Hypertension

EDITORIAL

# C-Type Natriuretic Peptide and Cardiovascular-Renal Protection in Sepsis

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C-type natriuretic peptide (CNP) is the third member of the genetically distinct but structurally similar family of endogenous natriuretic peptides (NPs), alongside atrial NP (ANP) and B-type NP (BNP).[1] CNP is unique and is produced primarily by endothelial cells, whereas ANP and BNP are synthesized and released by cardiomyocytes. Studies have established that ANP and BNP are the endogenous activators of the particulate guanylyl cyclase A receptor (GC-A, also called NPR-A or NPR1), whereas CNP is the natural activator of the GC-B receptor (also called NPR-B or NPR2). Through GC-A and GC-B, NPs mediate their actions via the effector molecule 3′,5′-cyclic guanosine monophosphate (cGMP). Work from the Hobbs laboratory has, in elegant pharmacological studies, advanced the concept that CNP may mediate biological actions via the natriuretic peptide clearance receptor (NPR-C), which is traditionally regarded as a clearance mechanism for the NP system.[2] Indeed, prior independent studies have reported that NPR-C possesses a signaling capacity, coupled to pertussis toxin-sensitive Gi/Go (G-protein alpha-i subunit/G-protein alpha-o subunit) proteins to inhibit adenylyl cyclase, and has been reported to activate phospholipase C-β.[2,3] Further, 2 subtypes of NPR-C have been reported: one with high affinity for CNP, in which activation reduces cAMP synthesis, and a low-affinity receptor involved in ligand internalization.[2] Beyond signaling differences, receptor distribution also shapes biological specificity. Importantly, the biological actions of the GC-A and GC-B differ, in part because of differences in the cellular expression of GC-A and GC-B across diverse cell types, with some targets enriched for GC-A and others possessing greater GC-B expression. The NPR-C is widely expressed in many cell types and often at higher expression levels than either GC-A or GC-B.

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The biological properties of GC-A support cardiorenal and metabolic homeostasis including blood pressure lowering, natriuretic, antihypertrophic, renin-angiotensin-aldosterone suppressing, lipolytic, and insulin-sensitizing actions.[1,4] ANP and BNP also function as a circulating hormone system via the GC-A/cGMP pathway. To date, novel GC-A agonists and ANP or BNP mimetics have been, and continue to be, investigated in heart failure, hypertension, and metabolic syndrome.[4–6] CNP circulates at lower concentrations and functions predominantly as an autocrine and paracrine system. It plays a major role in promoting bone growth. Notably, the CNP-based therapeutic vosoritide and the once-weekly CNP prodrug navepegritide are both Food and Drug Administration-approved for the treatment of achondroplasia, establishing the druggability of the CNP pathway. Furthermore, recent research has advanced our understanding of CNP in cardiovascular regulation. CNP demonstrates antifibrotic actions in multiple organs, vasodilation in the microcirculation, enhancement of myocardial relaxation, and antiinflammatory effects, with therapeutic efficacy in experimental models of pulmonary hypertension, myocardial infarction, and organ fibrosis.[1,2,7] A recently developed CNP analogue is in early clinical trials for heart failure,[8] while a novel dual GC-B and GC-A peptide activator is also being developed for human heart failure.[9]

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In the current issue of *Hypertension*, Moyes et al[10] extend our understanding of the biology and therapeutic potential of CNP in the clinically challenging setting of experimental sepsis. Sepsis represents a life-threatening clinical syndrome driven by a dysregulated immune response to systemic infection, frequently leading to multiorgan failure, particularly in older and hospitalized patients. Sepsis is characterized by reduced tissue perfusion, increased vascular leakage, widespread activation of inflammatory pathways, and, importantly, injury to the heart and kidney, culminating in high morbidity and mortality. The current armamentarium for drug therapy is limited and often inadequate, underscoring the need to better understand the pathobiology of sepsis and to develop innovative safe, and effective medicines. Based on the growing biology of CNP and reports linking elevated circulating CNP levels with outcomes in sepsis, the work reported by Moyes et al is both timely and compelling.

