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Invited critical review

Urinary C-type natriuretic peptide: An emerging biomarker for heart failure and renal remodeling

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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 pathophysiological correlates of urinary CNP, and its potential clinical utility as a diagnostic and prognostic biomarker in HF and renal disease states.

Contents

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 sobering: 50% of HF patients die within 5 years of diagnosis [3]. Thus, there remains a critical need for additional pathophysiological and clinical

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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 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 serological 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 pathophysiological 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

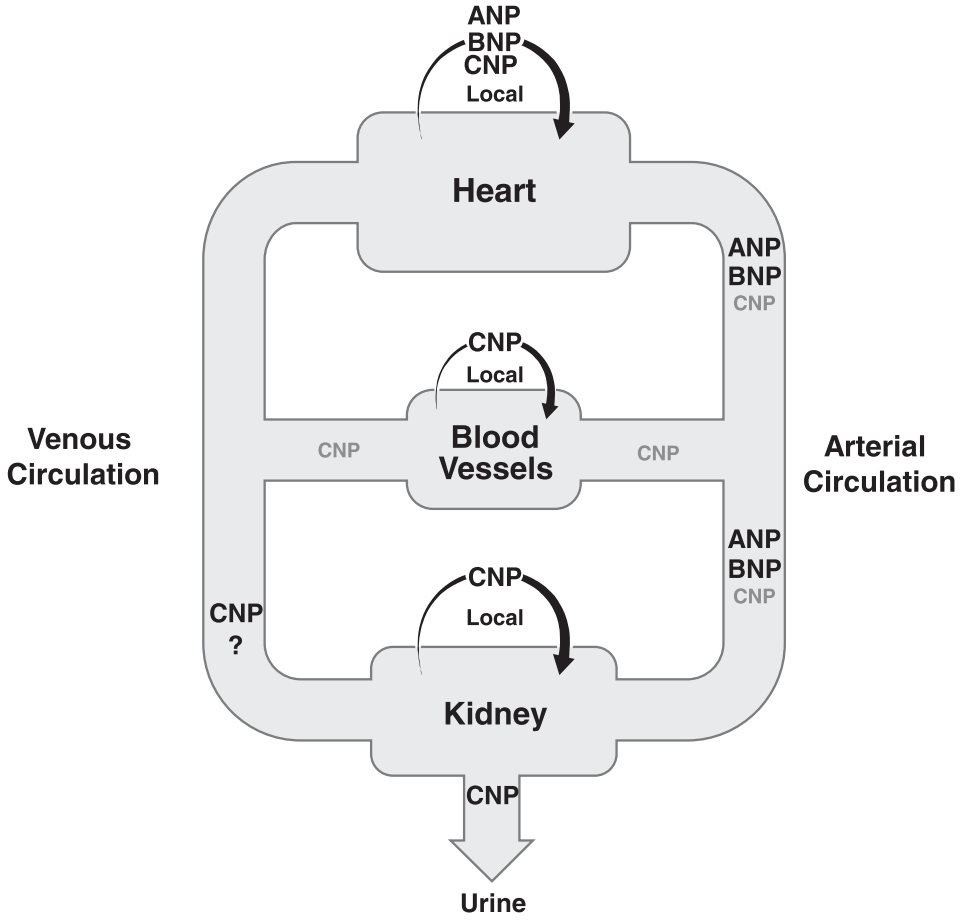

Fig. 1. Major sites of C-type natriuretic peptide (CNP) production include the vascular endothelium, kidney and heart, where it is believed to principally operate as an autocrine or paracrine factor. In patients with heart failure, circulating levels of ANP and BNP are higher than those of CNP; however urinary excretion of CNP is high.