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Urinary C-Type Natriuretic Peptide: An Emerging Biomarker for Heart Failure and Renal Remodeling

Rosita Zakeri, **John C. Burnett Jr.**, and **S. Jeson Sangaralingham**

Cardiorenal Research Laboratory, Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA, 55905

Abstract

The public health and economic burden of heart failure (HF) is staggering and the need for relevant pathophysiologic and clinical biomarkers to advance the field and improve HF therapy remains high. Renal dysfunction is common among HF patients and is associated with increased HF hospitalization and mortality. It is widely recognized that mechanisms contributing to HF pathogenesis include a complex bidirectional interaction between the kidney and heart, encompassed by the term cardiorenal syndrome (CRS). Among a new wave of urinary biomarkers germane to CRS, C-type natriuretic peptide (CNP) has emerged as an innovative biomarker of renal structural and functional impairment in HF and chronic renal disease states. CNP is a hormone, synthesized in the kidney, and is an important regulator of cell proliferation and organ fibrosis. Hypoxia, cytokines and fibrotic growth factors, which are inherent to both cardiac and renal remodeling processes, are among the recognized stimuli for CNP production and release. In this review we aim to highlight current knowledge regarding the biology and pathophysiologic correlates of urinary CNP, and its potential clinical utility as a diagnostic and prognostic biomarker in HF and renal disease states.

Keywords

C-type natriuretic peptide; biomarker; heart failure; cardiorenal syndrome; renal remodeling

1. Introduction

There are an estimated 23 million patients with heart failure (HF) worldwide and, as the elderly population increases, this prevalence is projected to rise [1, 2]. Despite greater utilization of current HF therapies and modest survival gains, the absolute mortality remains

Corresponding Authors: Rosita Zakeri, MB ChB, PhD, S. Jeson Sangaralingham, PhD, Cardiorenal Research Laboratory, Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, Fax: 507-266-4710; Phone: 507-284-4343, rosita.zakeri@doctors.org.uk, sangaralingham.jeson@mayo.edu.

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sobering: 50% of HF patients die within 5 years of diagnosis [3]. Thus, there remains a critical need for additional pathophysiologic and clinical insights to identify unresolved issues, improve the application of existing therapies, and inform the development of novel HF management strategies.

2. The cardiorenal axis in heart failure

Renal dysfunction is extremely common among HF patients and is associated with increased HF hospitalization and mortality [4, 5]. The term cardiorenal syndrome (CRS) has been used to describe the complex interaction whereby acute or chronic cardiac dysfunction can precipitate acute kidney injury (type I CRS) or chronic kidney disease (type II CRS) respectively [6]. Subsequent development of moderate to severe renal dysfunction marks an advanced stage of HF. Importantly however, worsening renal function and chronic kidney disease may also promote cardiac remodeling (types III and IV CRS) and increase the risk of adverse events [6]. Therefore, alterations in renal structure and function become relevant to all aspects of HF including pathogenesis, progression, decompensation and ensuing complications.

Timely recognition and optimal treatment of CRS have been identified as key evidence gaps in contemporary HF management guidelines [7]. Challenges arise because renal dysfunction may involve a combination of lesions within glomerular, tubulointerstitial, and vascular compartments of the kidney, while frequently only parameters of glomerular function are measured. Worsening renal function is generally defined by an increase in serum creatinine or reduction in glomerular filtration rate (GFR), which reflects a late decline in renal function and precludes early identification. Likewise, treatment of CRS is hampered by limited differentiation between transient but potentially cardio- and reno-protective increases in serum creatinine, related to diuretics (hemoconcentration) [8], angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs) [9, 10], versus a deleterious increase in creatinine due to progressive renal remodeling and fibrosis.