In their study, the authors confirmed in human sepsis that circulating NT-proCNP (N-terminal pro–C-type natriuretic peptide), a validated biomarker reflecting CNP biosynthesis, is elevated and correlates with improved oxygenation, consistent with less severe lung injury. To understand the biology of endogenous CNP in sepsis, the investigators used innovative mouse models with genetically reduced expression of CNP in the endothelium as well as in cardiomyocytes. To further define the receptor pathway mediating the actions of CNP, the study also incorporated mice with global NPR-C deficiency, allowing for direct comparison with wild-type mice that maintain intact CNP and NPR-C. From a therapeutic perspective, a subhypotensive dose of exogenous CNP was administered by osmotic minipump before endotoxemia in the presence or absence of NPR-C to determine whether CNP confers organ protection in the setting of experimental sepsis and whether any benefit requires NPR-C. Two clinically relevant models of sepsis were used, including lipopolysaccharide-induced endotoxemia and cecal ligation and puncture.

Loss of endothelial cell-derived CNP resulted in a worsened septic phenotype characterized by increased cytokine activation, greater tissue edema, and reduced microcirculatory perfusion, thus supporting a key protective role of endogenous CNP in maintaining cardiovascular homeostasis and serving as a brake on inflammation. In addition, recognizing that CNP production in the kidney is high compared with other organs and may be renoprotective, endothelium-restricted CNP deletion also produced greater glomerular injury relative to wild-type septic mice. This is a key observation, as sepsis is the leading cause of acute kidney injury (AKI) in hospitalized patients, and the development of AKI is associated with worse outcomes. Given that aging increases susceptibility to both sepsis and AKI, and that CNP deficiency has been reported with advancing age, these findings also support a potential role for CNP as a preventive strategy for sepsis and AKI. Supporting this concept, Jin et al[11] have reported that CNP reduces renal oxidative stress and tubular apoptosis in experimental AKI. It should be noted that the current study also highlights that neither the endothelium-derived mediators endothelin-1 nor nitric oxide, both of which are activated in sepsis and contribute to organ hypoperfusion, were altered by endothelial CNP deletion, supporting the conclusion that the observed phenotype is specific to the loss of CNP. In the human cohort, circulating CNP (the biologically active peptide) remained low and was not different between groups, despite higher circulating NT-proCNP in sepsis, suggesting increased CNP biosynthesis but rapid clearance or degradation, which highlights the therapeutic opportunity for CNP-based analogues in human disease.

The heart is a major organ injured in sepsis, leading to septic cardiomyopathy characterized by systolic and diastolic dysfunction, arrhythmias, and myocardial edema. As with renal injury, cardiac involvement markedly increases mortality. Here, the authors used a novel cardiomyocyte-specific CNP deletion model to define the contribution of myocardial CNP to the severity of septic cardiomyopathy. Importantly, in the absence of cardiomyocyte CNP, the septic heart exhibited more pronounced diastolic dysfunction, consistent with the loss of CNP's well-recognized lusitropic actions. In parallel, myocardial inflammation and myocytolysis were more prominent in endothelial-restricted CNP-deficient mice compared with wild-type mice, supporting a cardioprotective antiinflammatory role for endogenous CNP.

A major goal of the work by Moyes et al was to explore the role of the NPR-C in mediating the protective actions of CNP in sepsis. The authors have been pioneers in elucidating the importance of NPR-C, long regarded as a clearance receptor for NPs, as a signaling partner that mediates the biological actions of CNP and complements the well-established role of the GC-B receptor and cGMP pathway. Their prior studies have supported a role for CNP via activation of NPR-C in cardioprotection in mouse models of cardiac pressure overload and in maintaining aortic structural integrity during aneurysm formation.[2,12] In the current study, global deletion of NPR-C in mice worsened the septic phenotype, with greater inflammation, reduced microvascular perfusion, together with endothelial dysfunction, and greater tissue edema. Measures of renal and cardiac injury were also greater. These findings support the conclusion that NPR-C plays a role in CNP's protective actions, as the phenotype of mice with global NPR-C deficiency closely mirrored the phenotype of the endothelial depleted CNP mice.

