Nesiritide: A New Drug for the Treatment of Decompensated Heart Failure

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Nesiritide, a recombinant human B-type natriuretic peptide, is the first in a new drug class for the treatment of decompensated heart failure. The drug binds to receptors in the vasculature, kidney, adrenal gland, and brain, and overcomes resistance to endogenous BNP present in patients with CHF. Nesiritide administration leads to a rapid and balanced vasodilatory effect, which results in a significant decrease in right and left ventricular filling pressures and systemic vascular resistance and at the same time in an increase in stroke volume and cardiac output without a change in heart rate. These early hemodynamic changes result in a rapid improvement in symptoms of heart failure. In addition, nesiritide lowers aldosterone, catecholamines, and endothelin-1 levels and its effect on the kidney leads to an increased natriuresis and diuresis without effect on serum potassium or renal function. Prior to its approval for clinical use, nesiritide was studied in 10 different clinical trials involving 941 patients with moderate and severe CHF, including elderly patients, patients with both systolic and diastolic dysfunction, and patients with arrhythmias, renal insufficiency, and acute ischemic syndrome. In comparative studies with available vasoactive therapies frequently used for treatment of patients with decompensated heart failure, nesiritide was proven comparable in efficacy to inotropic drugs such as dobutamine, but superior in safety. In a recent study, nesiritide was found to be more effective and better tolerated than the vasodilator, nitroglycerin. The most common side effects expected with the use of nesiritide are headaches and decrease in blood pressure. At the recommended dose of nesiritide, headache was reported during the first 24 hours of treatment in 8% of patients and symptomatic hypotension in 4% of patients, compared to 20% and 5% in nitroglycerin-treated patients.

Key words: nesiritide, decompensated heart failure, natriuretic peptides.

Nesiritide (Natrecor®, human recombinant B-type natriuretic peptide) has been recently approved by the Food and Drug Administration for the intravenous treatment of patients with decompensated congestive heart failure. This article describes the physiologic background for the use of human B-type natriuretic peptides (BNP) and reviews the clinical experience with the use of nesiritide in the treatment of decompensated heart failure.

Natriuretic Peptides

The discovery of natriuretic peptides was preceded by the work of Kisch in 1956 (1), who was the first to describe the presence of granules located within the cardiac atria. This observation was confirmed 8 years later by Jamieson and Palade, who suggested that the atrial granules were secretory granules similar to those found in neuroendocrine cells (2). In 1981, DeBold and colleagues (3) found that the granularity of atrial tissue was altered by changes in water and electrolyte balance and that infusing an extract of atrial tissue into
rats caused a marked natriuresis (3,4). These findings led to the isolation and cloning of the atrial natriuretic peptide (ANP) and later of other natriuretic peptides (5).

The natriuretic peptide family consists of three peptides: ANP, BNP, and C-type natriuretic peptide (CNP) and plays an important role in the prevention of plasma volume expansion and hypertension (5,6). ANP, a 28-amino-acid peptide, is produced predominately in the cardiac atrium as a result of an increase in atrial wall tension that arises from an increase in intravascular volume. In addition, the secretion of ANP is stimulated by several hormones and neurotransmitters, including endothelin, arginine vasopressin, and catecholamines (5). The ANP gene is also expressed in the kidney and leads to the formation of urodilatin, a 32-amino-acid peptide, which plays a role in regulating sodium and water (7). BNP, a 32-amino-acid molecule, was initially identified in the porcine brain and, although it is also present in human brain, it is predominately found in cardiac ventricles. CNP, a 22-amino-acid molecule, is produced predominately in the central nervous system, anterior pituitary, heart, vascular endothelial cells, and the kidney and is found in a very low concentration in the plasma (5). The major effect of CNP in the heart and vasculature appears to be paracrine, leading to antimitogenesis and remodeling (8).

Three natriuretic peptide receptors (labeled A, B, and C) are found on the surface of target cells (5). The A and B receptors are linked to the cyclic guanosine monophosphate (cGMP)-dependent signaling cascade and are responsible for many of the cardiovascular and renal effects of the natriuretic peptides. The C receptor binds to ANP, BNP, and CNP with approximately equal affinity and is involved in the clearance of these peptides (9), which are internalized and degraded after binding to the receptor. Circulating natriuretic peptides are also inactivated by neutral endopeptidase, an enzyme that is present in the renal tubular and vascular cells (5,10).

Increased secretion of natriuretic peptides is stimulated by sodium intake and attendant volume expansion and leads to reduction of blood pressure and plasma volume through combined effects on the brain, adrenal gland, kidney, and the vasculature (5,11). Natriuretic peptides act in the brain stem to decrease sympathetic tone, and thus contribute to decreased vasoconstriction. In addition, these substances cause inhibition of salt appetite and water drinking (12), which complement their renal diuretic effect. Furthermore, natriuretic peptides inhibit the secretion of vasopressin and corticocritin through effects on the brain and pituitary gland (13).

