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Natriuretic peptides in heart failure: Potential role in diagnosis and therapy

By TEJ SHETH, MD AND GORDON W. MOE, MD

The natriuretic peptides have been the subject of intense research for over two decades. Both experimental and clinical studies have implicated the natriuretic peptides as an important neurohormonal system for regulating cardiorenal homeostasis in heart failure. Recent data have suggested that measurements of plasma natriuretic peptide levels may add diagnostic and prognostic value to patients with heart failure with impaired or preserved left ventricular systolic function. Furthermore, pharmacological manipulation of the natriuretic peptide system provides novel avenues of therapy for patients with both acute and chronic heart failure.

This year marks the 20th anniversary of the original report by de Bold et al which demonstrated that an intravenous bolus injection of atrial myocardial extracts elicited a brisk and potent diuretic response in rats.[1] Since that time, the role of cardiac natriuretic peptides in the integrated control of cardiovascular and renal function, in both health and disease, has been the subject of intense investigation. This issue of *Cardiology Rounds* reviews:

- **the physiology and pathophysiology of the natriuretic peptides in heart failure**
- **the potential role of natriuretic peptides in the diagnosis of acute and chronic heart failure**
- **the natriuretic peptide system as a therapeutic target in heart failure.**

Physiology of natriuretic peptides

The natriuretic peptide family consists of three structurally related peptides: atrial natriuretic peptide (ANP), brain or B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP).[2,3] As shown in Figure 1, all three peptides contain a 17-amino acid ring, formed by a disulfide bond; however, the prohormone of each peptide is encoded by a separate gene. ANP and BNP are derived mainly from cardiomyocytes. ANP is produced predominantly in the atria where increased atrial wall tension stimulates its release. The mRNA transcript for ANP encodes a 126-amino acid prohormone (pro-ANP). Processing of pro-ANP releases a 98-amino acid amino-terminal fragment (N-ANP), as well as a 28-amino acid carboxy-terminal fragment (C-ANP, also known as matured ANP). Both fragments circulate in the blood. BNP was originally found in extracts of porcine brain and was subsequently found to be abundant in the cardiac ventricles. This peptide is the most natriuretic among the natriuretic peptide family and its activation at the gene level, in response to hypertrophic stimuli, is also the most rapid. Human pro-BNP contains 108 amino acids; processing releases a 32-amino acid molecule (also called matured BNP) and a 76-amino acid amino-terminal fragment (N-BNP). Both circulate in the blood as N-BNP and C-BNP. CNP is derived from the endothelial cells. CNP is believed to function in an autocrine and paracrine manner for regulating vascular function; therefore, the plasma level of CNP is very low.

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Figure 1: Biochemical structure of the three human natriuretic peptides.

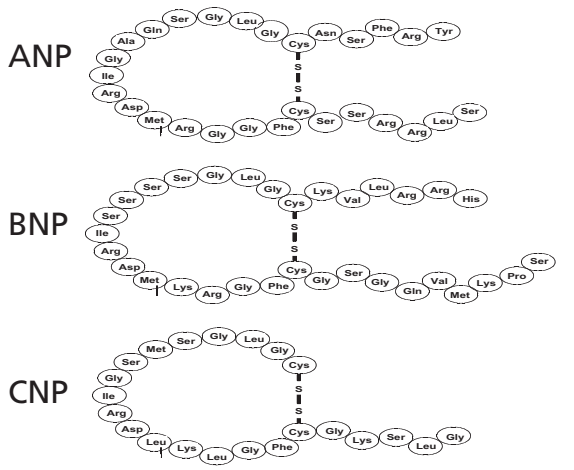
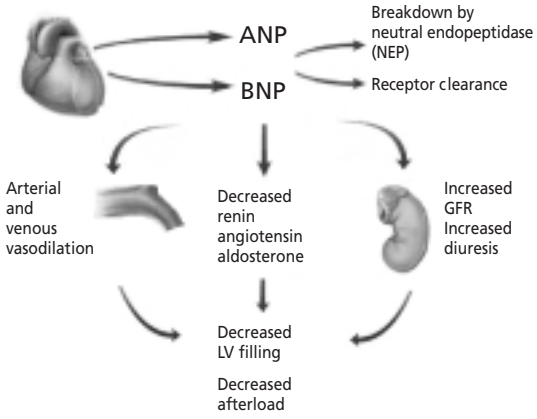


Figure 2: Physiologic effects of natriuretic peptides in patients with heart failure.