Direct measurement of proteins in the urine, as compared to serological assessment, has the potential to offer earlier and more specific insight into intrinsic renal injury and reparative processes. A number of novel urinary biomarkers have been proposed to detect renal tubular damage, including kidney injury molecule 1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and N-acetyl-β-D-glucosaminidase (NAG), which are elevated in the urine of HF patients before a rise in serum creatinine. However variable and modest correlations have been observed with clinical outcomes [11-14]. Given the prominent role of cardiac natriuretic peptides in the serologic diagnosis of HF and the sensitivity of NT-pro-B type natriuretic peptide (NT-proBNP) for cardiac stress, injury and remodeling, there has been increasing interest in a role for renal-derived C-type natriuretic peptide (CNP) as a urinary biomarker of renal dysfunction and chronic renal remodeling in HF and CRS. In this review we aim to highlight current knowledge regarding the biology and pathophysiologic correlates of urinary CNP, and its potential clinical utility in the diagnosis and management of HF and CRS.

3. C-type natriuretic peptide biology

3.1. Discovery and processing of CNP

CNP was first isolated from porcine brain in 1990 [15]; though subsequent studies have demonstrated the highest levels of CNP expression and production in the kidney [16-18]. CNP expression has also been detected in cardiomyocytes [19], vascular endothelium [20], and bone [21]. Among the family of natriuretic peptides, CNP is the most highly conserved between species and may in fact represent the ancestral precursor from which atrial (ANP) and B-type (BNP) natriuretic peptides evolved [22, 23]. However, whereas ANP and BNP are predominantly expressed in atrial and ventricular myocardium respectively, cardiac expression of CNP is typically low [24]. Furthermore, in the absence of disease, plasma levels of CNP are significantly lower than those of ANP and BNP, giving rise to the notion that CNP principally operates as an autocrine or paracrine factor [25-27] (Figure 1).

The CNP gene is located on chromosome 2, versus chromosome 1 for ANP and BNP [22, 28]. CNP is initially synthesized as a 103 amino acid (AA) prohormone, proCNP (AA 1-103), which is then cleaved into NT-proCNP (AA 1-50) and CNP53 (AA 51-103) by the ubiquitous convertase, furin [29]. At this stage CNP53 may be secreted [20] or undergo further biological processing resulting in two additional products: CNP22 (AA 82-103) and NT-CNP53 (AA 51-81, which may otherwise be referred to as NT-proCNP; Figure 2). Theoretically, CNP22 may be directly derived by alternative cleavage of proCNP, by an unidentified mechanism, which concurrently produces an accessory 81AA NT-proCNP (AA1-81; Figure 2). However this pathway has not previously been described and requires further validation.

Among the products of CNP processing, it is thought that CNP22 is the mature and biologically active form and has therefore been most extensively studied. However, CNP22 has a short half-life (2-6 minutes) [30], and thus detected levels may not accurately reflect CNP synthesis. CNP53 [14, 17] and NT-CNP53 [14] have been detected in urine from patients with HF and healthy controls. Under physiological conditions, approximately 70% of urinary protein content originates from the kidney and urinary tract, while only 30% from plasma [31]. In view of the low circulating levels of CNP, urinary CNP is predominantly thought to derive from local renal production and the CNP urinary excretion rate reflective of renal structural integrity and function.

3.2. Biological effects and role of CNP

The biological effects of CNP result from its selective activation of the cell surface particulate guanylyl cyclase receptor B (GC-B), which contrasts the selective activation of GC-A by ANP and BNP [32]. Binding of CNP to the GC-B receptor catalyzes the conversion of GTP to the downstream second messenger, cyclic guanosine monophosphate (cGMP). The bioavailability of CNP is modulated by three mechanisms: the transmembrane clearance receptor, NPR-C, which binds and sequesters ANP, BNP, and CNP from the circulation; enzymatic hydrolysis by the zinc metallopeptidase, neutral endopeptidase (NEP), which is found in heart, lung, kidney and endothelial tissue; and finally urinary excretion. CNP is the most rapidly degraded of the natriuretic peptides by NEP [33],

suggesting that enzymatic hydrolysis and/or urinary excretion may be more important for CNP regulation than receptor-mediated clearance.