At the renal level, natriuretic peptides lead to dilatation of afferent and constriction of efferent renal arterioles. These changes lead to pressure augmentation within the glomerular capillaries, resulting in an increased glomerular filtration rate (14). Glomerular filtration is also increased by relaxation of the mesangial cells, which results in enhancing effective surface area for filtration (15). The direct tubular actions of natriuretic peptides include inhibition of angiotensin II-stimulated sodium and water reabsorption in proximal convoluted tubules (16), inhibition of tubular water transport by antagonizing the action of vasopressin (17), and blockade of sodium absorption in the inner medullary collecting duct (18). In addition, natriuretic peptides indirectly accentuate natriuresis and diuresis by reducing plasma renin and aldosterone concentrations (19).

The cardiovascular effects of natriuretic peptides include reduction of peripheral vascular resistance and cardiac preload. Reduction in preload is caused mainly by vasodilation but also may occur as a result of decreased blood volume secondary to diuresis as well as from a shift in intravascular fluid into the extra vascular compartment secondary to an increase in permeability of the vascular endothelium (5,19,20). Vasodilation caused by natriuretic peptides is mediated not only by stimulation of receptors in the vascular walls but also through reduction in sympathetic tone caused by suppression of catecholamines release from autonomic nerve endings, and especially by suppression of sympathetic outflow from the central nervous system (21,22).

Under normal physiologic conditions, both ANP and BNP are produced solely by the atrial myocardi um (23). In heart failure, the ventricular myocardium becomes the principal source of these natriuretic peptides. In patients with congestive heart failure (CHF), the increased intracardiac volume and pressure causes a substantial increase in plasma concentrations of ANP and BNP, which correlates with the severity of the disease and its prognosis (24,25). Although increased levels of natriuretic peptides in cases of early left ventricular dysfunction help to inhibit activation of the renin-angiotensin-aldosterone system and progression of heart failure symptoms (11,26,27), the responsiveness to natriuretic peptides is decreased as heart failure worsens (5,23). The reason for the decreased responsiveness to natriuretic peptides is most likely multifactorial and may be due to excessive stimulation of the renin-aldosterone axis (11,28), receptor down-regulation (29), change in renal hemodynamics (30), and increased neutral endopeptidase and cGMP phosphodiesterase activity (31,32). The
administration of exogenous ANP and BNP (11) has been shown to overcome decreased responsiveness to natriuretic peptides in heart failure and is the rationale for the use of nesiritide in the treatment of patients with decompensated heart failure.

**Nesiritide Pharmacokinetics and Elimination**

Nesiritide is a sterile, purified preparation of human-B-type natriuretic peptide. It is manufactured from Escherichia coli using recombinant DNA technology and has the same 32-amino-acid sequence as the endogenous BNP produced by the ventricular myocardium. The intravenous administration of nesiritide results in a biphasic disposition from the plasma. The mean terminal elimination half-life of nesiritide in patients with heart failure is approximately 18 minutes (33). At steady state, plasma BNP levels increase from baseline endogenous levels by approximately 3-fold to 6-fold with nesiritide infusion doses ranging from 0.01 to 0.03 μg/kg/min (34).

Human BNP elimination from the circulation occurs by three independent mechanisms in order of decreasing importance: 1) by binding to cell surface natriuretic peptide clearance receptors (receptor C) with subsequent cellular internalization and isosome proteolysis; 2) proteolytic cleavage by neutral endopeptidases present within renal tubular cells and vascular cells; and 3) renal filtration clearance of nesiritide (5-10). The latter is proportional to body weight and supports weight-adjusted dosing of the drug. Clearance is not influenced significantly by age, gender, race, baseline endogenous BNP concentration, severity of heart failure, or concomitant administration of angiotensin converting enzyme (ACE) inhibitors (35). Although nesiritide is eliminated in part through renal clearance, clinical data do not suggest a need for dose adjustment in patients with renal insufficiency.

The effect of other cardiovascular medications on nesiritide pharmacokinetics has not been studied. However, nesiritide has been administered concomitantly with commonly used cardiac drugs, including diuretics, digoxin, ACE inhibitors, angiotensin receptor blockers, anticoagulants, oral nitrates, β-blockers, statins, Class III antiarrhythmic agents, calcium channel blockers, dobutamine, and dopamine (36,37). Nesiritide is physically incompatible with injectable formulations of heparin, insulin, etacrynic acid sodium, bumetanide, enalaprilat, hydralazine, and furosemide. Therefore, these drugs should not be coadministered as infusions with nesiritide through the same intravenous catheter. Nesiritide also binds to heparin and should not be administered through heparin-coated catheters.