The release, biologic actions, and metabolism of the natriuretic peptides are schematized in Figure 2. Once released to the circulation, ANP and BNP bind to the cell surface receptors of the target tissue: natriuretic peptide-A receptor (NPR-A) and natriuretic peptide-B receptor (NPR-B).[4] These receptors mediate the physiologic effects of these hormones. All three peptides are cleared by the equally high-affinity natriuretic peptide-C receptor (NPR-C) and are degraded by the ectoenzyme neutral endopeptidase (NEP).[2,3] BNP appears to be most resistant to degradation by NEP. The relative contribution of NPR-C and NEP to the metabolism of the natriuretic peptide is presently unclear. Other guanylate-cylcase linked receptors have been cloned, but their ligands have not yet been identified, suggesting therefore, that many more members of the natriuretic peptide family may exist.

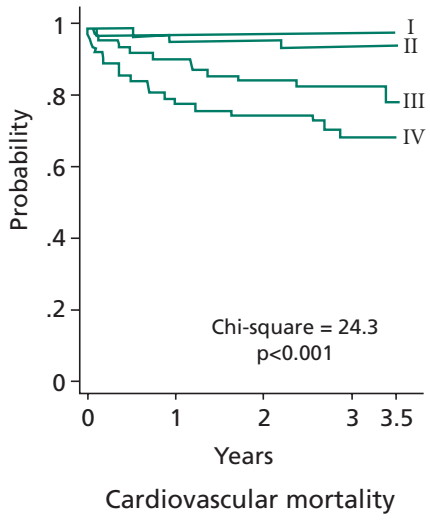
Evidence for counter-regulatory role of natriuretic peptides in heart failure

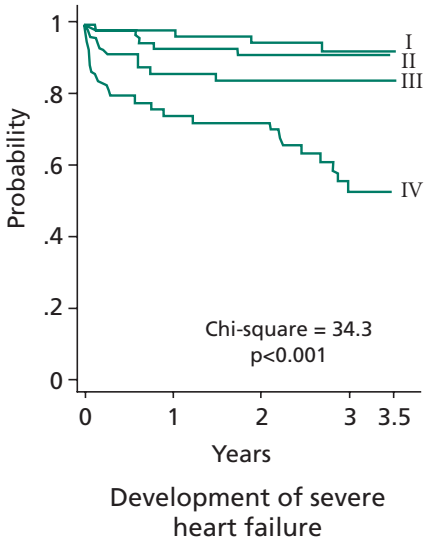
The hallmark of the heart failure phenotype is vasoconstriction and circulatory congestion, mediated substantially by the renin-angiotensin-aldosterone (RAA) system. As shown in Figure 2, ANP and BNP have multiple effects that are essentially antagonistic to the RAA system. They act on both arterial and venous vasculature to promote vasodilation and they increase the glomerular filtration rate by causing afferent renal arteriolar dilation and promoting efferent arteriolar vasoconstriction. They also directly inhibit production of renin and aldosterone, antagonizing the effect of angiotensin II, decreasing both Na and water retention through the kidney, and promoting vasodilation.[5]

There are two broad lines of evidence implicating the natriuretic peptides as an important neurohormonal system for regulating cardiorenal homeostasis in heart failure. The first line of evidence is derived from numerous reports on experimental models and on patients with heart failure showing increased circulating levels of ANP and BNP, as well as increased expression of the peptides in organs, including the heart.[2,3,5-12] The second, and possibly the more convincing line of evidence, is derived from studies using HS-142-1, a selective antagonist of NPR-A and NPR-B.[13] In a canine model of pacing-induced heart failure, intrarenal administration of HS-142-1 resulted in reduced renal excretory function, cGMP generation, and hastened the onset of severe heart failure.[14,15] Moreover, knockout mice completely lacking NPR-A receptors developed hypertension, cardiac hypertrophy, heart failure, and sudden death.[16] These data strongly support a functionally significant role for the endogenous natriuretic peptides in preserving renal function in heart failure.