Our understanding of the biological role of CNP continues to evolve. While ANP and BNP exhibit a number of homeostatic actions which are beneficial in HF, including diuresis, natriuresis, arterial vasodilation and renin-angiotensin-aldosterone system inhibition [34, 35], CNP lacks significant diuretic or natriuretic effects at physiologic concentrations [30]. However, unique among the natriuretic peptides, CNP has demonstrated significant anti-proliferative and anti-fibrotic properties. These include potent suppression of fibroblast proliferation and collagen production [36-39], inhibition of vascular smooth muscle cell proliferation [40, 41], and accelerated regeneration of endothelial cells [42, 43]. Moreover, CNP is a recognized vasodilator [34,35,36] and particularly potent venodilator [37], which appears to play an important role in the local regulation of vascular tone. Of relevance to HF and CRS, hypoxia [39] that may occur with renal congestion, and cytokines and fibrotic growth factors [25, 40], inherent to cardiac and renal remodeling, are all recognized stimuli for CNP production and release. Thus it is proposed that CNP represents a marker of reparative and restorative physiology as well as structural alterations, as will be outlined below.

3.3 Measurement of CNP

CNP molecular forms in the urine and plasma are currently assessed using proprietary radio- or sandwich immunoassays [14] [38] [44-46]. Reproducibility and a high degree of sensitivity and specificity have been reported within individual pre-clinical and clinical research studies, particularly with the use of the radioimmunoassays [14, 44, 47]. However a clinical laboratory platform for CNP measurement in clinical practice has yet to be developed. Important next steps towards translation of recent research findings to the clinical arena will include the development of a scalable platform, generalizable and consistent reporting of urinary CNP excretion rates adjusted for urinary creatinine, and the establishment of age and gender-specific normal reference ranges.

4. C-type natriuretic peptide in aging and disease

4.1. Aging

Physiologic aging has been associated with a progressive decline in renal function, which is not entirely due to age-related comorbidities [48, 49]. Reductions in glomerular filtration, renal perfusion and altered glomerular basement membrane (GBM) permeability may accompany advanced age, with eventual contributions from glomerulosclerosis and tubulointerstitial fibrosis [49]. Importantly, a concurrent reduction in muscle mass can maintain near-constancy of serum creatinine and initially mask the decline, as urinary creatinine excretion is proportional to muscle mass. By contrast, urinary CNP excretion has been shown to increase with normal aging and further exhibits a robust correlation with renal fibrosis in aging rodents, before the onset of significant proteinuria or blood pressure elevation [44]. In human kidney biopsy specimens, the localization of CNP was similar to aging rodents in both young and older kidney donors [44]. As GFR and plasma CNP also declined with age in this study, renal-derived, rather than filtered, CNP was suggested to

correlate with renal fibrosis [44]. It follows, therefore, that elevated urinary CNP excretion may represent a sensitive marker of renal structural remodeling prior to the development of overt symptoms and disease. This association with aging extends the reno-protection and reparative hypothesis, by suggesting that increased CNP expression and its subsequent excretion in the urine may be sustained over many months and years, in contrast to more fluctuant levels observed with other urinary biomarkers [50].

4.2. Heart failure

A potential role for urinary CNP in HF was first proposed in 1994 when Mattingly et al. [17] reported elevated urinary excretion of CNP53 and CNP22 in patients with stable HF. Subsequently, in the experimental setting, Borgeson et al. [51] observed a marked increase in urinary, but interestingly not plasma, CNP in a canine HF model of acute intravascular volume overload with increased left ventricular filling pressures. More recently significantly elevated levels of CNP molecular forms were detected in urine from patients with acute decompensated HF (ADHF) versus healthy controls, and exhibited poor correlation with plasma CNP levels [14, 52]. These data suggest activation of the renal natriuretic peptide system in HF, wherein elevated urinary excretion of CNP is purported to reflect increased renal interstitial pressure, renal tubular injury, hypoxia, and potentially renal fibrosis. Importantly, in the setting of ADHF, urinary NT-CNP53 excretion was significantly associated with prognosis and conveyed incremental prognostic information than was obtained from patient age, GFR, proteinuria, or plasma NT-proBNP, with respect to all-cause mortality and a combined endpoint of HF hospitalization and death [14]. Furthermore, the fact that urinary tubulospecific biomarkers KIM-1 and NGAL were not associated with clinical outcomes in the same study highlights a broader scope for urinary CNP as a biomarker of global renal processes beyond renal tubular injury alone.