An unresolved and important question, however, is the role of GC-B (NPR-B) in participating in the protective actions of CNP. Measurement of circulating and tissue cGMP in the presence and absence of endothelial- and

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cardiomyocyte-derived CNP would have provided insight into whether the CNP/GC-B/cGMP pathway is altered in sepsis. The authors importantly state that their data suggest that NPR-C, rather than NPR-B, is the superior therapeutic target for mediating the protective actions of CNP in sepsis. As they note, future studies in mice using cell-restricted deletion of GC-B (NPR-B) will be required to fully resolve this question.

A major advance of this study is the demonstration that exogenous CNP therapy confers organ protection in experimental sepsis. In mice infused with a subhypotensive dose of CNP initiated before the induction of sepsis, the authors observed improved microcirculatory perfusion, enhanced cardiac function and decreased cardiac inflammation. The suppression of the inflammatory response in sepsis by CNP is consistent with previous reports on antiinflammatory mechanisms of CNP.[13] The current study by Moyes et al underscores the widespread antiinflammatory role of CNP in sepsis and that CNP may reprogram macrophages, potentially via HIF-1α (hypoxia-inducible factor-1 alpha) pathways and CD36-mediated uptake, providing plausible mechanisms for limiting cytokine surges.[13] These protective actions strongly support the rationale for further laboratory-based investigations into CNP-based therapeutics for the prevention and treatment of sepsis and the concept of sepsis being a state of relative CNP deficiency, which benefits from CNP supplementation. Further studies should define the optimal timing of CNP administration and the dose-response relationship to determine the optimal dosing strategy, both before the induction of sepsis and as a postonset rescue intervention. It will also be important to

