Safety and Efficacy of Nesiritide for the Treatment of Decompensated Heart Failure

Charles L. Emerman, MD

Department of Emergency Medicine, Case Western Reserve University, Cleveland, OH

Nesiritide, the commercially available form of B-type natriuretic hormone, improved the overall clinical status of patients with acutely decompensated congestive heart failure and several indicators of cardiovascular function in randomized trials. In a trial comparing it to a variety of other agents, efficacy was similar, but fewer patients receiving nesiritide required intravenous diuretics. Nesiritide was associated with significantly lower 6-month mortality than dobutamine, which was found to be more proarrhythmic in an open-label trial. Nesiritide also caused a faster and greater improvement in pulmonary capillary wedge pressure than intravenous nitroglycerin. Adverse effects for nesiritide are generally lower than for other vasoactive agents used for heart failure. The primary adverse effect, hypotension, is dose related and causes symptoms in only about 4% of patients at the current recommended dose. Other side effects are minor or occur infrequently.
[Rev Cardiovasc Med. *2002;3(suppl 4):S28–S34*]

Key words: B-type natriuretic peptide • Congestive heart failure • Safety • Hypotension • Decompensation • Nesiritide

B-type natriuretic peptide (BNP) is an endogenous cardiac hormone produced primarily by the left but also by the right cardiac ventricle. It is released as a result of ventricular stress, hypertrophy, or volume overload caused primarily by congestive heart failure.[1] Pulmonary emboli[2] and severe cor pulmonale[3] may also lead to mildly elevated levels. BNP levels increase with increasing severity of heart failure and decrease with treatment.[4] Patients with elevated levels are at higher risk of death or repeat hospitalization over the next 6 months.[5] BNP is cleared from the system primarily by binding to cell surface C-receptors with subsequent lysosomal proteolysis and proteolytic cleavage by neutral endopeptidase. There is little renal clearance of BNP.

Nesiritide (Natrecor®, Scios Inc., Sunnyvale, CA) is the commercially available form of B-type natriuretic peptide. It is identical to the endogenously produced hormone. A major advantage of nesiritide, unlike a number of other agents, including dobutamine and nitroglycerin, is that this ability to maintain a set infusion allows heart failure patients to be cared for on lower-intensity units such as telemetry and observation units. The purpose of this article is to review the safety and efficacy data supporting the use of nesiritide.

Nesiritide is also the first agent shown to achieve significant reduction in acute heart failure symptoms while improving hemodynamics.

Nesiritide is approved for use in patients with acutely decompensated congestive heart failure with dyspnea at rest or with minimal activity. The infusion of nesiritide in patients with decompensated congestive heart failure leads to dose-related decreases in pulmonary capillary wedge pressure, pulmonary artery pressure, and systemic blood pressure, as well as to increased natriuresis, diuresis, and suppression of the renin-angiotensin-aldosterone axis.[6] Nesiritide is also the first agent shown to achieve significant reduction in acute heart failure symptoms, such as dyspnea, while improving hemodynamics, including pulmonary capillary wedge pressure, right atrial pressure, and cardiac index.[7]

Nesiritide has been studied in several major trials comparing it to a variety of other agents. Two of those trials were performed using a higher starting dose than is currently recommended for the initial infusion of nesiritide. The current recommendations are for an initial 2-μg/kg bolus followed by a 0.01 mcg/kg/min infusion, both based on actual body weight. This initial starting dose can be increased every 3 hours by giving another bolus at 1 μg/kg and then an increase in the infusion rate of 0.05 μg/kg/min to a maximum of 0.03 μg/kg/min.

Clinical trials have demonstrated that most patients do not require an adjustment of the dose and are maintained on the initial regimen.

Efficacy of Nesiritide for Decompensated Heart Failure

Early clinical trials of nesiritide demonstrated that it has properties beneficial in heart failure. When it is infused in patients with decompensated heart failure, there is a measurable increase in diuresis and urinary sodium excretion.[6] Increasing doses of nesiritide leads to a dose-related decrease in pulmonary capillary wedge pressure, pulmonary artery pressure, right atrial pressure, and mean arterial pressure. Because nesiritide leads to some degree of vagal stimulation, the decrease in mean arterial pressure is associated with little change in heart rate.[8] Both early and subsequent clinical trials show that nesiritide leads to an increase in cardiac index.[9]

Patients with elevated BNP levels are at higher risk of death or repeat hospitalization within 6 months.