**Nesiritide-Clinical Experience**

Nesiritide has been studied in 10 clinical trials (35) that included 941 patients, the majority of them at the New York Heart Association (NYHA) functional Class III (61%) or IV (36%) heart failure. The mean age of the studied population was 60 years, and 56% of all patients were women. Five of the trials were randomized, multicenter, placebo or active controlled studies in which 772 patients with decompensated heart failure received continuous infusions of nesiritide at doses ranging from 0.01 to 0.03 μg/kg/min. Agents used for comparison in the active-controlled studies were primarily dobutamine and nitroglycerin (36,37). Most patients (70%), were given nesiritide infusion for at least 24 hours, while 48% received the drug for 24 to 48 hours and 22% for longer than 48 hours. In controlled trials, nesiritide was used either alone or in combination with diuretics, digoxin, oral ACE inhibitors, anticoagulants, oral nitrates, statins, class III antiarrhythmic agents, β-blockers, dobutamine, calcium channel blockers, angiotensin II receptor antagonist, and dopamine (37). Nesiritide has been studied in a broad range of patients, including the elderly, women, and African Americans, and patients with a history of various cardiovascular conditions, including hypertension, diabetes, post myocardial infarct, atrial fibrillation/flutter, nonsustained ventricular tachycardia, left ventricular diastolic dysfunction, and acute coronary syndrome (37).

**Hemodynamic Effect**

Evaluation of a single bolus of nesiritide at doses of 0.3, 1, 3, 10, 15, and 20 μg/kg was performed by Hobbs et al (38) in patients with moderate or severe heart failure and depressed ejection fraction of (17 ± 5%). Nesiritide was associated with a rapid, dose-dependent, hemodynamic effect starting at the dose of 3 μg/kg. The dose of 10 and 15 μg/kg resulted in a marked (28%) decrease in right atrial pressure, a 41% reduction in pulmonary artery pressure, a 73% reduction in pulmonary capillary wedge pressure, and a 53% reduction in systemic vascular resistance. These changes were associated with a marked (72%) increase in stroke volume and a 68% increase in cardiac output.
Abraham et al. (39) evaluated the hemodynamic effect of a continuous 4-hour infusion of nesiritide at rates of 0.025 or 0.05 μg/kg/min in 16 patients with decompensated heart failure. In order to differentiate between the diuretic and vasodilatory effects of nesiritide, hourly volume replacement was made to compensate for urine output. In this study, nesiritide reduced right and left ventricular filling pressures (a 30% reduction in mean right atrial pressure and a 36% reduction in mean pulmonary wedge pressure), and increased the cardiac index by 28%, without a change in the heart rate. Because intravascular volume was kept constant by replacement of urinary output, this study illustrated the vasodilatory effect of nesiritide.

The effect of a sustained infusion of nesiritide for 24 hours was reported by Mills et al. (40), who studied 103 patients with moderate and severe heart failure in a placebo-controlled trial. Patients received a 0.25, 0.50, or 1 μg/kg bolus of nesiritide (or placebo) followed by infusion at a dose of 0.015, 0.03, 0.06, or 1.0 μg/kg/min for 24 hours. In this study, there was a dose-related reduction in mean right atrial pressure, pulmonary pressures, and mean pulmonary capillary wedge pressure as well as a reduction in systemic vascular resistance. This was associated with a marked increase in stroke volume and cardiac index without a significant effect on heart rate. The hemodynamic effect was noted at 1 hour and persisted for the duration of the infusion without any evidence of tolerance.

Hypotension was reported in 7% of patients receiving placebo and in 5%, 12%, and 27% of patients receiving nesiritide at 0.015, 0.03, or 0.06 μg/kg/min, respectively.

In a recent publication, Collucci et al. (36) described the changes in hemodynamic values at 6 hours after the initiation of nesiritide given as an intravenous bolus of 0.3 or 0.6 μg/kg followed by an infusion of 0.015 or 0.03 μg/kg/min, respectively. Both doses resulted in a significant reduction in pulmonary capillary wedge pressure, right atrial pressures, systemic vascular resistance, and pulmonary artery pressures. There was no significant change in heart rate, and systolic blood pressure was reduced by a mean of 4.4 mmHg and 9.3 mmHg, respectively, in the two groups.

The recently published Vasodilation in the Management of Acute CHF (VMAC) (37) provided information on the hemodynamic effect of currently recommended dose of nesiritide. This was a multicenter, randomized, and double-blind trial designed to compare the clinical effects of nesiritide to those of intravenous nitroglycerin when both were added to standard care in patients with decompensated heart failure. In this trial, 489 patients with dyspnea at rest due to decompensated heart failure were treated with either nesiritide, starting with a bolus of 2 μg/kg and followed by a continuous infusion of 0.01 μg/kg/min or intravenous nitroglycerin at a dose determined by the investigators. The mean systolic blood pressure for the entire group was 121 ± 22 mmHg. The mean pulmonary capillary wedge pressure (PCWP) was 28 ± 6 mmHg in 246 patients who received invasive hemodynamic monitoring. Hemodynamic changes during administration of both drugs are shown in Table 1. Nesiritide led to a significant reduction in PCWP, which was observed as early as 15 minutes, with further effect at 1 hour. The effect of nesiritide on PCWP was superior to that of nitroglycerin (Fig. 1).

