Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 50, No. 19, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.03.071

Impact of Nesiritide on Renal Function in Patients With Acute Decompensated Heart Failure and Pre-Existing Renal Dysfunction

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Objectives Our purpose was to evaluate the impact of nesiritide on renal function in patients with acute decompensated heart failure and baseline renal dysfunction.

Background Although nesiritide is approved for the treatment of acute decompensated heart failure, retrospective analyses have raised concerns that it may cause worsened renal function. To date, no randomized clinical trials have prospectively evaluated this issue.

Methods Consecutive patients with acute decompensated heart failure and baseline renal dysfunction were enrolled in this randomized, double-blind, placebo-controlled clinical trial. Subjects were randomized to receive nesiritide (0.01 μg/kg/min with or without a 2-μg/kg bolus) or placebo (5% dextrose in water) for 48 h in addition to their usual care. Predefined primary end points of the trial were a rise in serum creatinine by ≥20% and change in serum creatinine.

Results Seventy-five patients were enrolled (39 nesiritide, 36 placebo). The groups had similar baseline age (74.9 vs. 75.5 years, respectively), blood pressure (123/64 vs. 125/64 mm Hg) and serum creatinine (1.82 vs. 1.86 mg/dl). There were no significant differences in the incidence of a 20% creatinine rise (23% vs. 25%) or in the change in serum creatinine (−0.05 vs. +0.05 mg/dl). There were no significant differences in the secondary end points of change in weight (−2.19 vs. −1.58 kg), intravenous furosemide (125 vs. 107 mg), discontinuation of the infusion due to hypotension (13% vs. 6%), or 30-day death/hospital readmission (33% vs. 25%).

Conclusions In this randomized, double-blind, placebo-controlled clinical trial, nesiritide had no impact on renal function in patients with acute decompensated heart failure. (BNP-CARDS trial; http://www.clinicaltrials.gov/ct/show/NCT00186329?order=1; NCT00186329) (J Am Coll Cardiol 2007;50:1835–40) © 2007 by the American College of Cardiology Foundation

One of the main challenges in the treatment of acute decompensated heart failure (ADHF) is worsened renal function. Renal dysfunction independently predicts a worse outcome in heart failure in general and ADHF in particular (1–12). Importantly, it is during the treatment period for ADHF when the effects are most significant, as a decline in renal function during ADHF therapy is a worse prognostic factor than the presence of baseline renal dysfunction (6–8,10–12). Loop diuretics, the mainstay of therapy for ADHF, are associated with worsened renal function, activation of the renin-angiotensin-aldosterone axis, and potentially even increased mortality (12–19). The National Heart, Lung, and Blood Institute, in recognition of the importance of worsened renal function in heart failure, defined "cardiorenal syndrome" as a condition "in which therapy to relieve congestive symptoms of heart failure is limited by further decline in renal function" and stressed the need for urgent study of this condition (20).

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Manuscript received February 12, 2007; revised manuscript received March 26, 2007, accepted March 28, 2007.

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November 6, 2007:1835–40

Abbreviations and Acronyms

ADHF = acute decompensated heart failure

GFR = glomerular filtration rate

IV = intravenous

Nesiritide (human recombinant B-type natriuretic peptide), approved by the Food and Drug Administration in 2001, became the first new therapy for ADHF in 14 years. Although its primary mechanism of action is as a systemic and pulmonary vasodilator, it has multiple effects on the kidneys, including promoting natriuresis, diuresis, and inhibiting the renin-angiotensin-aldosterone axis (21–23). Previous studies evaluating non-heart failure patients and stable heart failure outpatients have demonstrated mixed results regarding the effect of nesiritide on glomerular filtration rate (GFR), with some studies suggesting an improvement in GFR (even partially attenuating the negative effects of loop diuretics) and others showing no impact (21,24–30).

Although nesiritide's effect on renal function was not a primary end point in prior trials, a meta-analysis published in 2005 found that treatment with nesiritide may be associated with *worsened* renal function (31). This study largely accounted for a dramatic decrease (up to 64%) in the clinical use of nesiritide for the treatment of ADHF (32). Despite this controversy and the importance of renal dysfunction in heart failure outcomes, no study of >15 patients prospectively evaluating this issue has been published to date, and no study has prospectively evaluated this issue in the usual clinical setting of attempted diuresis (33).

The purpose of this study was to evaluate the effect of nesiritide administration on renal function in a population with ADHF and pre-existing renal dysfunction in a prospective, randomized, double-blind, placebo-controlled clinical trial.