Increasing evidence suggests that plasma levels of natriuretic peptide, most notably of N-ANP and BNP, can provide prognostic information for patients with chronic heart failure and those with post-myocardial infarction.[9,17] In the large SAVE study that evaluated the use of captopril in post-myocardial infarction patients with reduced left ventricular ejection, the patients with the highest quartile of ANP were found to be at highest risk of death or progression to severe heart failure (Figure 3).[18] More recently, plasma N-BNP levels were found to strongly predict all-cause mortality, hospitalization for heart failure, as well as the response to β-blockade therapy in patients with ischemic left ventricular dysfunction.[10] Finally, plasma BNP has also been found to predict mortality, recurrent

Figure 3: Event-free probability of patients with heart failure according to quartile of plasma N-ANP levels.[18] Cardiovascular mortality and development of severe heart failure are shown.





ischemic events, and the development of heart failure at 10-months post-event in patients with a wide spectrum of acute coronary syndromes.[19]

Diagnostic potential of natriuretic peptides in heart failure

Recent studies attest to the role of natriuretic peptides in the diagnosis of heart failure. A random sample of 2000 patients, selected from the practices of primary care physicians, examined the effectiveness of plasma N-ANP and BNP in diagnosing systolic left-ventricular dysfunction and documented by echocardiography.[20] The sensitivity and specificity of BNP to detect left-ventricular systolic dysfunction was 77% and 87%, respectively. Because of the low prevalence of left-ventricular dysfunction (3%), the positive predictive value was only 16%. The test performed better in older patients with a history of ischemic heart disease who had a higher pre-test likelihood of the disease.

Traditional assays for natriuretic peptides have been time-consuming and cumbersome. The development and recent approval by the Food and Drug Administration of a rapid, point-of-care assay for BNP may allow for the rapid diagnosis of heart failure in a variety of settings. In patients referred for echocardiography, the point-of-care BNP measurement appeared to distinguish between patients with normal ventricular function and diastolic and systolic left-ventricular dysfunction (Figure 4).[21] A patient presenting to the emergency department with shortness of breath often challenges the ER physician to distinguish heart failure from other causes of dyspnea, (ie, chronic obstructive lung disease). Preliminary data suggest that plasma BNP levels, determined by the bedside test, may be useful in identifying dyspneic patients presenting with heart failure decompensation. This test may, in fact, perform better than the ER physician's diagnosis (Figure 5).[22] Finally, point-of-care BNP determinations may also be valuable in following the effect of therapy, as well as in predicting short-term clinical outcomes (ie, mortality and recurrent hospitalization) in patients with decompensated heart failure.[23]

Figure 4: Plasma BNP levels in patients referred for echocardiography by presence and type of ventricular dysfunction. In comparison to normal left ventricular function, both systolic and diastolic left ventricular dysfunction lead to elevated BNP levels. The highest levels were seen when both systolic and diastolic dysfunction co-existed.[21]

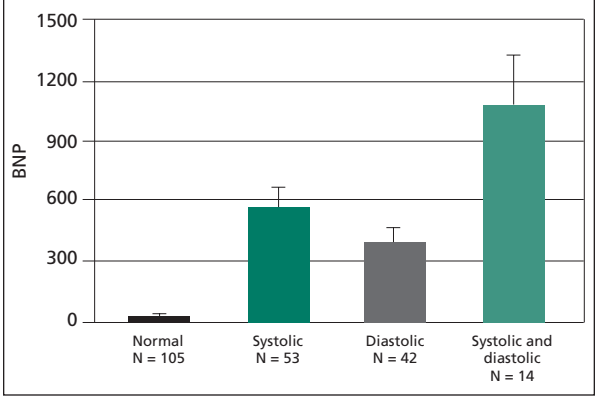


Figure 5: BNP and diagnosis of acute heart failure[22]

