nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

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*

ARTICLE INFO

*Article history:*
Received 1 September 2014
Accepted 9 March 2015
Available online xxx

*Keywords:*
B-type natriuretic peptide
N-terminal-pro-BNP
Heart failure
Chronic kidney disease (CKD)
Dialysis

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.



* *Corresponding author.*
E-mail addresses: csaraujo@med.up.pt, csa0207@gmail.com (C. Santos-Araújo).
http://dx.doi.org/10.1016/j.nefro.2015.03.002

## 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.



## 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