Methods

The BNP-CARDS (B-Type Natriuretic Peptide in Cardiorenal Decompensation Syndrome) trial was performed from March 1, 2004, to August 31, 2006, at Stanford University Hospital and from February 1, 2006, to August 31, 2006, at the Palo Alto Veterans Administration Hospital. All newly admitted inpatients during those periods with a primary diagnosis of ADHF were screened for the trial. Further inclusion criteria included a calculated GFR (using the Cockcroft-Gault formula) between 15 to 60 ml/min (changed from 15 to 50 ml/min in December 2004 to be consistent with the published definition of "moderate renal impairment"), and age ≥18 years (34,35). Exclusion criteria included baseline hypotension (systolic blood pressure <90 mm Hg), hemodynamically significant aortic stenosis, need for intravenous (IV) vasodilator therapy, admission to an intensive care unit, history of cardiac transplantation, allergy to nesiritide, and prior enrollment in the trial. Subjects were enrolled within 12 h of hospital admission. The protocol was approved by the human subjects committees at both study sites.

After written informed consent was obtained, patients were randomized in a 1:1 fashion to receive a fixed-dose nesiritide infusion (2-μg/kg IV bolus followed by a continuous infusion at 0.01 μg/kg/min for 48 h) or matching placebo (5% dextrose in water mimicking the same dosing). Randomization was performed by the research pharmacist at each site using a random number generator. The bolus could be held at the discretion of the treating physician (separate from the study investigators) if there was clinical concern for the development of significant hypotension, usually for baseline systolic blood pressure 90 to 109 mm Hg. The remainder of the medications administered to the patient (including diuretics) was at the discretion of the treating physician. Patients were monitored for adverse reactions to nesiritide, including hypotension. The infusion was discontinued at the discretion of the treating physician if the subject developed symptomatic hypotension. Serum creatinine was measured daily during the infusion. All clinicians and study personnel were blinded to the subject's randomization.

The predefined primary end points of the trial were:

1. A significant decline in renal function (defined as a peak serum creatinine increase of ≥20% at any time during the first 7 days of hospitalization compared with the admission creatinine).
2. Change in serum creatinine from the admission value to discharge and/or day 7 of hospitalization, whichever was sooner.

Secondary end points included net negative diuresis ≥1 l/day while on the infusion; change in weight during the infusion; need to discontinue the infusion due to hypotension; total diuretic use while receiving the infusion; median length of stay; death or rehospitalization within 30 days; and resource utilization—defined by need for dialysis, intensive care monitoring, pulmonary artery catheterization, and intubation. Results were analyzed by Student *t* test and chi-square analysis, as appropriate. The study had 80% power at an alpha of 0.05 to detect a 28% relative difference in the first primary end point assuming a 25% event rate, and to detect a creatinine difference of 0.20 mg/dl in the second primary end point assuming a standard deviation of 0.30 mg/dl. Data were analyzed in an intention-to-treat fashion.

Results

Of 514 consecutive patients admitted with ADHF, 75 met inclusion/exclusion criteria and provided informed consent.

The baseline characteristics of the 2 groups were similar (Table 1). In particular, average age and serum creatinine were very similar between the 2 groups. A large portion of patients in each group (46% in the nesiritide group, 50% of the placebo group) were over 79 years of age.

Table 1 Baseline Characteristics

Characteristics	Nesiritide (n = 39)	Placebo (n = 36)	p Value
Age, mean (yrs)	74.9	75.5	0.85
% male	67	61	0.62
Admission creatinine (mg/dl)	1.82	1.86	0.79
Admission GFR (ml/min, estimated)	35	33	0.48
% systolic dysfunction (LVEF <45%)	55	62	0.58
Outpatient furosemide dose (mg/day)	65	55	0.50
Systolic blood pressure (mm Hg)	123	125	0.77
Diastolic blood pressure (mm Hg)	64	64	0.87
% of patients taking			
Beta-blocker	72	58	0.22
ACE-I and/or ARB	51	47	0.73
Aldosterone antagonist	15	11	0.59
Digoxin	28	25	0.75
Amiodarone	21	6	0.06
Calcium blocker	23	25	0.85
Long-acting nitrate	23	28	0.64
Hydralazine	5	25	**0.02**
History of (%)			
Heart failure	90	89	0.90
Coronary artery disease	77	56	**0.0499**
COPD	26	19	0.52
Diabetes mellitus	56	44	0.30
Atrial fibrillation	44	36	0.51
Cerebrovascular accident	8	19	0.13

Values in **bold** indicate statistical significance.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction.

There was no difference in the primary end points of renal dysfunction—either a ≥20% increase in serum creatinine, or the change in creatinine from the admission value (Fig. 1, Table 2). There was no significant difference in net weight loss or net fluid balance between the 2 groups, with slight trends for more weight loss/net negative fluid balance in the nesiritide group balanced by a trend toward higher doses of diuretics administered to that group. There were no gender-based differences in the results in either group.

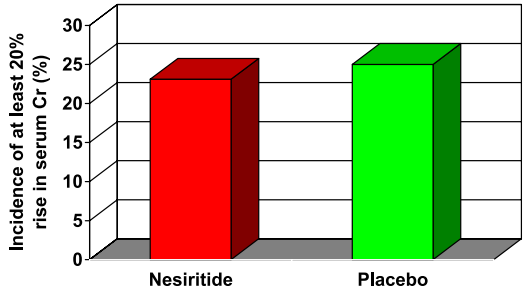

Figure 1 Incidence of Worsened Renal Function

Incidence of ≥20% rise in creatinine (Cr) by discharge or day 7 of the hospitalization. No significant difference was observed in the primary end point of worsened renal function (increase in serum creatinine ≥20%) (p = 0.85).