The administration of nesiritide was also associated with a significant reduction in right atrial pressure and peripheral vascular resistance. Systolic blood pressure was reduced by 4 ± 11 mmHg (3%) 15 minutes after the initiation of the nesiritide infusion, which was comparable to that of nitroglycerin (-3 ± 11 mmHg) at 15 minutes and smaller than nitroglycerin at 1 hour (3 ± 13 vs 6 ± 14 mmHg, P < 0.05 for nitroglycerin vs placebo and not significant for nesiritide vs placebo).

Nesiritide also had a significant effect on pulmonary vascular resistance and augmented cardiac output. Through 24 hours, nesiritide lowered PCWP to a significantly greater extent than nitroglycerin with no evidence of attenuation of effect. At 36 and 48 hours, PCWP continued to be reduced by a greater magnitude with nesiritide than with nitroglycerin.

**Effect on Symptoms**

The effects of nesiritide on symptoms of heart failure were evaluated in comparison to placebo, and to standard care that included the use of intravenous vasodilator drugs such as nitroglycerin, dobutamine, and milrinone. The double blind use of nesiritide infused for 6 hours in 127 Class III and IV heart failure patients resulted in a superior hemodynamic improvement compared to placebo, which was also associated with a marked improvement in heart failure symptoms, including dyspnea and fatigue (36). Another study compared the effect of nesiritide to that of standard care in a group of 305 patients admitted to hospitals for decompensated heart failure (36). In this study, 57% of patients randomized to standard care received dobutamine, 19% milrinone, 18% nitroglycerin, and 6% dopamine. Nesiritide administration was associated with improvement of heart failure symptoms with-
Table 1. Hemodynamic Variables (Baseline Value** and Change with Treatment):
Mean ± SD and [Median (25th, 75th percentiles)]

