Diagnostic and Therapeutic Utility of B-Type Natriuretic Peptide in Patients With Renal Insufficiency and Decompensated Heart Failure

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Chronic kidney disease (CKD) and congestive heart failure (CHF) are epidemiologically and pathophysiologically linked. A recent study in patients with severe CHF demonstrated that renal plasma flow was inversely correlated with pulmonary capillary wedge pressure, right atrial pressure, pulmonary pressure, and right ventricular ejection fraction. This article reviews the utility of B-type natriuretic peptide (BNP) levels in assessing cardiac function and volume status in patients with CKD and examines the safety and efficacy of BNP therapy in patients with renal insufficiency and decompensated heart failure.
[Rev Cardiovasc Med. *2004;5(1):16-25*]

Key words: Congestive heart failure • Renin-angiotensin-aldosterone system • B-type natriuretic peptide • Nesiritide • Chronic kidney disease

Only 16% of chronic kidney disease (CKD) patients who have reached end-stage renal disease (ESRD) have echocardiographically normal left ventricles,[1] and 40% have clinically diagnosed congestive heart failure (CHF).[2] The activation of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), and endothelin-1 by heart failure reduces

renal perfusion acutely and confers acquired diuretic resistance.[3,4] Chronic RAAS activation causes glomerulosclerosis, tubulointerstitial fibrosis, and proteinuria, as well as abnormal left ventricular remodeling and progressive cardiomyopathy.[5,6]

B-type natriuretic peptide (BNP), produced by the cardiac ventricles and, to a small degree, by the renal glomerular epithelial and mesangial cells,[7,8] is a counter-regulatory hormone that physiologically opposes and suppresses the RAAS endothelin-1 and the SNS.[8,9] Endogenous BNP and atrial natriuretic peptide (ANP) production maintain renal function and sodium balance when cardiac function acutely deteriorates.[10] However, as with other pathophysiologic derangements, further worsening of cardiac function, accompanied by greater activation of vasoconstrictive and sodium retentive hormonal systems, eventually overwhelms the capacity of the endogenous natriuretic peptides to maintain compensation.

Administration of exogenous intravenous (IV) BNP increases circulating levels by 2- to 6-fold[11,12] and has been empirically shown to rapidly improve hemodynamic, volume, neurohormonal, and symptomatic abnormalities in patients with acute decompensated heart failure[13-15] and to decrease rates of rehospitalization.[16,17] Nesiritide IV (human recombinant BNP) is approved for the treatment of acute decompensated CHF.

The physiologic effects of nesiritide include veno- and arterial dilatation[18] (without reflex tachycardia), diuresis, and natriuresis (without reduction in renal perfusion or function).[14] Thus, nesiritide increases cardiac index and reduces pulmonary capillary wedge pressure (PCWP).[14] In addition, nesiritide is lusitropic, anti-fibrotic, and inhibits the RAAS[8]; thus, nesiritide should stabilize renal function acutely and chronically while improving cardiac function and hemodynamics in CHF patients.

This paper reviews the utility of BNP levels in assessing cardiac function and volume status in CKD patients. It further summarizes the safety and efficacy of BNP as therapy for managing heart failure in patients with acute and chronic renal insufficiency. Emerging applications of BNP therapy in inpatients and outpatients with decompensated heart failure that are relevant to the practice of nephrology and cardiology are specifically discussed.

Chronic CHF and CKD may aggravate the progression of each other, leading to an inexorable vicious cycle and accelerated cardiac and renal fibrosis.

Chronic Kidney Disease and Congestive Heart Failure

Patients with CKD have a disproportionate burden of cardiovascular disease, including CHF. Undoubtedly, CKD is complicating the CHF epidemic we have observed over the past 15 years.[19] According to the U.S. Renal Data System (USRDS), 40% of incident dialysis patients have a known diagnosis of CHF.[2] When such patients are examined systematically, left ventricular abnormalities are highly prevalent.[1] In one study, cardiac echocardiography was performed in 432 consecutive dialysis patients. Of this group, only 16% had echocardiographically normal left ventricles and the rest had myriad abnormalities: systolic dysfunction (16%), concentric left ventricular hypertrophy (LVH) (41%), and left ventricular dilatation (28%). Although the rates of diastolic dysfunction in those with CKD and ESRD are currently unknown, they are expected to be high.[20] Left ventricular abnormalities are apparent long before CKD patients become end-stage. A multicenter Canadian cohort study of 446 patients[21] found the prevalence of concentric left ventricular hypertrophy among patients with glomerular filtration rates (GFRs) of 50 mL/min to 75 mL/min, 25 mL/min to 50 mL/min, and less than 25 mL/min to be approximately 30%, 33%, and 49%, respectively.