The Efficacy and Comparative Trials

Nesiritide was compared to a variety of other agents used in heart failure in this two-phase study published in January 2000.[7] In the Efficacy Trial, a double-blind, placebo-controlled design measured short-term efficacy of nesiritide with regard to hemodynamics and symptoms in 127 patients. Two doses of nesiritide (a 0.3 μg/kg bolus followed by a 0.015 μg/kg/min infusion or a 0.6 μg/kg bolus followed by a 0.03 μg/kg/min infusion) were compared against placebo infusions in patients in whom Swan-Ganz catheter pulmonary artery catheters had been placed. Measurements after 6 hours showed that nesiritide led to a significantly greater decrease in wedge pressure and an improvement in clinical symptoms compared to placebo therapy (Table 1). Cardiac index improved and systemic blood pressure fell, in contrast to the findings seen with placebo. About two thirds of patients receiving nesiritide had improvement in global clinical status. More than half of patients taking nesiritide reported improvement in symptoms of fatigue.

In the Comparative Trial, nesiritide was evaluated against a variety of other cardiovascular agents. Patients were randomly assigned to one of the same two doses of nesiritide given in the Efficacy Trial or to any other single vasoactive agent chosen by the investigator in an open-label study of 305 patients. The comparator agent was dobutamine in more than half of the patients. Patients were eligible for enrollment if they had been hospitalized for congestive heart failure requiring intravenous (IV) medication in addition to diuretics. Patients were excluded if they had received IV vasoactive drugs during the 4 hours prior to the start of the study.

Table 1
Effects of Nesiritide on Hemodynamics in the Efficacy Trial*

Variable	Placebo (n = 42)	0.015 µg/kg/min (n = 43)	0.030 µg/kg/min (n = 42)	*P* Value†
Pulmonary capillary wedge pressure (mm Hg)	+2.0 ± 7.2	–6.0 ± 7.2‡	–9.6 ± 6.2‡	<.001
Right atrial pressure (mm Hg)	+0.4 ± 4.6	–2.6 ± 4.4‡	–5.1 ± 4.7‡	<.001
Systemic vascular resistance (dyne-sec-cm^{-5})	+161 ± 481	–247 ± 492‡	-347 ± 499‡	<.001
Cardiac index (liters/min/m^2)	–0.1 ± 0.47	+0.2 ± 0.49§	+0.4 ± 0.69‡	<.001
Systolic blood pressure (mm Hg)	+0.3 ± 11	–4.4 ± 10.2	–9.3 ± 12.6‡	.001
Systolic pulmonary artery pressure (mm Hg)	+1.7 ± 8.2	–9.4 ± 10.3‡	–12.9 ± 12.5‡	<.001
Mean pulmonary artery pressure (mm Hg)	+2.0 ± 5.9	–7.0 ± 6.9‡	–7.7 ± 7.6‡	<.001
Pulmonary vascular resistance (dyne-sec-cm^{-5})	+26 ± 197	–62 ± 100	–2 ± 142	.03
Heart rate (bpm)	+1.4 ± 7.5	–1.6 ± 7.1	+0.0 ± 8.8	.22

Changes in baseline hemodynamic values at 6 hours in the Efficacy Trial.
*Plus-or-minus values are means ± SD. Plus signs denote an increase and minus signs a decrease.
†*P* values are for the comparison among all three groups and were 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.

The use of a Swan-Ganz catheter was left to the discretion of the investigator, and catheters were used in about 20% of patients. Treatment was open label with regard to standard care but blinded with respect to the specific nesiritide dose. Nesiritide was administered in this trial at doses 50% and 300% above the current recommended infusion dose. The IV medication dose could be increased at the discretion of the investigator. IV medication, including nesiritide, could be continued for up to 7 days at the discretion of the investigator.

Most patients do not require an adjustment of the dose and are maintained on the initial regimen.

The efficacy of nesiritide in this trial was similar to that of the comparator vasoactive agents. Significant improvements in global clinical status and reductions in dyspnea and fatigue were noted in all groups. Fewer patients receiving nesiritide required intravenous diuretics.