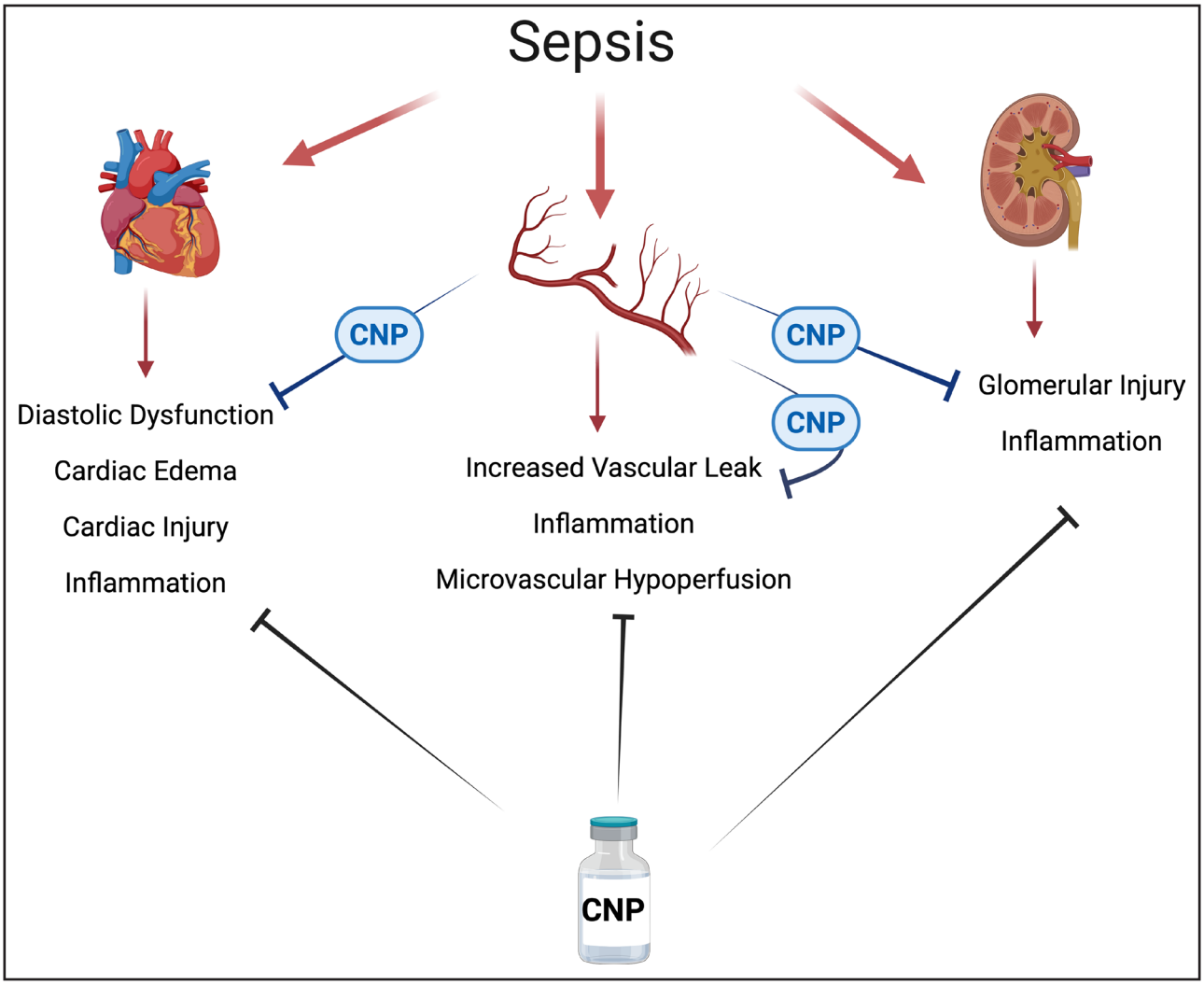


**Figure. Sepsis triggers endothelial injury with increased vascular leak, inflammation, and reduced microvascular perfusion in the blood vessels, diastolic dysfunction, edema, and inflammatory injury in the heart and glomerular injury with inflammatory infiltration in the kidney.**

Loss of endogenous C-type natriuretic peptide (CNP) from the endothelial cell or global natriuretic peptide clearance receptor (NPR-C) worsens injury across all 3 organs, while therapeutic administration of CNP at a subhypotensive dose partially rescues these pathologies, highlighting CNP's cardiovascular-renal protective actions in sepsis. Figure created using Biorender, Sangaralingham, J. (2026) https://BioRender.com/vs7xek.


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determine potential synergistic co-therapies. Validation of these current findings in a large animal model may also be important to strengthen translational relevance. It is noteworthy that the protective actions of exogenously administered CNP were absent in the global NPR-C knockout mice, reinforcing an essential role of this receptor in mediating the therapeutic effects of synthetic CNP.

What are the key take-home messages of this elegant study? First, in the broadest sense, this report underscores the growing consensus that CNP is a key endogenous mediator of cardiovascular and renal protection, extending its influence across the vascular-cardiac-renal axis. Moyes et al convincingly demonstrate this using innovative genetic mouse models of tissue-specific CNP deletion and global NPR-C deficiency, each of which amplified the detrimental syndrome of sepsis, including worse myocardial and renal injury, reduced tissue microperfusion, greater edema and increased inflammation. Second, the study expands the therapeutic landscape for CNP, complementing prior work in models of pulmonary hypertension, organ fibrosis, and myocardial infarction.[2,7] Currently, an early phase clinical trial using an innovative CNP analogue is underway in human heart failure and the findings from that study will be important in advancing the cardiovascular and renal protective actions of CNP in humans.[8] Finally, although CNP was infused at a nonhypotensive dose in the current study, it is nevertheless relevant to highlight that both NPR-C and the CNP/GC-B/cGMP axis participate in blood pressure regulation. In mice, endothelial deletion of CNP or cell-specific GC-B deletion increases blood pressure.[14] Conversely, NPR-C agonism lowers blood pressure in spontaneously hypertensive rats, and in humans, blood pressure raising NPR-3 variants reduce NPR-C expression in vascular smooth muscle cells.[2,15] Collectively, these data support NPR-C as a vascular regulator and potential antihypertensive target (See Figure).

In summary, Moyes et al are to be congratulated for providing new insights into the biology and therapeutic potential of CNP, advancing the natriuretic peptide field and opening avenues for novel interventions in sepsis.

## ARTICLE INFORMATION

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### Disclosures

J.C. Burnett serves as Chair of the Scientific Advisory Board at E-Star BioTech and S.J. Sangaralingham is a member of E-Star BioTech's Scientific Advisory Board.

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