The common co-occurrence of CKD and CHF is not surprising given that classical cardiovascular risk factors, such as hypertension and diabetes, are also risk factors for CKD. It is also plausible that chronic CHF and CKD may aggravate the progression of each other, leading to an inexorable vicious cycle and accelerated cardiac and renal fibrosis (Figure 1).[22] Systemic and tissue-level activation of the RAAS, as seen in heart failure, is strongly implicated in numerous adverse functional and structural cardiac and renal effects (Table 1).[5,6,23]

Indeed, many of the therapeutics that improve chronic heart failure and/or CKD outcomes, such as angiotensin-converting enzyme (ACE) inhibitors[24,25] and aldosterone-receptor blockers,[26] inhibit the RAAS. Selective aldosterone blockade with spironolactone[27] also reduces mortality in subsets of patients with chronic CHF; there is a strong rationale for utilizing aldosterone blockade to reduce the rate of renal functional loss in CKD patients.[5,6,23] The limitations of the aforementioned therapeutics in the population of patients with CKD and CHF are hyperkalemia and

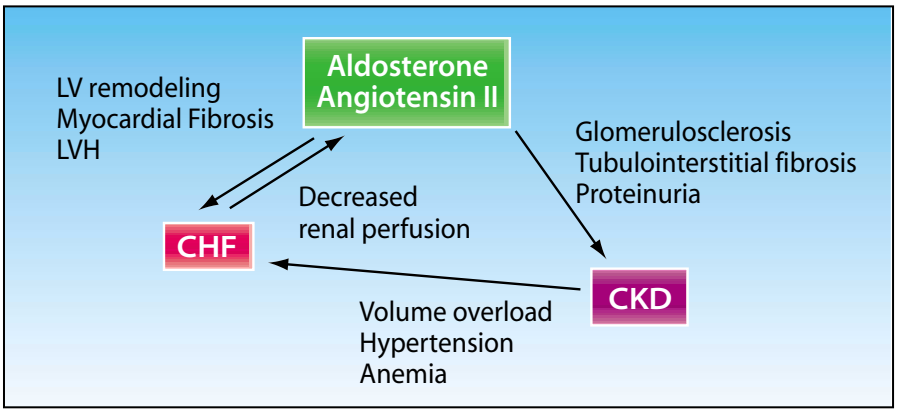

Figure 1. *Central role of the renin-angiotensin-aldosterone axis in progressive cardiomyopathy and chronic kidney disease. CHF, congestive heart failure; CKD, chronic kidney disease; LVH, left ventricular hypertrophy.*

acute worsening of renal filtration function. The difficulty of use of ACE inhibitors in this high-risk population is reflected by studies of patients with advanced CHF (and mean serum creatinine (Cr) of 1.5–1.6 mg/dL) in which baseline therapy with ACE inhibitors was far from universal (VMAC, 69%[15]; OPTIME, 69%[28]).

Renal Function as a Predictor of Outcome

The major prognostic importance of renal insufficiency, volume status, and systemic perfusion was evident with blood urea nitrogen (BUN) and serum creatinine as 2 of the 3 strongest independent predictors of mortality among U.S. patients who were hospitalized with a primary diagnosis of acute CHF.[29] A discharge serum Cr greater than 2.5 mg/dL also was a significant predictor of 60-day hospital readmissions among a Medicare cohort (N = 2176) with an index hospitalization for acute CHF.[30] In addition, several studies have found that, independent of age, left ventricular ejection fraction, diabetes, and discharge Cr level, even small deteriorations in renal function (Cr elevations of 0.2 mg/dL) during hospitalization for acute CHF, are predictors of increased mortality.[31,32] Worsening renal function during hospitalization is the most frequent reason for the use of the intensive care unit and IV inodilators in patients with acutely decompensated CHF.[33]

