# Nesiritide: A Unique Therapeutic Cardiac Peptide

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*Nesiritide is the generic name for recombinant human B-type natriuretic peptide. This drug represents the first of a new class of agents for the treatment of decompensated congestive heart failure. The properties of B-type natriuretic peptide include a balanced arterial and venous vasodilatation and a marked natriuresis and diuresis, making it an excellent drug for the management of heart failure. We review the physiology and pathophysiology of the natriuretic peptides and the clinical data for nesiritide. In addition, the hemodynamic effects of the drug as well as its efficacy and safety in the treatment of heart failure are critiqued. Nesiritide is a new class of therapeutic peptide for the treatment of heart failure that appears to offer unique and safe hemodynamic properties.* [Rev Cardiovasc Med. *2001;2(suppl 2):S25–S31]*



**Key words:** Natriuretic peptides • Congestive heart failure • Nesiritide • Vasodilators

The natriuretic peptides are a family with unique biochemical and physiological properties. In 1981, de Bold and colleagues reported that infusing an extract of atrial tissue into rats resulted in an impressive natriuresis.[1] Subsequent work by numerous investigators led to the isolation and cloning of human atrial natriuretic peptide (hANP), first reported by Kangawa and colleagues in 1984.[2] Subsequently, three additional members of the natriuretic peptide family have been isolated, including B-type natriuretic peptide (hBNP), C-type natriuretic peptide (CNP), and recently a fourth member of the family, Dendroaspis natriuretic peptide (DNP).[3,4] Recombinant human B-type natriuretic

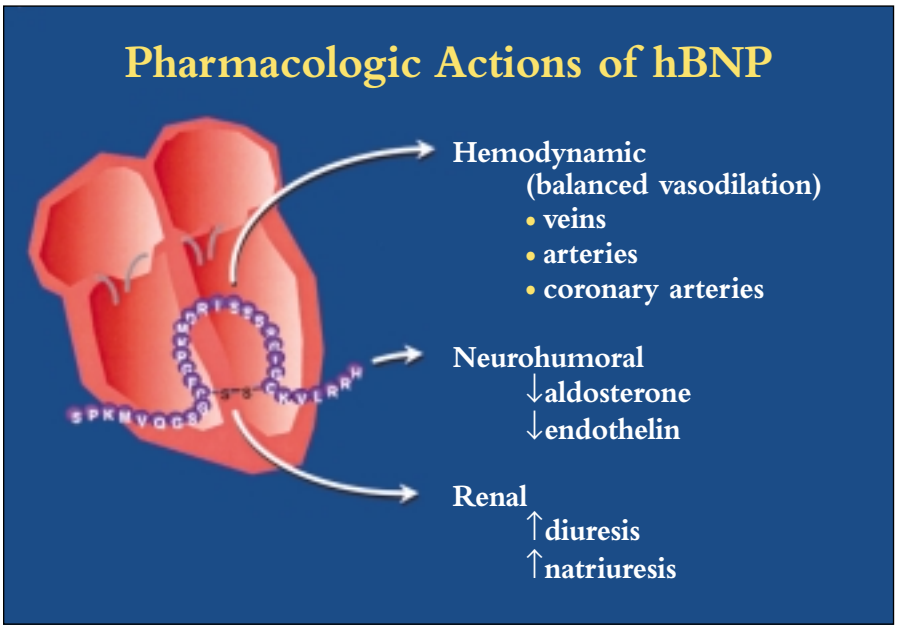


**Figure 1.** *Pharmacologic actions of hBNP.*

peptide will become the first natriuretic peptide commercially released in the United States as a pharmaceutical agent.

## Structure and Function

The natriuretic peptides have related but distinct protein structures with unique genetic encoding, distribution, effects, and regulation.[3] All appear to play an endocrine role in the regulation of cardiorenal homeostasis. Three distinct natriuretic peptide receptors have been identified—somewhat unfortunately labeled A, B, and C. These labels do not reflect an association with the similarly labeled natriuretic peptides, leading to a confusing nomenclature. hANP and hBNP bind to the A-type receptor and CNP binds to the B-type receptor. Both the A- and B-type receptors activate guanylyl cyclase when stimulated, resulting in an increase in intracellular cGMP in the target tissues. This appears to be the primary mechanism of action of the natriuretic peptides. The C-type receptor is capable of binding hANP, hBNP, and CNP in approximately equal affinity and serves primarily as a clearance receptor. Further clearance of the natriuretic peptides is accomplished by cleavage via neutral endopeptidases. Binding characteristics for DNP have not yet been reported.