<table>
<thead>
<tr>
<th></th>
<th>Nitroglycerin</th>
<th>Nesiritide</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Baseline PCWP (mm Hg)</td>
<td>26.0 ± 5.7 [20.0, 24.0, 31.5]</td>
<td>27.8 ± 7.1 [25.5, 22.0, 32.5]</td>
<td>27.7 ± 5.4 [26.0, 24.0, 30.0]</td>
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<td>15 min</td>
<td>-1.2 ± 0.7 [-1.0 to 0]</td>
<td>-3.5 ± 5.3 [-1.0 to 6.0, 0.0]</td>
<td>-1.2 ± 3.6 [-1.0 to 2.0, 0.0]</td>
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<td>1 hour</td>
<td>-2.8 ± 4.1 [-2.0 to 6.0, 0.0]</td>
<td>-5.5 ± 6.3 [-5.5 to 0.0, -3.0]</td>
<td>-1.2 ± 4.8 [-1.0 to 5.0, 1.0]</td>
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<tr>
<td>3 hours</td>
<td>-3.8 ± 5.3 [-3.0 to 8.0, 0.0]</td>
<td>-5.8 ± 6.5 [-5.0 to 0.0, -1.0]</td>
<td>-3.0 ± 4.2 [-2.0 to 5.0, 0.0]</td>
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<tr>
<td>Baseline Mean RAP (mm Hg)</td>
<td>16 ± 7.0 [15.0, 11.0, 20.0]</td>
<td>15 ± 7.0 [14.0, 10.0, 18.0]</td>
<td>14 ± 7.0 [14.0, 10.0, 17.5]</td>
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<tr>
<td>1 hour</td>
<td>-1.0 ± 3.3 [-1.0 to 3.0, 0.0]</td>
<td>-2.6 ± 4.9 [-2.0 to 5.0, 0.0]</td>
<td>-0.2 ± 3.3 [-1.0 to 1.0, 1.0]</td>
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<tr>
<td>3 hours</td>
<td>-1.6 ± 3.5 [-2.0 to 5.0, 0.0]</td>
<td>-3.1 ± 4.6 [-3.0 to 5.0, 0.0]</td>
<td>0.0 ± 4.4 [0.0 to 2.0, 2.0]</td>
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<tr>
<td>Baseline SBP (mm Hg)</td>
<td>124 ± 23 [118, 105, 139]</td>
<td>120 ± 23 [117, 102, 134]</td>
<td>121 ± 21 [117, 104, 134]</td>
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<tr>
<td>15 min</td>
<td>-3.1 ± 1.9 [-1.0 to 1.0, 4.0]</td>
<td>-3.0 ± 1.3 [-1.0 to 3.0]</td>
<td>1.0 ± 1.3 [0.5 to 1.9, 5.0]</td>
</tr>
<tr>
<td>1 hour</td>
<td>-6.3 ± 4.9 [-4.0 to 12.0, 2.0]</td>
<td>-5.2 ± 3.7 [-3.0 to 11.0, 5.0]</td>
<td>-1.5 ± 1.2 [-1.5 to 0.0, 5.0]</td>
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<tr>
<td>3 hours</td>
<td>-6.5 ± 4.9 [-4.0 to 13.0, 3.0]</td>
<td>-5.6 ± 2.9 [-5.5 to 13.5, 3.0]</td>
<td>-2.5 ± 1.1 [-2.0 to 9.0, 3.0]</td>
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<tr>
<td>Baseline PVR (dyne/sec/cm²)</td>
<td>271 ± 178 [272, 133, 376]</td>
<td>258 ± 168 [203, 141, 329]</td>
<td>236 ± 174 [187, 128, 269]</td>
</tr>
<tr>
<td>1 hour</td>
<td>-38 ± 124 [-5 to 137, 47]</td>
<td>-27 ± 104 [-274, 85, 35]</td>
<td>28 ± 122 [-31, 76, 84]</td>
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<tr>
<td>3 hours</td>
<td>-18 ± 115 [-7.8 to 56, 48]</td>
<td>-21 ± 115 [-9.0 to 73, 49]</td>
<td>21 ± 105 [29, -36, 73]</td>
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<tr>
<td>Baseline SVR (dyne/sec/m²)</td>
<td>1569 ± 607 [1435, 984, 1883]</td>
<td>1441 ± 589 [1334, 1084, 1672]</td>
<td>1384 ± 563 [1289, 994, 1767]</td>
</tr>
<tr>
<td>1 hour</td>
<td>-136 ± 458 [-172, 340, 157]</td>
<td>-216 ± 507 [-151, 422, 161]</td>
<td>-8 ± 204 [-21, 147, 200]</td>
</tr>
<tr>
<td>3 hours</td>
<td>-105 ± 520 [-122, -345, 125]</td>
<td>-144 ± 447 [-102, -350, 84]</td>
<td>-45 ± 218 [-40, -175, 151]</td>
</tr>
<tr>
<td>Baseline CI (L/min/m²)</td>
<td>2.1 ± 0.8 [2.0 to 6.2, 2.5]</td>
<td>2.2 ± 0.7 [2.1, 1.7, 2.6]</td>
<td>2.2 ± 0.7 [2.1, 1.7, 2.6]</td>
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<tr>
<td>1 hour</td>
<td>0.1 ± 0.5 [0.1, 0.4, 0.4]</td>
<td>0.3 ± 0.5 [0.1, 0.6, 0.6]</td>
<td>-0.1 ± 0.5 [0.1 to 0.4, 0.2]</td>
</tr>
<tr>
<td>3 hours</td>
<td>0.2 ± 0.5 [0.2 to 0.7, 0.4]</td>
<td>0.1 ± 0.5 [0.1 to 0.1, 0.4]</td>
<td>0.0 ± 0.6 [0.0 to 0.3, 0.2]</td>
</tr>
</tbody>
</table>

*P < 0.05, active therapy compared to placebo; **P < 0.05, nesiritide compared to nitroglycerin; ***There were no significant differences between groups for hemodynamics at baseline. (With permission from JAMA 2002;287:1538, 2002)

![Graph A: All Catheterized Patients Through 3 Hours](image1)
![Graph B: All Catheterized Patients Through 48 Hours (Excludes Placebo Patients Through 3 Hours)](image2)

*P < 0.05 for nesiritide or nitroglycerin compared with placebo; **P < 0.05 for nesiritide compared with nitroglycerin.

Fig. 1. Changes from baseline in pulmonary capillary wedge pressure (the VMAC Study) (with permission from JAMA 2002;287:1538, 2002)
in the first 6 hours in most of the patients, and the rate of improvement was similar to that seen with standard care (Fig. 2). The VMAC study compared the effect of nesiritide with placebo and intravenous nitroglycerin when added to standard heart failure treatment (37). The patients' self-assessed dyspnea score at 3 hours was significantly improved in the nesiritide group compared to placebo ($P < 0.034$) (Fig. 3). The effect of nitroglycerin on the change in the dyspnea score at 3 hours was not statistically significant ($P = 0.191$) compared to placebo (Fig. 3).

**Neurohumoral Effect**

In animals with CHF, release of ANP was found to inhibit production of catecholamines, angiotensin II, aldosterone, and endothelin-I, while infusion of antagonists of natriuretic peptide A and B receptors led to a significant increase in the levels of these hormones (41). In the study recently reported by Colucci et al (36), the administration of nesiritide at doses of 0.015 and 0.03 μg/kg/min was associated with a significant decrease in plasma aldosterone levels compared to placebo.
An evaluation of the neurohormonal effect of nesiritide vs dobutamine was performed in a subset of 82 patients with decompensated CHF (42). This study showed a significant decrease in endothelin 1 levels during nesiritide infusion compared to a significant increase during dobutamine treatment. There was no significant change in plasma levels of norepinephrine, tumor necrosis factor alpha, and interleukin-6.