Neurohormonal Activation

Worsening of renal function during treatment of CHF and acute worsening of renal function at the time of presentation with acute decompensated CHF are typically due to renal hemodynamic alterations mediated by activation of myriad renal vasoconstrictive hormonal systems. Such systems include the RAAS, the SNS, thromboxane A2, and endothelin-l.[9,34,35] RAAS and SNS activation is further aggravated by the universal utilization of loop and thiazide diuretics during treatment of acute CHF. IV diuretics have been shown to cause significant increases in plasma renin and norepinephrine within 20 minutes of administration.[36] Hence, while helpful in clearing pulmonary congestion, the early and singular use of IV loop diuretics further activates the RAAS and SNS while leading to elevations in Cr in many patients.

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Natriuretic Peptides and Acute Heart Failure

ANP and BNP are produced by the atria in response to volume overload and by the ventricles in response to

Table 1
Adverse Consequences of Chronic Systemic and Tissue Level RAAS Activation

Kidney	Heart
• Hypoxia/vasoconstriction	• Adverse left ventricular remodeling
• Intra-glomerular hypertension	• Left ventricular hypertrophy
• Proteinuria/increased nephrin	• Myocardial fibrosis
• Glomerulosclerosis	• Endothelial dysfunction
• Tubulointerstitial fibrosis	• Coronary atherosclerosis vasoconstriction
	• Prothrombotic effects/increased plasminogen activator inhibitor

RAAS, renin-angiotensin-aldosterone system
Data from: Epstein M,[5] Brewster UC, et al,[6] and Hostetter TH, et al.[23]

pressure overload, respectively.[8] BNP is also expressed under physiologic conditions by human glomerular epithelial and mesangial cells in smaller quantities.[7] Both peptides agonize the guanylate cyclase-coupled natriuretic peptide receptor A (NPR-A) and are cleared by the clearance receptor, natriuretic peptide receptor C (NPR-C), both of which are present in high density within renal parenchyma.[8] Evidence also exists for a novel receptor that binds BNP, but not ANP.[37,38] Both ANP and BNP are cleared by neutral endopeptidase (NEP 24.11), which is found on endothelial cell surfaces and within the kidneys. Interestingly, renal NEP appears to degrade ANP with much greater efficiency than it degrades BNP.[39] The 50-fold lower potency of ANP compared with BNP in increasing cGMP in kidney cells was equalized by an inhibitor of NEP, suggesting that the higher potency of BNP may be related to a longer half life within the kidney.[39] The production of BNP by renal epithelial and mesangial cells and lower renal degradation of BNP compared with that of ANP suggests that BNP may serve as a renal paracrine hormone.

Compared to ANP, equimolar doses of BNP produce a greater increase in GFR and sodium excretion[40] and more reduction of filling pressures and increases in cardiac output.[38] The physiologic response to ANP may be less than that of BNP because of a decoupling, in heart failure, of cGMP response of the NPR-A receptor to ANP, mediated by a protein phosphatase (PP5).[41] Shorter circulating half life of ANP (3 minutes) versus BNP (18 minutes)[11] may also contribute to the differences in physiologic response.

Acute inhibition of the NPR-A in dogs with rapid ventricular pacing-induced acute heart failure leads to a reduction in the glomerular filtration and sodium excretion rates,[42] suggesting that the elevated levels of ANP and BNP seen in acute heart failure are important in preventing volume overload and maintaining renal function. The mechanism for preservation of renal function and sodium excretion likely include the peptides' ability to directly inhibit the vasoconstrictive and sodium- and water-retentive hormones and hormonal systems, RAAS, norepinephrine, and endothelin-1, and vasodilatory effects that serve to lower filling pressures. At the cellular level, interaction of BNP with the renal RAAS on GFR may be, at least in part, related to modulation by BNP of the voltage response of mesangial cells induced by angiotensin II. (BNP increases potassium conductance and hyperpolarization of renal mesangial cells.) Further, this increase in the K+ conductance seems to be additive to that inducible by adenosine, indicating that different K+ channels are activated by BNP.[43] In addition, vasodilatory action of BNP—at least in coronary circulation—is attenuated by prostaglandin blockade, suggesting that BNP's effects may be, in part, mediated by effects on prostaglandins.[44]