As its name implies, hANP is produced predominately in the human atria, with lower concentrations found in the ventricles and kidney (in the form of urodilatin).[3] hBNP was initially identified in an extract of porcine brain, but is actually far more abundant in human heart ventricular tissue than in the brain.[5] The release of both hANP and hBNP is stimulated by several hormones and neurotransmitters as well as by direct mechanical stretching of the atrial or ventricular tissue. CNP resides primarily in the CNS as well as renal cells and vascular endothelial cells, and has a very low concentration in plasma. DNP likewise, exists in very low levels in the plasma of normal humans.[4]

Nesiritide is the generic name assigned to recombinant human B-type natriuretic peptide.[6] The physiologic effects of hBNP are very similar to those of hANP. Both peptides result in increased venous capacitance, decreased vascular tone due to decreased sympathetic stimulation, and inhibition of the renin-angiotensin-aldosterone axis.[7] (See Figure 1.) One of the unique properties of hANP and hBNP is the ability to decrease cardiac preload without a resultant reflex tachycardia.[8] In addition to these vascular properties, hBNP has a direct effect on renal hemodynamics and function. Increased glomerular filtration is the result of an unbalanced vasodilatation of the afferent arterioles and vasoconstriction of the efferent arterioles. There also appears to be a direct tubular effect on sodium and water handling, resulting in natriuresis and diuresis as well as the above-mentioned inhibition of aldosterone. The net effect of these properties is balanced vasodilatation of the arterial and venous beds as well as natriuresis and diuresis. Additional evidence suggests a direct vasodilatory effect on the coronary arteries.[9] The natriuretic peptides also appear to exhibit an antimitogenic effect in the heart and other organ systems, suggesting a potential role in the modulation of cell growth.[3]

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**Table 1**
**Summary of Hemodynamic Effects of Nesiritide in Decompensated Heart Failure**

| Study | N | Dose | Duration | Δ PCWP | Δ CI | Δ UO | % DC |
|---|---|---|---|---|---|---|---|
| Hobbs[16] | 6 | 10 or 15 μg/kg bolus | NA | –73% | 68% | NR | NA |
| Yasue[18] | 7 | 0.1 μg/kg/min | 30 min | –33% | NR | 562% | 0 |
| Marcus[17] | 20 | 0.003–0.1 μg/kg/min | 90 min | –47% | 25% | 34% | 5% |
| Abraham[19] | 6 | 0.025 μg/kg/min | 4 hour | –41% | 28% | NA | 0 |
| | 6 | 0.05 μg/kg/min | 4 hour | * | * | NA | 0 |
| Mills[21] | 22 | 0.25 μg/kg; 0.015μg/kg/min | 24 hours | –28% | 11% | NR† | 0 |
| | 26 | 0.5 μg/kg; 0.03 μg/kg/min | 24 hours | –14% | 0% | NR† | 8% |
| | 26 | 1 μg/kg; 0.06 μg/kg/min | 24 hours | –29% | 21% | NR† | 23% |
| Colucci[22] | 43 | 0.3 μg; 0.015 μg/kg/min | 6 | –21% | 11% | 47% | 0 |
| | 42 | 0.6 μg; 0.03 μg/kg/min | 6 | –34% | 21% | 73% | 2% |
| Young[23‡] | 124 | 2 μg/kg; 0.01 μg/kg/min | 3 | –20% | NR | NR | 0 |

Dose, represents bolus, infusion rate or both; Δ PCWP, Δ CI, Δ UO, % change in pulmonary capillary wedge pressure, cardiac index and urine output; % DC, % of patients requiring discontinuation of nesiritide due to hypotension or excessive effect; NA, not applicable; NR, not reported.

* Data presented grouped for both dosages.

† No statistically significant difference from placebo.

‡ Based on oral abstract presentation, full publication of data pending; % changes are estimated from data presented.

## Natriuretic Peptides in Disease

Circulating levels of hANP and hBNP are elevated in patients with heart failure (CHF) and congestion.[10] In fact, much of our understanding of the physiologic role for the natriuretic peptides comes from observation of their effects in pathophysiologic states. Although there is some disparity in the literature, it appears that levels of hBNP correspond to the severity of heart failure. Measurement of hBNP levels may be useful for the diagnosis[11] and prognosis[12] and potentially even for monitoring the effectiveness of therapy in CHF.[13] The physiologic effects of the natriuretic peptides are diminished in patients with CHF with a decrease in the vasodilatory and natriuretic response to exogenous administration.[14] The mechanism for this apparent resistance is likely a combination of factors, including downregulation of natriuretic peptide receptors, an increase in neutral endopeptidase activity resulting in enhanced degradation, and decreased delivery of sodium to the distal tubule due to hemodynamic and hormonal effects in the kidney.[15] The natriuretic peptides also appear to play a role in the pathophysiology of hypertension.[3]