**Effect on Urine Output**

In an efficacy trial (36) where patients were blindly randomized to either placebo (42 patients), nesiritide at a dose of 0.015 μg/kg/min (43 patients), or nesiritide at a dose 0.03 μg/kg/min (42 patients), and intravenous diuretics were withheld for 4 hours before baseline measurements and for first 6 hours of the infusion, the mean urine output over 6 hours was 560 mL and 650 mL in the groups assigned to nesiritide and 380 mL in the placebo group (P = 0.004) (Fig. 4).

In a comparative trial (34) where patients were randomized to standard care including other vasoactive medications, or to nesiritide given as a bolus of 0.3 or 0.6 μg/kg followed by infusion of 0.015 or 0.03 μg/kg/min and intravenous diuretics could be added at any time, intravenous diuretics were given to fewer patients in the groups assigned to nesiritide (84% and 74%, respectively), than in the standard therapy group (96%, P < 0.001 for both comparisons) (Fig. 5). These observations are consistent with the direct renal effect of nesiritide and suggest that the drug may be helpful in the clinical management of fluid overload in patients with congestion and failure (36).

**Effect on Renal Function**

Marcus et al (43) evaluated the hemodynamic and renal excretory effects of nesiritide in 20 patients with severe CHF who were randomized in a double-blind, placebo-controlled, cross-over trial. On 2 consecutive days, they received either an incremental 90-minute infusion of nesiritide at doses of 0.003, 0.01, 0.03, and 0.1 μg/kg/min, or placebo. The infusion of nesiritide at the highest completed dose was associated with a
marked improvement in cardiac output as well as a reduction in right atrial and pulmonary pressures. Mean arterial pressure decreased from 85 ± 2 to 75 ± 2 mmHg. These hemodynamic changes were associated with a significant increase in urine volume (34%) and urine sodium excretion (86%), while creatinine clearance and urinary potassium excretion did not change (Fig. 6).

**Safety**

The most common adverse events reported during the first 24 hours of treatment with both nesiritide and nitroglycerin in the VMAC study (37) are shown in Table 2.

The most common adverse effect associated with the administration of currently recommended doses of
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![Image](image.png)

**Fig. 6.** Effects of human brain natriuretic peptide (hBNP) and placebo infusion on (A) Urinary sodium excretion, (B) urinary volume, (C) urinary potassium excretion and (D) creatinine clearance. (With permission Circulation 94:3187, 1996).

| Table 2. Adverse Events During First 24 Hours After Start of Study Drug (All Treated Subjects, as Randomized) |
|--------------------------------------------------|---------------------------------|----------|
| Adverse Event                                    | Nitroglycerin (n = 216) | Nesiritide (n = 273) | *P value* |
| Any Adverse Event                                | 146 (68%)                 | 140 (51%)           | <0.001    |
| General Headache                                 | 44 (20%)                  | 21 (8%)             | <0.001    |
| Pain                                             |                             |                      |           |
| General                                          | 11 (5%)                   | 11 (4%)             | 0.662     |
| Abdominal                                        | 11 (5%)                   | 4 (1%)              | 0.032     |
| Catheter                                         | 11 (5%)                   | 4 (1%)              | 0.032     |
| Nausea                                           | 13 (6%)                   | 10 (4%)             | 0.283     |
| Cardiovascular                                   |                             |                      |           |
| Hypotension                                      |                             |                      |           |
| Asymptomatic                                     | 17 (8%)                   | 25 (8%)             | 0.869     |
| Symptomatic                                      | 10 (5%)                   | 12 (4%)             | 1.000     |
| Non-Sustained VT                                 | 11 (5%)                   | 9 (3%)              | 0.362     |
| Anginapectoris                                   | 5 (2%)                    | 5 (2%)              | 0.756     |

*Calculated using the Fisher exact tests. (With permission JAMA 287:1539, 2002).*

Nesiritide used in the VMAC study (2 μg/kg bolus followed by an infusion of 0.01 μg/kg/min in most patients) was headache, which was reported by 8% of the patients. This adverse effect, however, occurred significantly less often in patients treated with nesiritide than in those treated with nitroglycerin (20%) (*P* = <0.001).

Symptomatic hypotension was reported in 4% of the patients treated with nesiritide compared to 5% of those receiving nitroglycerin. In another study, decreases in blood pressure were found to be dose-dependent, and symptomatic hypotension was reported in 11% of patients with decompensated heart failure during an infusion of 0.015 μg/kg/min and in 17% patients receiving 0.03 μg/kg/min (36).