Although it is commonly believed that renal perfusion in CHF is predominantly a function of cardiac index and blood pressure, a recent study in patients with severe CHF demonstrated that renal plasma flow was inversely correlated with PCWP, right atrial pressure, pulmonary pressure, and right ventricular ejection fraction. Renal perfusion did not correlate with cardiac index, systemic vascular resistance, or blood pressure (Table 2).[45]

Table 2
Correlation of Systemic Hemodynamic Parameters to Renal Plasma Flow in Heart Failure Patients[45]

Hemodynamic Parameter	r-value for Correlation With RPF	*P* Value
PCWP	-0.69	< .001
PAP	-0.65	< .01
RAP	-0.47	< .05
RVEF	+0.49	< .05

Renal plasma flow did not correlate significantly with cardiac index, systemic vascular resistance index, or blood pressure.
PCWP, pulmonary capillary wedge pressure; PAP, pulmonary artery pressure; RAP, right atrial pressure; RVEF, right ventricular ejection fraction. Data from: Kos, et al.[45]

Both ANP and BNP have direct renal tubular sodium excretory effects.[46] Interestingly, BNP levels achieved during sodium loading or seen in mild heart failure produce distal tubular effects, whereas BNP levels achieved with pharmacologic administration of this peptide have both proximal and distal tubular effects.[46] This phenomenon may be explained by the observation that human proximal tubular cells express new NPR-A receptors when exposed to exogenous BNP.[47] The clinical trial data have supported the idea that the physiologic response to exogenously administered natriuretic peptide is of a greater magnitude than what was observed with endogenously produced peptide. For example, when 127 patients with acute decompensated CHF and mean baseline (endogenous) BNP level > 1000

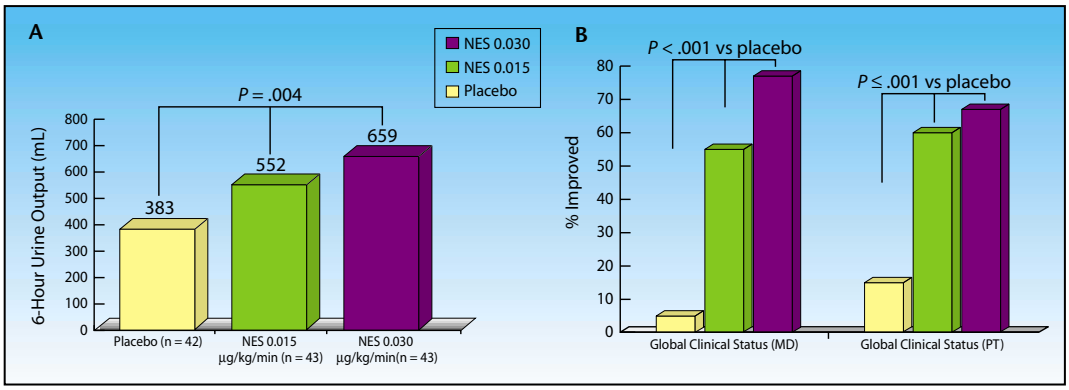

Figure 2. (A) *Effect of nesiritide (NES) on urine volumes over 6 hours.* **(B)** *Effect of nesiritide on clinical improvement over 6 hours judged by blinded patients (PT) and physicians (MD).*

pg/mL were randomized to 1 of 2 doses of nesiritide or placebo as first-line monotherapy, patients who received nesiritide had a dose-dependent increase in urine volume (Figure 2A).[14]

BNP Levels in Patients With Renal Disease

A number of studies have examined BNP levels in dialysis patients[48-51] and in patients with lesser degrees of renal insufficiency.[52] Whereas the studies typically have reported that higher-than-normal mean BNP levels are associated with estimated glomerular filtration rate less than 60 mL/min/1.73 m^2,[52] BNP levels were not elevated in patients with ESRD who had normal cardiac function and no LVH on echocardiography.[48] Therefore, the abnormalities in BNP levels frequently observed in patients with renal insufficiency and ESRD are a reflection of a high prevalence of left ventricular abnormalities, such as LVH and the ensuing cardiac pressure overload. Consistent with a lack of accumulation of endogenous BNP in ESRD patients are clinical observations that physiologic effects of exogenously administered BNP are similar in patients with moderate-to-severe renal insufficiency, compared to individuals with normal renal function.