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## hBNP as a Therapeutic Agent

Given its physiologic actions of vasodilatation, natriuresis, and diuresis, it is not surprising that hBNP has been developed as a therapeutic agent. Nesiritide is a purified, recombinant, human B-type natriuretic peptide identical in structure to the peptide found in human plasma. To date, over 1000 patients with CHF have received intravenous nesiritide in the setting of clinical trials. We will review the efficacy and safety data from these trials. A summary of pertinent findings is presented in Table 1.

## Hemodynamic and Natriuretic Effects of Nesiritide

The first clinical experience with

nesiritide in patients with heart failure was reported by Hobbs and colleagues in 1996.[16] They studied 27 patients with CHF who received a single intravenous bolus of nesiritide in an ascending dose study. The patients were predominately in New York Heart Association (NYHA) Class III (19 patients) and received an IV bolus at one of six doses—0.3, 1, 3, 10, 15, or 20 μg/kg. The baseline characteristics of these patients were evenly distributed among the groups, with an overall average ejection fraction of 17%. Baseline hemodynamics were likewise similar among all groups with a cardiac index (CI) of 2.2 L/min/M$^2$ and a pulmonary capillary wedge pressure (PCWP) of more than 25 mm Hg. Pulmonary artery catheter measurements of hemodynamics were made at several time points after the bolus injection and demonstrated a dose-dependent effect that achieved statistical significance in the 10 and 15 μg/kg groups. The 10 and 15 μg/kg doses caused a dramatic reduction in PCWP of over 70% from baseline, with a less pronounced effect on right atrial (RA) and mean arterial pressure (MAP) of 28% each. The CI increased in these groups by 68% from baseline and this appeared to be due to a comparable increase in stroke volume (72%) without a significant change in heart rate. This early, single-dose study demonstrated the predominate hemodynamic effects of nesiritide—balanced vasodilatation of the venous and arterial beds with a secondary rise in CI due to an increase in stroke volume.

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Subsequent studies of nesiritide in heart failure have utilized a continuous infusion ranging from 90 minutes to several days. Marcus and colleagues reported the effect of sequential 90-minute infusions of varying doses of nesiritide or placebo in 20 patients with CHF.[17] The baseline hemodynamics of these patients were similar to those studied by Hobbs, with a PCWP of 25 mm Hg and a CI of 2.0 L/min/M$^2$. Patients received infusions of 0.003, 0.01, 0.03, and 0.1 μg/kg/min. or placebo for a period of 90 minutes, with washout periods in between doses. At the highest tolerated dose in each individual patient, PCWP decreased nearly 50% to 13.2 mm Hg and CI increased 25% to 2.5 L/min/M$^2$. The MAP fell from 85 mm Hg to 75 mm Hg with larger drops noted in some patients. Marcus also reported a significant effect on urinary volume and urinary sodium excretion in this study, confirming the diuretic and natriuretic properties of nesiritide in CHF patients. Urinary volume increased from 67 to 90 mL/h and urinary sodium excretion from 1.4 to 2.6 mEq/h.

Yasue and colleagues studied the effects of nesiritide infusion and compared it directly to infusions of hANP in 13 patients with CHF.[18] They used a single dose of 0.1 μg/kg/min of each agent, and their results were remarkably similar to those of Marcus, with a reduction in PCWP from 21 to 14 mm Hg and 23% increase in the stroke volume index. Likewise, they demonstrated an increase in urine volume and urine sodium excretion.

In 1998, Abraham and colleagues reported the effect of a 4-hour infusion of nesiritide in 16 patients with decompensated CHF.[19] Twelve patients received active treatment with either 0.025 or 0.05 μg/kg/min of nesiritide and four patients received placebo. Hemodynamic measurements were made during a baseline stabilization period, 4 hours of treatment, and a posttreatment period. Unique to this study was the replacement on an hour-by-hour basis of urinary volume losses in an effort to isolate the hemodynamic effects of nesiritide from the diuretic effects. In the overall treatment group, PCWP decreased 40% from baseline and increased CI by 28%. Abraham also evaluated the effect of nesiritide infusion on the neurohormonal milieu and demonstrated a reduction in plasma norepinephrine and aldosterone levels in the treatment group. By holding intravascular volume relatively constant, these authors were able to demonstrate the vasodilatory effects of nesiritide independently from its natriuretic properties.