Intrinsic renal damage in HF may result from kidney hypoperfusion due to arterial underfilling or increased renal outflow impedance due to venous congestion. In some cases renal hypoxia and tubular necrosis may occur, and subclinical or overt renal dysfunction persist despite decongestion. Whereas tubulospecific biomarkers such as KIM-1, NAG, and NGAL, have been shown to rise early and markedly in the course of renal tubular dysfunction in HF, their levels have been shown to fall with diuretic therapy [50]. Serum creatinine is a late marker of overt renal dysfunction. CNP, on the other hand, has been localized to the renal tubules and may represent an additional marker of renal tubular integrity. Moreover its positive association with prognosis in ADHF [14] suggests a greater sensitivity or even detection of a different type of renal dysfunction in HF, thus better characterizing the evolution of CRS. However, further prospective studies are needed to evaluate the specific type of kidney injury detectable by urinary CNP and its response to HF therapies.

Remarkably, the adverse prognosis associated with increased (ostensibly renal-derived) urinary CNP in HF appears to conflict with a postulated renoprotective effect of CNP, which would be expected to improve overall prognosis. It is reasonable to speculate that CNP activation in the kidney is initially compensatory and reparative, but in HF and CRS these homeostatic mechanisms are exceeded. Thus, an increase in urinary NT-CNP53 may

represent a failure or a deficiency of the renal natriuretic peptide system's counter-regulatory mechanisms in HF [14]. Notably, the biological activity and role of different CNP molecular forms remain unclear and further investigation may provide relevant pathophysiologic and prognostic insights. These may be particularly important in HF syndromes strongly associated with comorbidities such as HF with preserved ejection fraction (HFpEF). In the proof of concept study by Zakeri et al. [14], consecutive patients hospitalized with acute decompensated HF and reduced ejection fraction (HFrEF) were assessed. To our knowledge, the clinical utility of urinary CNP testing in HFpEF, compared with either HFrEF or healthy controls has not been directly examined.

4.3. Renal disease states

Examination of urinary CNP in experimental and human nephropathy has advanced our understanding of its relationship to renal structure and function. In experimental nephropathy secondary to ureteral obstruction, Hu et al. [53] reported an increase in urinary CNP excretion well before changes were observed in urinary protein, albumin, blood urea nitrogen, and creatinine. Importantly, experimental nephropathy was associated with histological evidence of tubulointerstitial fibrosis, higher urine than plasma concentrations of CNP, and no significant arteriovenous CNP concentration gradient. Taken together, these findings suggest enhanced renal expression of CNP and subsequent elevation in urinary excretion of CNP may serve as an early marker of tubulointerstitial fibrosis in obstructive nephropathy [53].

Diabetes is a recognized cause of cardiac and renal remodeling. In rats with streptozotocin-induced diabetes, increased renal CNP synthesis (via mRNA expression) and a parallel increase in urinary CNP excretion was observed by Shin et al. [54]. Notably renal CNP synthesis was attenuated by dietary salt-restriction, which highlights a potential for dynamic alterations in CNP expression. Conceivably decreased renal interstitial pressure may reduce mechanical stimulation of CNP production [54].

Moreover in normotensive patients with nephrotic syndrome, which exhibits some similarities to diabetic nephropathy, urinary CNP excretion was elevated compared to healthy control subjects of similar age and body mass [55]. After administration of a low protein diet, urinary, but not plasma, CNP levels were reduced without a detectable change in creatinine clearance. This corroborates a role for urinary CNP in the early detection of renal dysfunction. Although a concurrent improvement in urinary albumin was also observed in this study, decreases in CNP were of greater magnitude [55], suggesting that urinary CNP exhibits heightened sensitivity to changes in glomerular function and/or detects extra-glomerular renal disease.