BNP levels in ESRD patients do not appear to correlate well with venous and interstitial volume status. In one study, the r-value for the correlation between BNP levels in dialysis patients with echocardiographic measurements of inferior vena cava diameter was 0.27 and was 0.39 for total body water using bioimpedance.[53] BNP levels do not normalize following hemodialysis[50,53] and, in some studies, are

Table 3
Physiologic Effects of B-Type Natriuretic Peptide

Observed Physiologic or Clinical Effect	Known or Presumed Mechanism	Reference
Increased urine volume and/or reduced diuretic need	Increased proximal and distal tubular sodium (and water) excretion Direct inhibition of aldosterone, renin, norepinephrine Improvement in renal perfusion secondary to improvements in cardiac function and inhibition of endothelin-1, norepinephrine, and angiotensin II	14,15,62
Maintenance of glomerular filtration rate and renal blood flow	Angiotensin II inhibition balanced by inhibition of renal vasoconstrictive hormones and improved cardiac function	13,62
Neutral effects on serum potassium	Enhanced potassium secretion secondary to natriuretic effects balanced by aldosterone inhibition	55
Reduction in cardiac filling pressures and pulmonary artery pressures	Direct venodilation Direct arterial dilation Direct pulmonary vasodilation Decreased PA pressures due to cardiac functional improvements	14,15
Neutral effects on heart rate	Arterial dilatation and potential reflexive effect on heart rate balanced by suppression of norepinephrine	14,15
Absence of proarrhythmia	Suppression of norepinephrine Absence of inotropic effects	14,69,70
Improved coronary blood flow	Direct coronary vasodilation Improved diastolic and systolic function	15,71
Reduced longer term mortality	Anti-fibrotic/anti-remodeling effects Neurohormonal suppression	8,16,66,67,69

apparently unchanged after patients are returned to their clinically determined stable dry weight, suggesting that BNP is not significantly (if at all) cleared by hemodialysis. The fact that BNP does not decrease in parallel with fluid removal on dialysis also suggests that it is not an optimal marker of volume status; however, the relative reduction in BNP with a dialysis session may prove to be an important indicator of optimally reduced left ventricular wall tension.[54]

Physiologic Effects of BNP

BNP has myriad physiologic and clinical effects (Table 3), many of which are relevant when managing patients with combined kidney failure and CHF. As a therapy, BNP is the only available compound that creates improvements in both renal and cardiac function when used short-term. Although other available IV therapies, including nitroglycerin, nitroprusside, phosphodiesterase inhibitors (amrinone, milrinone), catecholamines (dobutamine, dopamine), and diuretics (furosemide, torsemide) improve some aspects of cardiac hemodynamics, they either reduce renal filtration function or activate adverse neurohormonal systems (SNS, RAAS, endothelins).

Improvements in Cardiopulmonary Hemodynamics and Heart Failure Symptoms

Nesiritide consistently and rapidly lowers elevated filling pressures, such as PCWP, right atrial pressure, and pulmonary artery pressures, and it increases cardiac index in a dose-dependent manner. In addition, it has no significant inotropic or chronotropic effects (Table 4). Nesiritide produced favorable reductions in systolic blood pressure (SBP) in patients with elevated baseline SBP and did not negatively impact patients with low baseline SBPs. Decreases in SBP were proportional to baseline SBP and consistent with the low incidence of symptomatic hypotension in all patients (including those with low baseline SBP), indicating that the vasodilatory effects of nesiritide may be self-regulatory.[55]

plus standard therapies. The findings among patients with systolic and diastolic dysfunction were similar (Scios Inc., data on file). Dyspnea was improved with nesiritide, but not nitroglycerin, over placebo. Hemodynamic effects of nesiritide were statistically significant within 15 minutes of initiating therapy.

Nesiritide was significantly better at reducing PCWP than placebo plus standard therapies and intravenous nitroglycerin plus standard therapies.

In a large, randomized, double-blind clinical trial[15] (N = 489), nesiritide, nitroglycerin, or placebo was added to existing therapies (including IV diuretics, oral and transdermal nitrates, ACE inhibitors, ß-blockers, digoxin, hydralazine, dopamine, and dobutamine). The trial was conducted in hospitalized patients with refractory CHF, PCWP > 20 mm Hg, and dyspnea at rest or with minimal exertion despite ongoing standard treatment. Nesiritide was significantly better at reducing PCWP than were placebo plus standard therapies and IV nitroglycerin Nesiritide was associated with significantly fewer adverse events than nitroglycerin in this trial. Incidence of symptomatic hypotension was similar (4% with nesiritide and 5% with nitroglycerin, over 24 hours).