The PRECEDENT Trial

The Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy (PRECEDENT) trial treated 246 patients with New York Heart Association (NYHA) functional class III or IV heart failure hospitalized for acute decompensation.[10] In this open-label trial, patients were randomized to one of three treatment groups: nesiritide 0.015 µg/kg/min, nesiritide 0.03 µg/kg/min (both doses above the current recommended dose and in this case given without a bolus dose), or dobutamine (at a minimum dose of 5 µg/kg/min). Patients underwent Holter monitor-

ing for 24 hours prior to and during the first 24 hours of treatment. Patients could receive nesiritide for up to 7 days and dobutamine for as long as appropriate. The primary objective of the PRECEDENT study was to compare the effects on heart rate and arrhythmias of two dose strengths of nesiritide to those of dobutamine during the first 24 hours of treatment of acutely decompensated congestive heart failure. Secondary endpoints included couplets, triplets, and ventricular tachycardia as well as clinical symptoms associated with therapy. Patients had either received stable doses of oral antiarrhythmic therapy or no antiarrhythmic agents for the 48 hours prior to enrollment. Randomization was stratified by whether or not subjects had a known history of ventricular tachycardia. There was no difference in the percentage of patients with a history of sustained (8%) or nonsustained (27%) ventricular tachycardia between the groups. The duration of therapy with the study drugs averaged 88 hours in the dobutamine group, 51 hours in the nesiritide 0.015 μg/kg/min group, and 44 hours in the nesiritide 0.030 μg/kg/min group. Ventricular tachycardia occurred in a higher proportion of patients receiving dobutamine (13%) than it did in those in either of the two nesiritide groups (6%). The incidence of PVCs and repetitive beats increased in the dobutamine-treated patients and decreased in the nesiritide-treated patients. Dobutamine was significantly more proarrhythmic than nesiritide according to two different proarrhythmia criteria. More patients in the dobutamine group were readmitted within 21 days. The 21-day readmission rate and the 6-month mortality rate were higher for the dobutamine group than for the lower-dose nesiritide group. There was significantly lower 6-month mortality for patients receiving the lower dose of nesiritide than for those receiving dobutamine in both PRECEDENT and the Comparative Trial.

The VMAC Trial

The Vasodilation in the Management of Acute Congestive (VMAC) heart failure trial evaluated the hemodynamic and clinical effects of nesiritide in addition to standard care compared to standard care plus IV nitroglycerin or placebo in 489 patients with acute decompensated congestive heart failure and dyspnea at rest.[11] Randomization in this blinded study was stratified by the investigator's decision to use a right heart catheter. Catheterized patients in the nesiritide group received either a fixed dose of nesiritide (2 μg/kg/min bolus followed by a 0.01 μg/kg/min infusion) or adjustable-dose nesiritide (same as fixed dose during first 3 hours). Following the 3-hour placebo-controlled period, placebo patients were randomized in blinded fashion to fixed-dose nesiritide or IV nitroglycerin. The IV nitroglycerin dose was determined by the investigator and could be adjusted during the study.

Dobutamine was significantly more proarrhythmic than nesiritide according to two different criteria.

The VMAC trial demonstrated that patients treated with nesiritide had a more rapid and greater improvement in pulmonary capillary wedge pressure than those treated with IV nitroglycerin (Figure 1). Beginning at 15 minutes and during the first 3 hours of treatment, nesiritide, added to standard care, produced a significantly greater decrease in pulmonary capillary wedge pressure than did standard care with or without nitroglycerin. After the first 3 hours of treatment, patients in the standard care (placebo) arm were crossed over to receive either nitroglycerin or nesiritide. Through 24 hours, nesiritide significantly improved pulmonary capillary wedge pressure compared to results with nitroglycerin. In contrast to the nitroglycerin treatment group, in the nesiritide group additional favorable effects on right atrial pressure, cardiac index, and systemic vascular resistance were observed. After 24 hours of therapy, patients treated with nesiritide had greater improvement in dyspnea and global clinical status than those treated with nitroglycerin.

Nesiritide has been used successfully in patients with diastolic dysfunction. Its effectiveness in this patient population was similar to that of nitroglycerin. Similarly, the VMAC trial included patients with renal insufficiency, and nesiritide's efficacy in that population was superior to nitroglycerin's. The VMAC trial also included patients who had an acute coronary syndrome episode within 7 days of enrollment. The 30-day readmission rate and the 6-month mortality for nesiritide were not higher than those for nitroglycerin in this setting.