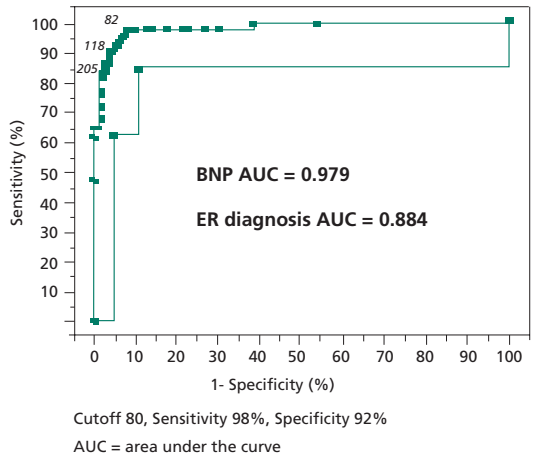
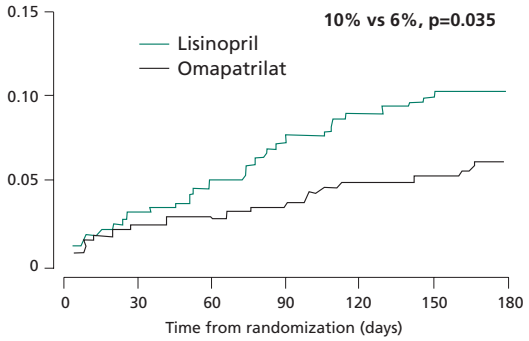


Figure 6: Secondary endpoints of the IMPRESS study. Rates of death, hospitalization for worsening heart failure, or discontinuation of treatment for heart failure favoured omapatrilat with a risk of adverse outcome of 6% versus 10% for lisinopril.



Number at risk							
Lisinopril	284	274	267	255	247	242	35
Omapatril	289	281	280	276	271	265	34

Therapeutic role of the natriuretic peptides

There are two broad approaches for targeting the natriuretic peptide system in the treatment of heart failure.

The first approach is to inhibit NEP, and therefore, reduce the breakdown of endogenous natriuretic peptides, as well as other vasodilator neurohormones degraded by NEP, (ie, bradykinin, prostaglandins, and adrenomedullin). Early studies, involving a small number of patients, examined the effects of candoxatril, an orally active NEP inhibitor, in patients with heart failure. These studies demonstrated either modest or no effects on hemodynamics or exercise tolerance.[24] In experimental models of hypertension and heart failure, the co-administration of NEP inhibitors and angiotensin converting enzyme (ACE) inhibitors appears to be more effective than selective inhibitors administered alone. To date, clinical experience with omapatrilat, a vasopeptidase inhibitor that inhibits both NEP and ACE, has been encouraging. In the IMPRESS study, the effect of omapatrilat and the ACE inhibitor, lisinopril, on exercise treadmill test (ETT) time was compared in 573 patients with heart failure.[25] There was no difference between omapatrilat and lisinopril in the primary endpoint of ETT time at 12 weeks. However, at 6-month follow-up, there was a trend in favor of omapatrilat on the combined endpoint of death or admission for worsening heart failure (Figure 6). In a recently completed neurohormone substudy of the IMPRESS trial, the favorable effect of omapatrilat was accompanied by an increase in plasma C-ANP levels, suggesting that augmentation of natriuretic peptides is a potential mechanism of benefit for vasopeptidase inhibition.[26] The potentially beneficial effect of vasopeptidase inhibition on clinical outcome will await the completion of the ongoing phase III trial (OVERTURE) of over 4000 patients comparing the effects of omapatrilat and the ACE inhibitor, enalapril, in patients with severe heart failure.

The second approach for targeting natriuretic peptides is to administer synthetic analogues of the peptides. Several studies have reported beneficial hemodynamic and renal effects of synthetic ANP in patients with heart failure.[27,28] However, studies comparing its effects in normal subjects and in patients with heart failure, demonstrated markedly attenuated diuretic and natriuretic responses to ANP in the patients with heart failure.[29,30] Nesiritide, a human recombinant BNP, is the only natriuretic peptide that has been evaluated extensively for use in a large number of patients with heart failure.[31] This agent mimics the actions of endogenous natriuretic peptides. In patients with decompensated heart failure, nesiritide (0.015 ug/kg/min and 0.03 ug/kg/min) exerts beneficial dose-dependent hemodynamic effects that are rapid in onset and sustained for the duration of drug infusion. The drug promotes diuresis, improves symptoms of fatigue and dyspnea, and appears to be well tolerated.

