated with higher plasmatic BNP levels; a finding presumed to result from the chronic fluid retention and increased LV hypertrophy caused by lower ultrafiltration frequently observed in APD patients when compared to CAPD patients.[58]

### *Prognostic value of NP plasmatic levels in dialysis patients*

In both HD and PD patients, cardiac NP are reliable predictors of death independently of the effect of dialysis modality on fluid volume control and the presence of other clinical and biochemical markers recognized as risk factors for all cause and CV mortality.[59] However, not all members of the NP family have the same predictive value. Indeed, some studies directly comparing BNP and NT-pro-BNP plasmatic levels suggest that NT-pro-BNP may be slightly superior to BNP in predicting death, a finding attributed to the longer half-life of NT-pro-BNP and to the better accurate index of this peptide for LV hypertrophy.[60] For all this, some authors suggest that BNP, and particularly NT-pro-BNP, may be of value simultaneously in guiding risk stratification and in targeting therapeutic interventions in the CKD population.[61]

### *NP in renal transplant*

The clinical value of NP has been previously addressed in renal transplant recipients (RTR) in selected clinical settings. Indeed, elevated NP levels have been shown to predict hypervolemia and allograph dysfunction in stable RTR, what may be valuable in the objective measurement of extracellular volume status in these patients.[62] Additionally, NP may be useful for the detection of LV diastolic dysfunction in RTR, particularly if GFR is considered as a confounding factor.[63] Plasmatic levels of NP also have a positive relation with LV hypertrophy in hypertensive RTR and were proposed in this clinical setting to screen transplant patients at risk of LV hypertrophy.[64] In living kidney transplant the information concerning the clinical value of NP is scarce and studies evaluating the significance and utility of NP levels in living donors are virtually inexistent.

## Key concepts

- BNP and NT-pro-BNP are cardiac biomarkers of cardiovascular morbidity and mortality in patients with normal renal function and have diagnostic, therapeutic and prognostic value in patients with heart failure.
- The role of NP in sodium homeostasis after renal mass ablation seems to be significantly influenced by the local modulation of the renal NP system and may differ according to the degree of functional renal mass loss.
- Renal function affects the plasmatic levels of both BNP and NT-pro-BNP and may limit their utility as hemodynamic biomarkers in renal failure.
- NP plasmatic levels have been correlated to left ventricular structure and function in both hemodialysis and peritoneal dialysis patients, but this association may be significantly affected by other factors operating in severe renal function deterioration.
- The usefulness of NP in the diagnosis of volume status in patients on dialysis is still widely debated and partially depends on the degree of peptide clearance by the different dialysis techniques.
- Despite this, in dialysis patients cardiac NP are reliable predictors of death independently of the dialysis modality and of the degree of fluid volume control and may be of value in the early identification of a subgroup of patients at a higher mortality risk.

## Conflict of interest

The authors declare no conflict of interest.

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