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In a small study of 9 CHF patients and 10 control patients, Jensen and colleagues studied the natriuretic effects of a 60-minute infusion of 2 pmol/min/kg of nesiritide.[20] Urinary sodium excretion increased 60% in the CHF patients and 70% in the control subjects, but the authors noted no increase in urinary flow

rate. Further analysis demonstrated that although CHF patients responded with an increase in urinary sodium excretion, the effect was markedly blunted in absolute terms as compared to controls. This supports the observations previously made that there is resistance to hBNP in the setting of CHF.

In 1999, Mills and colleagues were the first to report the effects of a sustained infusion of nesiritide in CHF patients.[21] One hundred and three patients were enrolled and received either placebo (29 patients) or one of three doses of nesiritide (0.015, 0.03, or 0.06 μg/kg/min) for 24 hours. The treatment protocol allowed for a single 50% reduction in the infusion rate for excessive hemodynamic effect (hypotension or a decrease in PCWP to less than 10 mm Hg). Patients could also be removed from the study for worsening heart failure. Increases in infusion rate were not allowed in this protocol. The majority of patients were in NYHA Class III at the time of enrollment, and baseline characteristics were evenly distributed among the study groups. Baseline hemodynamics values were likewise evenly distributed among the groups, with a PCWP of 29 mm Hg and a CI of 1.9 L/min/M$^2$. The hemodynamic effects of nesiritide were seen within 1 hour of starting the infusion, with a decrease in PCWP of 5% in the placebo group and 17%, 12%, and 28% in the nesiritide treatment groups. Peak hemodynamic effects were seen at 3 to 6 hours after the start of the infusion in all patients and were maintained throughout the 24-hour infusion period. A similar pattern of increases in the CI was demonstrated in all treatment groups, with an initial rise in the first hour, a peak effect at 3 to 6 hours, and a sustained increase throughout the 24-hour infusion. Several patients in the treatment groups required a 50% dose reduction due to excessive hemodynamic effect but continued to demonstrate beneficial effects throughout the study. Once again there were relatively minor changes noted in heart rate throughout the study with a slight but non-statistically significant decrease in heart rate in the two lower-dose infusion groups and a slight increase in the highest-dose infusion group. Intriguingly, there were no differences noted among the groups in urine output or urinary sodium excretion in this trial, in contrast to the studies of Marcus and Yasue discussed above.

## Efficacy of Nesiritide in the Treatment of CHF

Three sentinel trials involving 530 patients with decompensated heart failure have been reported. The first two trials were reported by Colucci and colleagues and included a double-blind, placebo-controlled efficacy trial with 127 patients and an open-label comparator trial (blinded to dose of nesiritide only) in 305 patients.[22] Entry criteria for both trials included patients with chronic heart failure requiring admission to the hospital for treatment of decompensation. A pulmonary artery catheter was required in the efficacy trial with specific hemodynamic entry criteria and was allowed in the comparator trial at the discretion of the treating physician. In the efficacy trial, patients received either placebo or nesiritide at a dose of 0.015 or 0.03 μg/kg/min after an appropriate bolus. The infusion was continued for at least 6 hours with a 50% dose reduction allowed for hypotension. The primary endpoint in the double-blind trial was a decrease in PCWP at 6 hours with several secondary endpoints, including other hemodynamic measures

### Main Points

- Recombinant human B-type natriuretic peptide, under the name generic nesiritide, will be the first natriuretic peptide commercially released in the United States as a pharmaceutical agent.
- The natriuretic peptides all appear to play an endocrine role in the regulation of cardiorenal homeostasis.
- Both hANP and hBNP cause increased permeability of the vascular endothelium, increased venous capacitance, decreased vascular tone due to decreased sympathetic stimulation, and inhibition of the renin-angiotensin-aldosterone axis.
- One of the unique properties of hANP and hBNP is the ability to decrease cardiac preload without a resultant reflex tachycardia; in addition, hBNP has a direct effect on renal hemodynamics and function.
- Levels of hBNP appear to correspond to the severity of heart failure, and measurement of hBNP levels may be useful for diagnosis and prognosis, and potentially for monitoring the effectiveness of therapy in CHF.
- Over 1000 patients with CHF have received intravenous nesiritide in the setting of clinical trials.
- In the various clinical trials reported to date, the primary adverse event reported in the use of nesiritide is hypotension.

and patient global clinical status and symptoms. PCWP decreased by 6 and 9.6 mm Hg in the two treatment arms versus a 2 mm Hg rise in the placebo arm ($P < .001$). Statistically significant decreases in right atrial pressure, systemic vascular resistance, and mean arterial pressure were also noted. There was a modest increase in CI in the treatment arms (0.2 and 0.4 L/min/M$^2$) which was also statistically significant. Both patient and physician assessment of global status were improved in a higher percentage of treatment patients than placebo. Specific symptoms such as dyspnea and fatigue were also improved in the treatment arms more than in the placebo group. Plasma aldosterone levels were decreased with nesiritide treatment, but no change was noted in plasma norepinephrine levels. Urine output was increased in the nesiritide groups.