In the VMAC trial (37), symptomatic hypotension reported during the first 24 hours of treatment in the nesiritide patients was of longer duration than in patients receiving nitroglycerin (2.2 hours with nesiritide and 0.7 hours with nitroglycerine), most likely due to the longer half-life of nesiritide. None of those episodes resulted in adverse sequelae in either treat-
ment group. Most hypotensive episodes were considered mild to moderate, and only one subject in each treatment group experienced an event that the investigator classified as severe. Most events resolved either spontaneously after a dose decrease or discontinuation, or with an intravenous volume challenge of 250 mL or less. The potential for hypotension may be increased by combining nesiritide with other vasodilators. In the VMAC trial, the frequency of symptomatic hypotension during the first 24 hours of treatment in nesiritide patients who received concomitantly an oral ACE inhibitor was 6%, compared to 1% in patients not receiving ACE inhibitors (37). This was similar for nitroglycerin patients who were on concomitant ACE inhibitors.

Heart Rate and Arrhythmias
The effect of nesiritide on heart rate and ventricular arrhythmias was evaluated and compared to that of dobutamine in the PRECEDENT Study (Prospective, Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy) (44). In this study, patients received nesiritide administered at one of two doses (0.015 μg/kg/min or 0.03 μg/kg/min) or dobutamine at a minimum dose of 5 μg/kg/min. The effect of the therapy was assessed by Holter monitoring performed for 24 hours during drug infusion, which was compared to a recording for a similar period of time before treatment. The study included 246 patients with heart failure at the NYHA Class III or IV; 51% of these patients had ischemic cardiomyopathy. In contrast to the dobutamine group, which showed a significant increase in heart rate and proarrhythmic effect, the lower nesiritide dose showed no significant effect on heart rate and a significant decrease in the number of couples, triplets, and episodes of nonsustained ventricular tachycardia. The higher nesiritide dose was associated with no significant change in heart rate or ventricular ectopic beats. In addition, when two independent criteria for proarrhythmic effect were used, dobutamine, but not nesiritide, was found to be proarrhythmic in 10% (CAPS criteria) (45) and 23% (Velebit criteria) (46) of the cases (47) (Fig. 7). The proarrhythmic effect of dobutamine was seen in patients with and without a finding of ventricular ectopy on baseline Holter monitoring (47) and in patients with both ischemic and nonischemic cardiomyopathies (44).

Effect of Nesiritide on Short-Term Outcome
A subgroup analysis was conducted on 261 patients who were included in two studies comparing effects of dobutamine to nesiritide in hospitalized patients with decompensated heart failure (48). It demonstrated that although there was no difference in length of stay

![Fig. 7. Mean changes from baseline in ventricular ectopy in patients treated with dobutamine or nesiritide.](image-url)
between the two groups, the use of dobutamine was associated with a longer duration of drug infusion compared to nesiritide (25 hours longer compared to the group receiving nesiritide 0.015 μg/Kg/min and 39 hours longer compared to nesiritide 0.03 μg/kg/min, both \( P < 0.001 \)) and a higher rate of readmission to the hospital during the first 31 days after discharge (20% versus 8%, \( P < 0.05 \) and 11%, \( P \) not significant, respectively). The readmissions for heart failure (13% versus 4% for both groups, \( P = 0.081 \)) was also higher in the dobutamine group. When compared to nitroglycerin in the VMAC study, there was no difference in rate of 30-day readmissions between the nesiritide and the nitroglycerin groups (37).

The effect of nesiritide on 6-month mortality was compared to that of dobutamine (49) and nitroglycerin (37). The effect of nesiritide on long term survival compared to that of dobutamine was evaluated in 261 patients who were treated with either dobutamine (\( n = 58 \)) or two different doses of nesiritide (0.06 μg/kg bolus and 0.03 μg/kg/min infusion in 100 patients and 0.03 μg/kg bolus followed by 0.015 μg/kg/min in 103 patients). Despite similar baseline characteristics, the use of dobutamine was associated with higher mortality compared to patients receiving nesiritide (48) (Fig. 8). The difference in the 6-month mortality rate between patients receiving dobutamine and nesiritide at 0.015 μg/kg/min was statistically significant (\( P = 0.04 \)).

![Log-rank Test](image)

**Fig. 8.** Kaplan-Meier estimate of mortality. Circle = dobutamine (\( n = 58 \)); square = nesiritide 0.6 μg/kg/min (\( n = 100 \)); triangles = nesiritide 0.3 μg/kg; 0.015 μg/kg/min (\( n = 103 \)). (With permission J Am Coll Cardiol 39:802, 2002)
A comparison between nesiritide and nitroglycerin in the VMAC study showed no significant difference in 6-month mortality between patients receiving these two therapies.