Finally, patients with cirrhosis and concomitant renal dysfunction were reported to have higher urinary CNP excretion compared to patients with cirrhosis and normal renal function, or healthy controls [47]. Urinary CNP demonstrated an inverse correlation with urinary sodium excretion and following interventions, which improved renal perfusion and pressures (transjugular intrahepatic portosystemic shunt insertion or ornipressin infusion), urinary CNP excretion declined. Plasma CNP concentrations were not affected and no arteriovenous (femoral artery-renal vein) CNP concentration gradient was observed, excluding major renal

extraction of circulating CNP as a potential cause [47]. In sum, these observations are compatible with increased and dynamic renal CNP activation resulting in greater urinary CNP excretion in conditions of renal stress. It is possible that more advanced renal remodeling and fibrosis may be reflected in constancy and plasticity of urinary CNP excretion, however this hypothesis requires further validation.

5. Future directions and conclusion

Renal remodeling and fibrosis are key pathological processes underlying progression to chronic kidney disease, which adversely impacts prognosis in HF and CRS. Unique among the family of natriuretic peptides, CNP is synthesized in the kidney, where it acts in a predominantly autocrine/paracrine fashion, and appears to be activated in HF and renal disease states. CNP and its various molecular forms are detectable in the urine and may enable early diagnosis of renal congestion, renal injury and structural remodeling due to disease or physiologic aging. Evidence for a reno-protective effect of CNP is also mounting and deserves further exploration as a potential therapeutic mechanism. At present there is no specific therapy for renal fibrosis or CRS. Current data suggest that elevated urinary CNP may predict the evolution and progression of renal fibrosis and may therefore be of clinical utility as a pragmatic endpoint for trials of novel anti-fibrotic agents, where existing clinical endpoints mandate long and expensive follow-up. Further investigation is also needed to elucidate the relative biological significance and relationships between urinary CNP molecular forms in HF with reduced and preserved ejection fraction and in CRS. Evidence to date suggests that urinary CNP may offer relevant, non-invasive insight into intrinsic renal processes, which are incompletely described by existing parameters of renal function. Among the new wave of urinary biomarkers, CNP holds great promise for translation to new diagnostic and therapeutic strategies, which are urgently needed to improve outcomes for patients with HF and CRS.

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Highlights

- C-type natriuretic peptide (CNP) is synthesized in the kidney, where it acts in a predominantly autocrine/paracrine fashion, and is an important regulator of cell proliferation and organ fibrosis.
- CNP molecular forms can be detected in urine and are elevated in patients with heart failure and in renal disease states.
- Urinary CNP excretion may enable early diagnosis of renal congestion, renal injury and structural remodeling and predict the evolution and progression of renal fibrosis.