Safety of Nesiritide

Nesiritide is generally safe for administration to patients with decompensated heart failure (Table 2). The primary side effects are headache and dose-related hypotension and nausea. When nesiritide is administered at the recommended starting dose of a 2-μg/kg bolus followed by

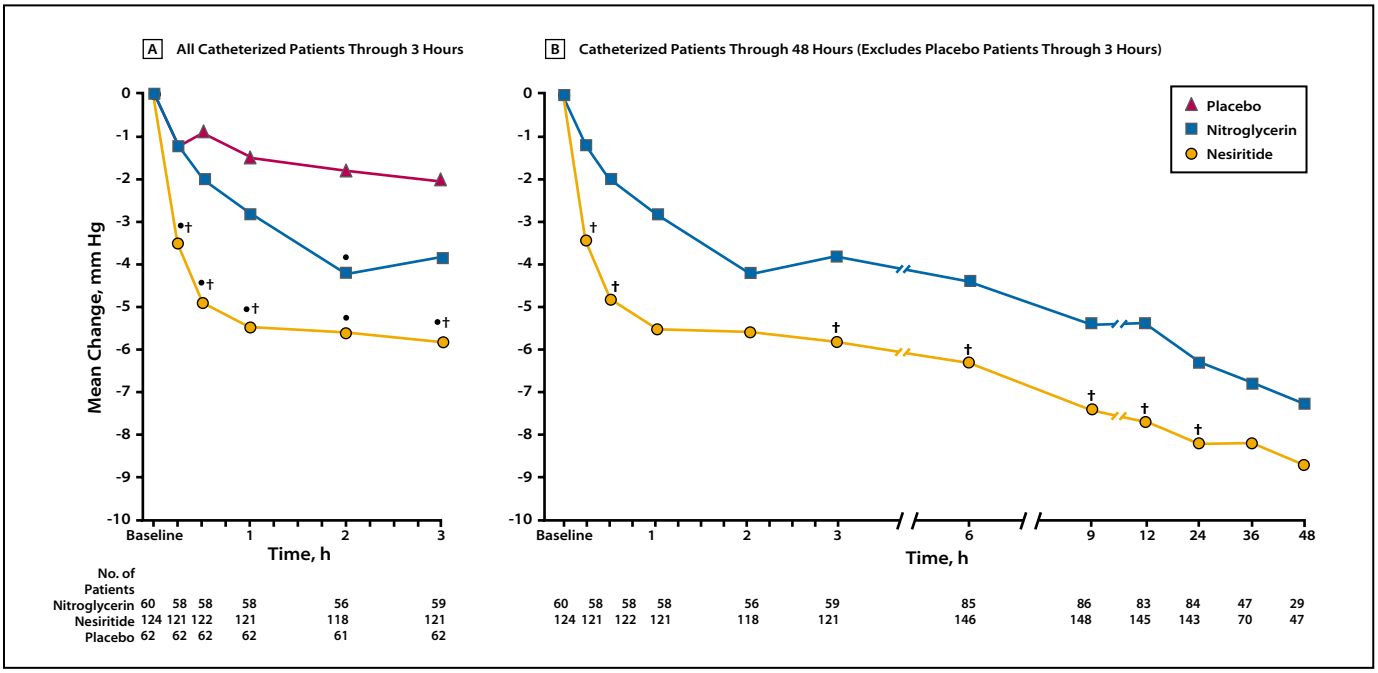

Figure 1. *Changes in hemodynamics in the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial. Reprinted from VMAC Investigators,[11] with permission from the publisher.*

a 0.01-μg/kg/min infusion, the incidence of hypotension is not significantly different from that reported with intravenous nitroglycerin.[11] In the three Phase III trials, including the Efficacy/Comparative Study, the PRECEDENT trial, and VMAC, 1040 subjects were enrolled, 639 of them treated with nesiritide and 401 treated with a variety of other vasoactive agents, primarily dobutamine and nitroglycerin. We have combined these data to provide a picture of nesiritide safety compared to the safety of other cardiovascular drugs given by IV infusion.

A decrease in blood pressure is a desired result of treatment with agents with vasodilating properties. During the first 24 hours after admission, the incidence of hypotension (11%) at the currently recommended nesiritide dose of 0.01 μg/kg/min (Table 2) has not been significantly different from that in all control patients (10%) or in those receiving nitroglycerin (12%).