**Tachyphylaxis**

Tachyphylaxis, which results in a rapid and significant attenuation of hemodynamic effects, has been described with the use of continuous infusion of nitroglycerin and limits the usefulness of this drug in the treatment of patients with decompensated heart failure (49). In a study by Mills et al (40), the hemodynamic effects of nesiritide seen at 1 hour after initiation of drug infusion were sustained throughout the 24-hour infusion time. Similarly, the hemodynamic effect of nesiritide was maintained throughout the 24 hours of study period in the VMAC study (37). These findings indicate that, unlike nitroglycerin, continuous administration of nesiritide is not associated with the development of tolerance to the drug.

**Concomitant Use of β-Blockers**

The increasing use of β-blockers in patients with chronic heart failure may attenuate the effect of dobutamine when it is used for the treatment of decompensated heart failure. A recent analysis of the hemodynamic effect of nesiritide in 123 out of 489 patients included in the VMAC trial (50) showed that nesiritide significantly reduced filling pressure in patients concomitantly treated with β-blockers. The effect on left ventricular filling pressure was similar to that observed in patients not treated with β-blockers. Symptomatic hypotension was seen in the first 24 hours in 3% of patients receiving nesiritide concomitantly to β-blockers, compared to 4% in patients receiving nitroglycerin.

**Summary**

Nesiritide, a recombinant human B-type natriuretic peptide, is the first in a new drug class for the treatment of decompensated heart failure. The drug binds to receptors in the vasculature, kidney, adrenal gland, and brain and overcomes resistance to endogenous BNP present in patients with CHF. Nesiritide administration leads to a rapid and balanced vasodilatory effect, which results in a significant decrease in right and left ventricular filling pressures and systemic vascular resistance, and at the same time, an increase in stroke volume and cardiac output without a change in heart rate. These early hemodynamic changes result in a rapid improvement in symptoms of heart failure. In addition, nesiritide may lower aldosterone, catecholamines and endothelin-1 levels and its effect on the kidney leads to an increased natriuresis and diuresis without effect on serum potassium or renal function.

Prior to its approval for clinical use, nesiritide was studied in 10 different clinical trials involving 941 patients with moderate and severe CHF, including elderly patients, patients with both systolic and diastolic left ventricular dysfunction, and patients with arrhythmias, renal insufficiency, and acute ischemic syndrome. In comparative studies with available vasoactive therapies frequently used for treatment of patients with decompensated heart failure, nesiritide was proven comparable in efficacy to inotropic drugs such as dobutamine, but superior in safety. In a recent study, nesiritide was found to be more effective and better tolerated than the vasodilator, nitroglycerin. The most common adverse effects expected with the use of nesiritide are headaches and a decrease in blood pressure. At the recommended dose of nesiritide, headache was reported during the first 24 hours of treatment in 8% of patients and symptomatic hypotension in 4% of patients, compared to 20% and 5% in nitroglycerin-treated patients.

**Recommendation for Use**

Because of its significant hemodynamic and symptomatic benefits and its relatively superior safety profile, nesiritide appears to be the preferred vasoactive drug for the treatment of volume-overloaded patients admitted to the hospital for decompensated heart failure who have dyspnea at rest or with minimal activity. Nesiritide has been used successfully in clinical trials without central hemodynamic monitoring and can therefore be used with appropriate monitoring of blood pressure, in areas other than intensive care units as well as the emergency departments. Because of its lack of tachycardic or arrhythmogenic effect, continuous electrocardiographic monitoring should not be required during nesiritide infusion. The dose-limiting adverse effect is hypotension, so nesiritide should not be started at a dose that is higher than the recommended dose of a 2 μg/kg bolus followed by an infusion of 0.01 μg/kg/min, and blood pressure should be closely monitored. In case of symptomatic hypotension, the dose of nesiritide should be reduced or discontinued. Because patients with systolic blood pres-
sure of less than 85 mmHg were not included in the clinical trials, use of nesiritide in such patients is not recommended.

In the VMAC trial, experience (23 patients, all of whom had central hemodynamic monitoring) with increasing the dose of nesiritide above the recommended dose was limited. In those patients, the infusion dose of the drug was increased by 0.005 μg/kg/min (preceded by a bolus of 1 μg/kg) no more frequently than every 3 hours up to a maximum dose of 0.03 μg/kg/min.

Nesiritide has usually been used in conjunction with diuretic therapy. Because of the proven natriuretic and diuretic effects of the drug, diuretics may be reduced when given simultaneously with nesiritide. Nesiritide may also be given in conjunction with other vasoactive drugs such as dobutamine and dopamine. Concomitant heart failure therapy, including ACE inhibitors, β-blockers, digoxin, and spironolactone may be continued with appropriate dose adjustment, if indicated. Nesiritide is physically and/or chemically incompatible with injectable formulations of heparin, insulin, ethacrynic acid, bumetanide, enalaprilat, hydralazine, and furosemide. These drugs should not be coadministered as infusions with nesiritide through the same intravenous catheter. Nesiritide binds to heparin and, therefore, should not be administered through heparin-coated catheters. Intravenous nesiritide is usually administered for 24 to 48 hours, or until a significant clinical improvement is achieved.

References