In the 498 patients of the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial, nesiritide produced a more pronounced

Figure 7: Primary endpoints of the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial.

Nesiritide	*vs.* Placebo	*vs.* NTG
↓ PCWP at 15 min.	*P* = 0.001	*P* = 0.002
↓ PCWP at 3 hrs.	*P* = 0.001	*P* = 0.027
↓ PCWP at 24 hrs.	na	*P* = 0.036
↓ Dyspnea at 3 hrs.	*P* = 0.034	na

na = data not available;
NTG = intravenous nitroglycerin;
PCWP = pulmonary capillary wedge pressure

and sustained decline in pulmonary capillary wedge pressure and an improvement in dyspnea, compared to intravenous nitroglycerin (Figure 7). Adverse events, including headaches, were less frequent than with nitroglycerin. The incidence of systemic hypotension was similar with the two drugs. Nesiritide has just been approved by the Food and Drug Administration for short-term intravenous treatment in patients with acute, decompensated, heart failure. It will be the first natriuretic peptide to be used clinically in the treatment of heart failure.

Conclusion

In summary, 20 years after the initial discovery, there have been major advances in understanding the cardiac natriuretic peptides. There is no doubt that the cardiac natriuretic peptides play an important role in maintaining circulatory homeostasis for patients with heart failure. The concept that the heart acts not only as a pump, but also as an endocrine organ to regulate blood pressure and volume, is well-established. Plasma levels of natriuretic peptides, especially BNP, can serve as important diagnostic and prognostic markers for heart failure. The approval of nesiritide opens up a new therapeutic avenue in the treatment of patients with decompensated heart failure.

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Abstract of Interest

Natriuretic peptides in chronic stable heart failure patients treated with omapatrilat, a vasopeptidase inhibitor: The IMPRESS Neurohormone Substudy

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Background: The IMPRESS trial demonstrated favourable effects of the vasopeptidase inhibitor, omapatrilat (OMA), compared to the angiotensin converting enzyme inhibitor (ACEi), lisinopril (LIS), in patients with CHF. In a prospectively planned substudy, we examined neurohormonal activation and the impact of vasopeptidase inhibition.

Methods: The neurohormone substudy enrolled 120 patients age >18 with NYHA functional class II to IV and LVEF <40%. Trough levels of neurohormones (approximately 24 hours after dosing) were assessed at baseline, 12 weeks, and 24 weeks. Neurohormones assayed included brain natriuretic peptide (BNP), N-terminal atrial natriuretic peptide (N-ANP). C-terminal atrial natriuretic peptide (C-ANP). Clinical outcomes were measured as the composite of emergency visit or hospitalization for worsening heart failure (WHF), discontinuation of study medication or addition of diuretic for WHF, and death.

Results: At baseline, significant negative correlations were seen between EF and BNP (rho = - 0.391, $p < 0.001$), N-ANP (rho = - 0.355, $p < 0.001$) and C-ANP (rho = - 0.301, $p < 0.001$). In univariate cox proportional hazards modelling, elevated C-ANP at baseline was associated with a relative risk (RR) of 4.6 ($p = 0.052$) for adverse clinical outcome. BNP (RR = 2.8) and N-ANP (RR = 2.6) were associated with increased relative risk that was not statistically significant. On treatment, C-ANP levels fell in patients taking lisinopril (mean – 0.154) and increased in patients treated with omapatrilat (mean 0.071, $p = 0.029$ for difference). N-ANP showed a similar trend while BNP decreased in both groups.

Conclusion: C-ANP was the most powerful predictor of clinical outcome and therapy with OMA was associated with an increase in C-ANP levels in comparison to patients with LIS. These data provide valuable insight into the mechanism of vasopeptidase inhibition, a novel therapeutic modality in CHF.

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