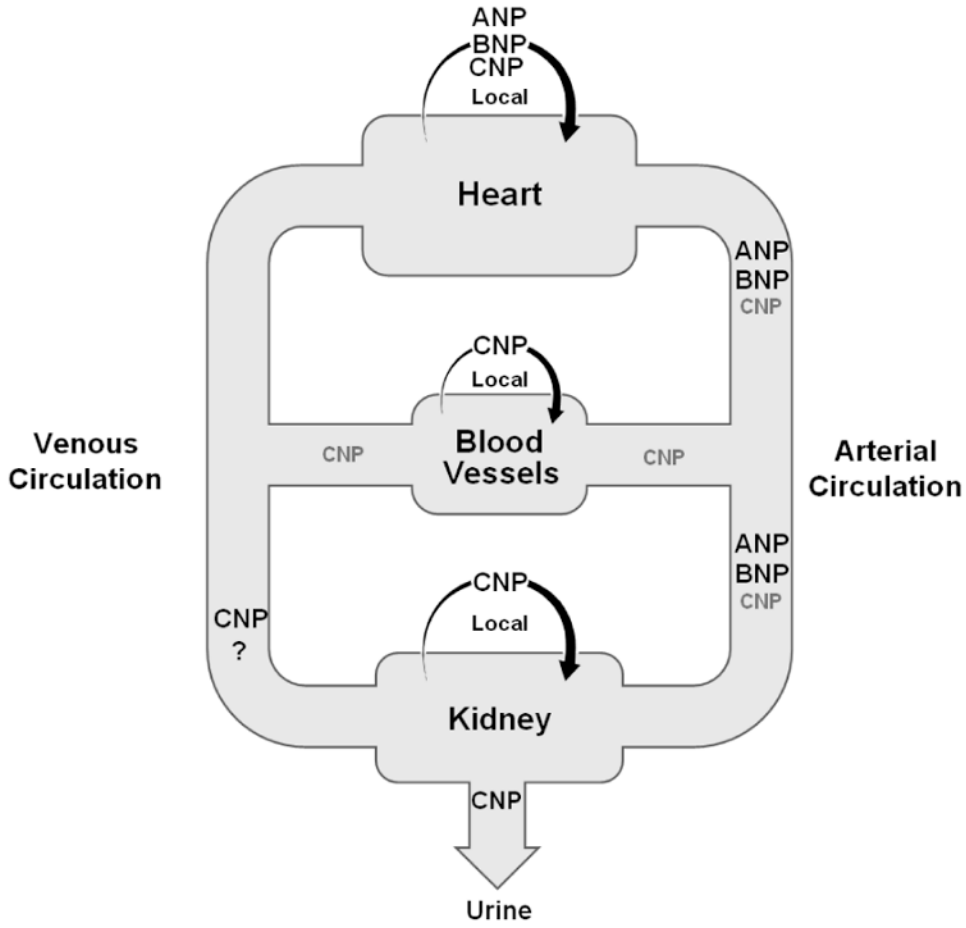

Figure 1.

Major sites of C-type natriuretic peptide (CNP) production include the vascular endothelium, kidney and heart, where it is believed to principally operate as an autocrine or paracrine factor. In patients with heart failure, circulating levels of ANP and BNP are higher than those of CNP; however urinary excretion of CNP is high.

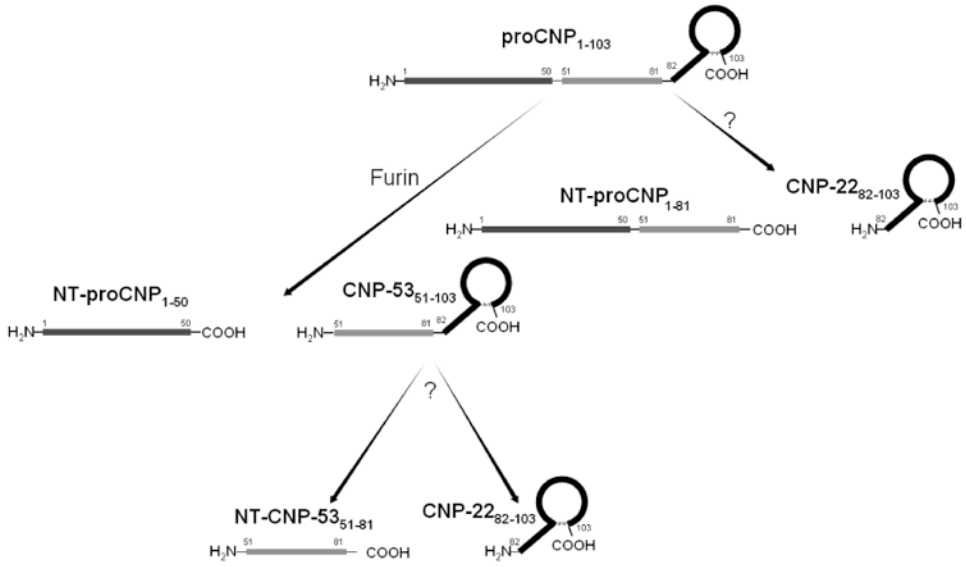

Figure 2.

Schematic diagram of the biological processing pathways of pro C-type natriuretic peptide (proCNP) to downstream CNP molecular forms.