In the comparative trial, patients were randomized to receive open-label "standard" therapy (defined as a single IV vasoactive agent routinely used for the treatment of decompensated CHF) versus infusion of nesiritide at 0.015 or 0.03 μg/kg/min after an appropriate bolus. Patients were maintained on therapy for up to 7 days at the discretion of the treating physician, with global patient status and clinical symptoms at 6 and 24 hours being the prespecified endpoints. An increase in dose or change in initial agent was allowed in this study at the discretion of the investigator, but the dose of nesiritide administered was blinded. Comparable changes in global patient status and symptoms were reported in all groups. A statistically smaller number of patients in the nesiritide group received IV diuretic therapy during treatment.

Preliminary results of the Vasodilator in the Management of Acute CHF (VMAC) trial were presented in November 2000.[23] The VMAC trial was a unique trial involving 498 patients with acutely decompensated, severe CHF from a wide variety of causes, including acute coronary syndromes and CHF due to diastolic dysfunction as well as patients with renal insufficiency and a history of arrhythmias. Patients were stratified based on the investigator's decision to use invasive hemodynamic monitoring. The 246 patients who received a pulmonary artery catheter were randomized to placebo, IV nitroglycerin, fixed-dose nesiritide (2 μg/kg bolus followed by a 0.01 μg/kg/min drip), or adjustable-dose nesiritide (same starting dose but allowed to increase up to 0.03 μg/kg/min after 3 hours). Patients initially randomized to placebo were reassigned after the first 3 hours to either nitroglycerin or fixed-dose nesiritide. Background therapy could include standard heart failure medications, including IV dobutamine. The 243 patients not catheterized were randomized to placebo, IV nitroglycerin, or fixed-dose nesiritide, and again the placebo group was reassigned after 6 hours. Primary endpoints were PCWP at 3 hours in the catheterized group and patient assessment of dyspnea in all patients. Numerous secondary endpoints were also studied. The key findings included a significantly greater drop in the PCWP at 3 and 24 hours with nesiritide versus nitroglycerin. Nesiritide resulted in improved dyspnea at 3 hours versus placebo, but no statistically significant difference versus nitroglycerin was noted. The full results of this trial are pending publication.

*Although hypotension can occur consistent with the drug's effect, the overall safety profile appears acceptable.*

## Safety and Tolerability of Nesiritide

In the various clinical trials reported to date, the primary adverse event reported in the use of nesiritide is hypotension. In the 24-hour infusion trial reported by Mills and colleagues, 8 of 74 patients treated with nesiritide required protocol-mandated premature termination of the study drug due to hypotension and an additional 4 due to excessive reduction in PCWP.[21] Only 5 of 74 patients in this study had symptomatic hypotension at any point. In the combined efficacy and comparative trials reported by Colucci and colleagues,[22] 35 of 288 patients reported symptomatic hypotension versus 4 of 102 standard therapy patients. Sixteen patients in the two trials had the study drug discontinued due to symptomatic hypotension. In the VMAC trial, the incidence of symptomatic hypotension with nesiritide was approximately 4% and was similar to nitroglycerin.[23]

Burger and colleagues recently reported the occurrence of ventricular arrhythmias in 261 patients in the comparative trial who received nesiritide (0.015 or 0.03 μg/kg/min) or dobutamine as the open-label comparator.[24] There was a higher incidence of arrhythmias classified by the investigator as life-threatening (sustained ventricular tachycardia or cardiac arrest) in the dobutamine group than in either nesiritide group. Nonsustained VT was also more common in the dobutamine group, but there was a trend to a higher incidence of bradycardia noted with nesiritide.

## Summary

Nesiritide is a unique agent with properties of balanced arterial and venous vasodilatation that has been shown efficacious and safe in the treatment of decompensated CHF. The tendency of nesiritide to promote natriuresis and diuresis, seen in most studies, provides an additional benefit. Although hypotension can occur consistent with the drug's effect, the overall safety profile appears acceptable and may have an advantage of fewer arrhythmic complications compared with dobutamine. Nesiritide offers a new and useful form of therapy for the treatment of decompensated CHF. ■

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