About half of patients with nesiritide-induced hypotension are symptomatic. The incidence of symptomatic hypotension is dose related, and at the 0.01 μg/kg nesiritide dose (4%), it is not significantly different from that in all control patients (4%) or that in patients receiving nitroglycerin (5%). Most patients (66%) with symptomatic hypotension respond well to discontinuation of nesiritide infusion with re-initiation at a lower dose following resolution. Thirty-three percent of nesiritide (all doses) patients with symptomatic hypotension require intervention, with a median duration of hypotension of 100 minutes. In comparison, the mean duration of symptomatic hypotension in VMAC for nitroglycerin was about 30 minutes. Most patients with symptomatic hypotension respond to a small crystalloid infusion, although an occasional patient may require the initiation of dobutamine.

Ventricular tachycardia is less likely to occur in patients receiving nesiritide than in control patients, particularly at the 0.01-μg/kg/min dose. Dobutamine in particular has been found to be arrhythmogenic in patients with heart failure.[12] The incidence of ventricular tachycardia in nesiritide patients is not dose related. Ventricular tachycardia occurred in 5% of nesiritide patients, but the incidence was higher (11%) in patients treated with dobutamine and the same (5%) in patients treated with nitroglycerin. Bradycardia occurs in fewer than 1% of comparator group patients and was reported in 3% of all nesiritide patients. The incidence of bradycardia is also dose related. Headache is a more common complaint in control patients (15%) than in all nesiritide patients (8%) and is most common in patients receiving nitroglycerin (20%).

There has been no difference in the incidence of nausea between all nesiritide and all control treatment

Table 2
Adverse Effects: Nesiritide Compared to Other Agents Used for Heart Failure

Adverse Event	All Control (n = 401)	Nesiritide 0.01 µg/kg/min (n = 211)
Hypotension	41 (10%)	24 (11%)
Symptomatic	16 (4%)	10 (5%)
Asymptomatic	28 (7%)	17 (8%)
Ventricular tachycardia	31 (8%)	6 (3%)
Sustained	2 (<1%)	0 (0%)
Nonsustained	30 (7%)	6 (3%)
Bradycardia events	2 (<1%)	2 (1%)
Bradycardia	0 (0%)	1 (<1%)
Sinus bradycardia	2 (<1%)	1 (<1%)
Tachycardia	13 (3%)	1 (<1%)
Atrial fibrillation	1 (<1%)	4 (2%)
Headache	62 (15%)	19 (9%)
Catheter site pain	12 (3%)	3 (1%)
Dizziness	9 (2%)	7 (3%)
Nausea	23 (6%)	7 (3%)
Vomiting	5 (1%)	3 (1%)
Increased serum creatinine level	1 (<1%)	0 (0%)

groups (Table 2). Nausea is also dose related and occurs in about 3% of patients at the lower dose. Abdominal pain is also uncommon (1%) at the low dose, significantly lower than in patients receiving nitroglycerin.

The currently recommended nesiritide dose may be associated with a small, insignificant increase in serum creatinine. One percent of all nesiritide patients have an elevation in serum creatinine, which is not significantly different from the findings in all control groups. The mean increase in serum creatinine has been 0.1 mg/dL in all the nesiritide dose groups.

The VMAC trial included an analysis of the development of acute cardiac events during the study period (14 days). Myocardial infarction occurred in 1.4% of nitroglycerin patients, compared to 0.7% of nesiritide patients. The incidence rates of angina (7%) and ventricular tachycardia (13%) both in the nitroglycerin group and in all the nesiritide treatment groups were the same. These findings were not unexpected as nesiritide is a potent coronary vasodilator. Nesiritide is thus a more effective and better tolerated vasodilator than nitroglycerin and is useful in both ischemic and non-ischemic patients with acutely decompensated heart failure.

Nesiritide has vasodilating properties and decreases preload. Some patients are dependent on preload, and caution should be used with these patients when using agents that may decrease right ventricular filling pressures. This includes patients with constrictive pericarditis, critical aortic stenosis, or hypertrophic obstructive cardiomyopathy.

Our tendency is to start therapy early, with diuretics and other preload-reducing agents followed by initiation of nesiritide in the emergency department (ED). As noted above, our drug utilization review has found a good response with this protocol. Nesiritide is indicated for patients requiring IV therapy for decompensated heart failure. Generally, this means that patients with NYHA class III or class IV heart failure will be selected for treatment. Patients who will benefit from nesiritide treatment in the ED generally have evidence of fluid overload, manifested by weight gain, pedal edema, jugular venous distention, rales, and/or radiographic findings. Individual signs, symptoms, and findings may be absent in a particular patient. Nesiritide may be useful in other situations, outside of the scope of this article.