In patients with renal insufficiency (serum Cr > 2, mean 3 mg/dL, range 2–11.1 mg/dL), nesiritide was safe and improved hemodynamics and dyspnea to an extent similar to that in nesiritide-treated patients with serum Cr < 2.0 mg/dL (mean Cr = 1.2 mg/dL). Effects of nesiritide versus nitroglycerin in patients with renal insufficiency mimicked the

Table 4
Hemodynamic Effects of Nesiritide

	Placebo	Nesiritide 0.015 µg/kg/min	Nesiritide 0.030 µg/kg/min	*P* Value
PCWP (mm Hg)	+2.0 ± 7.2	-6.0 ± 7.2*	-9.6 ± 6.2*	< .001
RAP (mm Hg)	+0.4 ± 4.6	-2.6 ± 4.4†	-5.1 ± 4.7*	< .001
SVR (dynes/s/cm^{-5})	+161 ± 481	-247 ± 492*	-347 ± 499*	< .001
CI (L/min/m^2)	-0.1 ± 0.47	+0.2 ± 0.49†	+0.4 ± 0.69*	< .001
SBP (mm Hg)	+0.3 ± 11	-4.4 ± 10.2	-9.3 ± 12.6*	< .001

Values are means + SD. *P* values are for the comparison among all three groups, calculated with the omnibus F test.
* $P < .001$ for the pairwise comparison with placebo, by the F test.
† $P < .05$ for the pairwise comparison with placebo, by the F test.
PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SVR, systemic vascular resistance; CI, cardiac index; SBP, systolic blood pressure.

overall results of the Vasodilation in the Management of Acute CHF (VMAC) trial.[56,57] It was noted that the presence of oliguric ESRD did not prevent robust hemodynamic and symptomatic effects of nesiritide, even in the absence of urine output.

The latter observation suggests that the significant and rapid reductions in pulmonary artery pressures and filling pressures and symptomatic improvement seen with nesiritide are not only a function of its diuretic and natriuretic effects. Indeed, in the efficacy trial described above,[14] the extent of urine output observed, although statistically significant and dose-dependent, did not appear to fully explain the even greater magnitude of improvements in clinical status (Figure 2B). It previously has been shown that ANP can improve oxygenation in oligo-anuric patients with CHF without affecting urine volume.[58] One study reported that hemodialysis patients presenting in the "middle of the night" with acute CHF were successfully stabilized with improvements in oxygenation, filling pressures, and symptoms with nesiritide administration until dialysis could be performed.[59]

Natriuresis and Renal Function Preservation in Heart Failure

The presence of CKD or acute deterioration of renal function in the setting of CHF portends a poor outcome and heralds a significant therapeutic challenge, including inability to adequately diurese. The addition of diuretics in this setting, although necessary, is associated with the risk of further neurohormonal activation,[36] sodium retention between doses or diminishing efficacy of continuous infusions, and worsening renal function.[60]

The ability of nesiritide to suppress sodium retentive and renal vasoconstrictive neurohormonal systems while exerting natriuretic effects predicts that its use as a natriuretic should not be hindered by worsening renal function, as occurs with conventional diuretics. Indeed, in studies in CHF patients,[13,61-63] no reductions in either renal blood flow or GFR occurred (despite natriuresis).

It may be possible, with the early use of nesiritide in combined kidney failure and CHF, to reduce the use of additional therapies, including inodilators.

In theory, nesiritide (by suppressing renin and, in turn, angiotensin II) may cause an ACE inhibitor-like effect on renal hemodynamics; however, one would expect this phenomenon to be balanced by increased renal perfusion and glomerular filtration occurring in conjunction with improved cardiac function. Whereas the new addition of an ACE inhibitor in patients with severely decompensated CHF would be intolerable due to renal functional decline in a large fraction of patients, such acute deteriorations in renal function are not observed in nesiritide clinical trials in this population of patients. In the VMAC trial, a study of highly compromised and refractory acute CHF patients, mean change in serum Cr from baseline (after a typical treatment course of 48 hours) was: 0 +/- 0.41 mg/dL on day 2; 0.1 ± 0.59 mg/dL on day 5; 0.2 ± 0.85 mg/dL on day 14; and 0.1 ± 0.75 mg/dL on day 30 (Scios Inc., data on file).

In fact, in patients with acute worsening of renal function in the setting of acute CHF, nesiritide would be expected to improve renal function by inhibiting renal vasoconstrictive hormones that are mediating the renal functional decline. The current literature on this potential use of nesiritide is encouraging[64,65]; however, no large trials in patients with CHF and acute renal insufficiency have been conducted. It may be possible, with the early use of nesiritide in combined kidney failure and CHF, to reduce the use of additional therapies, including inodilators. Thus, the use of additional hospital resources and risks of invasive hemodynamic monitoring and arrhythmias could be avoided.

Management of Patients With Chronic Kidney Disease and Chronically Decompensated Heart Failure

Patients with moderate and severe CKD and advanced cardiomyopathy are difficult to manage because both their renal function and cardiac function are exquisitely sensitive to circulating volume. Both renal and cardiac function in these patients typically decline progressively despite attempts to treat with ß-blockers, ACE inhibitors, spironolactone, and angiotensin receptor blockers. Is there a rationale for treating such patients with nesiritide in an attempt to break the vicious cycle leading to progressive nephropathy and cardiomyopathy? (See Figure 1.)

Mouse transgenic models that overexpress BNP have greatly attenuated tissue damage, mesangial expansion, and proteinuria in response to immune-mediated renal injury compared with littermates that do not overexpress BNP.[66] Mice overexpressing BNP also have reduced glomerular injury and pro-

teinuria after subtotal nephrectomy induced by resection of the renal poles.[67] In the BNP over expressing transgenic mice, expressions of transforming growth factor-ß (TGF-ß) and fibronectin are suppressed. Long-term hydralazine treatment in nephrectomized, nontransgenic mice failed to inhibit glomerular hypertrophy, suggesting that the observed effects of BNP under reduced renal mass are not due merely to systemic blood pressure reduction.

In cultured mesangial cells, natriuretic peptides counteract the effects of angiotensin II with regard to extracellular signal-regulated kinase phosphorylation and fibrotic action. Because angiotensin II has been shown to play a pivotal role in the progression of nephritis through induction of TGF-ß and monocyte chemoattractant protein-1 (MCP-1) that may be extracellular signal-regulated kinase-dependent, the protective effects of BNP are likely to be exerted, at least partly, by antagonizing the RAAS locally.[66]

The duration of beneficial clinical effects of acute neurohormonal suppression following short-term treatment of CHF with nesiritide is not known. In one randomized trial of 306 patients, short-term (< 5 days) treatment with nesiritide .015 µg/kg/min was associated with significantly lower CHF readmission rates over 21 days and a lower 6-month mortality rate compared with treatment with dobutamine.[16] In another trial of 237 patients randomized to treatment with nesiritide or placebo added to standard emergency department management, the use of nesiritide (mean duration < 24 hours) was associated with reduced readmissions over 30 days (10% vs 23%, $P = .06$), and the number of hospital days during the 30-day follow-up period was significantly lower in patients receiving nesiritide than in those receiving standard therapies (5.5 vs 10.2 days, $P = .05$).[17]

Based on the above observations and the hypothesis that chronic neurohormonal suppression with nesiritide may improve outcomes by reducing left ventricular remodeling and maintaining renal function over time, an open-label pilot study was recently conducted. Follow Up Serial Infusions of Nesiritide (FUSION) used serial outpatient infusions of nesiritide in patients with advanced CHF at a high risk for rehospitalization. Investigators enrolled 210 patients (NYHA class III/IV; 6-min walk test = 400 m) receiving optimal therapy (as determined by the investigators) (71% ß-blockers; 57% ACE inhibitors; 14% ARBs) who had more than 2 acutely decompensated HF events requiring intravenous (IV) therapy in the past 12 months. Patients were randomized to standard care (which could include inotropes at the investigator's discretion) or weekly nesiritide, administered intravenously at a dose of .005 or .01 µg/kg/min over 6 hours and preceded by a bolus as high as 2 µg/kg. Nesiritide-treated patients were not permitted to receive outpatient IV inotropic therapy. Patients in all three groups were required to visit the clinic weekly irrespective of treatment with IV therapies. The frequency of nesiritide infusions could be adjusted based on symptomatology, from every other week to twice weekly. Patients were treated for 12 weeks and further followed for another month. Echocardiograms were obtained at baseline and at week 12 in 92 patients, and measurements were conducted in a blinded fashion using a central laboratory. Randomization was stratified by low or high risk for rehospitalization based on 7 prognostic factors. Patients with 4 of the following criteria were stratified into a high-risk group: SCr > 2.0 mg/dL, NYHA class IV, age > 65, history of sustained ventricular tachycardia, ischemic etiology of CHF, history of diabetes, outpatient use of nesiritide or inotropes in the past 6 months.[68]