Summary

Nesiritide is an effective agent for the treatment of heart failure. Its major advantages over dobutamine are that it is not arrhythmogenic and leads to a more rapid improvement in dyspnea. Patients treated with dobutamine have a higher readmission rate and a higher 6-month mortality rate. Milrinone has not been extensively compared against nesiritide; however, the OPTIME study recently demonstrated that milrinone causes a significant increase in side effects over baseline therapy.[13] Nesiritide leads to a more rapid and sustained improvement in pulmonary capillary wedge pressure than is seen with nitroglycerin. The low incidence of symptomatic

hypotension and the infrequent need for dose adjustment allows nesiritide to be administered safely in observation and telemetry units. At the current recommended initial dose of a 2-μg/kg bolus followed by a 0.01-μg/kg/min infusion, nesiritide has a favorable safety profile compared to other vasoactive infusion agents. The symptomatic side effects at this dose occur in less than 5% of patients and are generally easily treated. ■

References

1. Maisel A. B-type natriuretic peptide in the diagnosis and management of congestive heart failure. *Cardiol Clin*. 2001;19:557–571.
2. Tulevski II, Hirsch A, Sanson BJ, et al. Increased brain natriuretic peptide as a marker for right ventricular dysfunction in acute pulmonary embolism. *Thromb Haemost*. 2001;86:1193–1196.
3. Bando M, Ishii Y, Sugiyama Y, Kitamura S. Elevated plasma brain natriuretic peptide levels in chronic respiratory failure with cor pulmonale. *Respir Med*. 1999;93:507–514.
4. Kazanegra R, Cheng V, Garcia A, et al. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. *J Card Fail*. 2001;7:21–29.
5. Harrison A, Morrison LK, Krishnaswamy P, et al. B-type natriuretic peptide predicts future cardiac events in patients presenting to the emergency department with dyspnea. *Ann Emerg Med*. 2002;39:131–138.
6. Marcus LS, Hart D, Packer M, et al. Hemodynamic and renal excretory effects of human brain natriuretic peptide infusion in patients with congestive heart failure: a double-blind, placebo-controlled, randomized crossover trial. *Circulation*. 1996;94:3184–3189.
7. Colucci WS, Elkayam U, Horton DP, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. *N Engl J Med*. 2000;343:246–253.
8. Thomas CJ, Head GA, Woods RL. Similar baroreflex bradycardic actions of atrial natriuretic peptide and B and C types of natriuretic peptides in conscious rats. *J Hypertens*. 1999;17:801–806.
9. Abraham WT, Lowes BD, Ferguson DA, et al. Systemic hemodynamic, neurohormonal, and renal effects of a steady-state infusion of human brain natriuretic peptide in patients with hemodynamically decompensated heart failure. *J Card Fail*. 1998;4:37–44.
10. Berger A, Horton D, LeJemtel T. Differential effects of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias: the PRECEDENT study. *Am Heart J*. In press.
11. VMAC Investigators. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA*. 2002;287:1531–1540.
12. Burger AJ, Elkayam U, Neibaur MT, et al. Comparison of the occurrence of ventricular arrhythmias in patients with acutely decompensated congestive heart failure receiving dobutamine versus nesiritide therapy. *Am J Cardiol*. 2001;88:35–39.
13. Cuffe MS, Califf RM, Adams KF Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287:1541–1547.

Main Points

- Nesiritide is identical to endogenously produced B-type natriuretic peptide, a cardiac hormone released as a result of ventricular stress, hypertrophy, or volume overload caused primarily by congestive heart failure.
- Nesiritide reduces pulmonary capillary wedge pressure, pulmonary artery pressure, and systemic blood pressure and increases natriuresis, diuresis, and suppression of the renin-angiotensin-aldosterone axis in patients with decompensated congestive heart failure.
- With a low incidence of symptomatic hypotension and infrequent need for dose adjustment, nesiritide can be administered safely in observation and telemetry units.
- Nesiritide has a favorable safety profile at the currently recommended dosage.
- Nesiritide has vasodilating properties and must be used with caution in patients dependent on preload.