FUSION data suggest that serial outpatient infusions of nesiritide given to patients with advanced heart failure who are at high risk for hospitalization potentially reduces morbidity and mortality due to heart failure.

FUSION demonstrated that weekly infusions of nesiritide in an outpatient setting in patients with advanced CHF were well tolerated. Compared to use of standard care, the use of nesiritide infusions was associated with trends towards fewer hospitalizations, reduced mortality, reduced aldosterone and endothelin levels, improved ejection fraction, and an improvement in clinical status as assessed by the physician.

Patients identified as high risk for rehospitalization appeared to have the greatest benefit from nesiritide treatment; for example, this group had a reduced incidence of worsening heart failure, less hypotension, and fewer adverse renal events (such as increased serum creatinine). There was also a trend towards reduced mortality in this group.[68]

FUSION data suggest that serial outpatient infusions of nesiritide given to patients with advanced heart failure who are at high risk for hospitalization potentially reduces morbidity and mortality due to heart failure. The observed reduction in

neurohormonal activation and known antifibrotic effects of BNP may underlie the clinical benefit seen.

The above results suggest that there may be a role for long-term intermittent treatment with nesiritide in high-risk patients with advanced cardiomyopathy and CKD. Additional clinical trials are planned.

Conclusion

Patients with CHF and CKD and those with acute worsening of renal function are challenging to manage because of increased vulnerability to further deterioration of renal function, diminished sensitivity to diuretics, and proarrhythmia potential. The neurohormonal suppressive, lusitropic, vasodilatory, and blood pressure effects of nesiritide, as well as its safety, make it an attractive drug for managing such patients. Clinical trial data indicate that patients with renal insufficiency respond well to nesiritide in the acute setting. Results from an open-label pilot study using serial outpatient infusions of nesiritide in patients with advanced CHF show that chronic administration of nesiritide is safe and may improve clinical outcomes in high-risk patients with advanced decompensated CHF. The role of nesiritide in "bridging" patients with acute heart failure to an acute dialysis treatment or of "bridging" patients with CKD and advanced CHF until the initiation of chronic dialysis is yet to be fully defined. ■

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Main Points

- B-type natriuretic peptide (BNP), produced by the cardiac ventricles and, to a small degree, by the renal glomerular epithelial and mesangial cells, is a counter-regulatory hormone that physiologically opposes and suppresses the RAAS endothelin-1 and the SNS.
- Baseline renal function and renal functional changes are important predictors of outcome in acute heart failure.
- Independent of age, left ventricular ejection fraction, diabetes, and discharge Cr level, even small deteriorations in renal function (Cr elevations of 0.2 mg/dL) during hospitalization for acute CHF, are predictors of increased mortality.
- As a therapy, BNP is the only available compound that creates improvements in both renal and cardiac function when used short term.
- The ability of nesiritide to suppress sodium retentive and renal vasoconstrictive neurohormonal systems while exerting natriuretic effects predicts that its use as a natriuretic should not be hindered by worsening renal function, as occurs with conventional diuretics.
- In patients with acute worsening of renal function in the setting of acute CHF, nesiritide would be expected to improve renal function by inhibiting renal vasoconstrictive hormones that are mediating the renal functional decline.
- FUSION demonstrated that weekly infusions of nesiritide in an outpatient setting in patients with advanced CHF were well tolerated.
- There may be a role for long-term intermittent treatment with nesiritide in high-risk patients with advanced cardiomyopathy and CKD.

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