Table 2 Outcomes

Outcome	Nesiritide (n = 39)	Placebo (n = 36)	p Value
Change in creatinine (mg/dl)	−0.05	0.05	0.46
Diuresis >1 l/24 h (%)	49	48	0.91
Length of stay (median days)	4	4	
Length of stay (mean days)	5.85	5.67	0.91
Weight loss (kg)	2.19	1.58	0.26
Net fluid balance (l)	−1.99	−1.90	0.86
IV furosemide during infusion (mg)	124.5	106.7	0.53
Oral furosemide during infusion (mg)	34.8	28.8	0.45

IV = intravenous.

There were no statistically significant differences in complications/adverse outcomes between the 2 groups, although there was a nonsignificant trend for the infusion being stopped more frequently in the nesiritide group due to hypotension (Table 3). Systolic and diastolic blood pressures trended lower in the nesiritide group at almost all time points, with significantly lower values than in the placebo group at 3, 6, and 12 h (Fig. 2).

Thirty-five percent of subjects had their bolus held by the treating physician (33% randomized to nesiritide, 36% randomized to placebo, p = NS). Subjects who received a bolus had higher baseline systolic blood pressures than subjects who had the bolus withheld (132 vs. 110 mm Hg, $p < 0.0001$). Subjects who received a nesiritide bolus had a nonsignificant trend (p = 0.15) toward a larger drop in systolic blood pressure 1 h after the infusion started (−8.6 mm Hg) than those who had the bolus held (−0.9 mm Hg). There was no significant association between receiving a bolus and any of the predefined end points.

Discussion

The main finding of this study was that, in a cohort of patients with baseline renal insufficiency and ADHF, administration of nesiritide in addition to standard therapy did not result in worsened renal function. Importantly, administration of nesiritide did not protect against the development of renal dysfunction either. Therefore, whereas nesiritide appears to be safe in this population of patients from a renal standpoint, this trial provided no evidence for a therapeutic role to protect renal function.

One possible explanation for the disparate findings between this and previous studies is the use of a bolus dose. In

Table 3 Adverse Events

Event	Nesiritide (%) (n = 39)	Placebo (%) (n = 36)	p Value
Infusion stopped for hypotension	5 (13)	2 (6)	0.28
Transfer to intensive care unit	4 (10)	3 (8)	0.77
Dialysis	0 (0)	1 (3)	0.29
Mechanical ventilation	0 (0)	1 (3)	0.29
30-day mortality	4 (10)	2 (6)	0.45
30-day mortality/readmission	13 (33)	9 (25)	0.43

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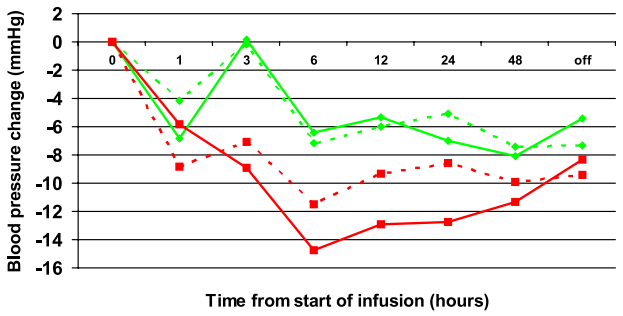

Figure 2 **Blood Pressure Change During Infusion**

Blood pressure change is recorded in reference to the start of the infusion (time = 0). Time "off" refers to 3 h after the infusion was stopped (**solid lines** = systolic blood pressure change; **dashed lines** = diastolic blood pressure change; **green** = placebo; **red** = nesiritide). $p < 0.05$ versus placebo at 6 and 12 h for systolic blood pressure, and at 3 h for diastolic blood pressure.

most previous studies, a 2-μg/kg IV bolus dose was administered to patients, as per the protocol in the VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) trial (36). The majority of the VMAC trial population consisted of patients who, in the clinicians' judgment, required a pulmonary artery catheter for management before being enrolled in the trial (36). Their clinical characteristics—an average pulmonary capillary wedge pressure of 28 mm Hg, an average systemic vascular resistance of over 1,400 dynes/s/cm^5, and the clinical need for a pulmonary artery catheter—were such that a large bolus of a vasodilator might be desirable. This represents a very different population from many ADHF patients, who rarely require a pulmonary artery catheter and who can usually afford the 1 to 2 h necessary to gradually reach steady-state concentration of the drug. Indeed, for a drug with a half-life of approximately 20 min, steady-state concentrations are reached relatively quickly with the continuous IV infusion without administering a bolus. It is certainly conceivable that any positive or neutral effects of nesiritide on GFR might be overcome by significant hypotension occurring with the bolus dose, possibly accounting for some of the worsened renal function seen in other retrospective analyses. The recently published NAPA (Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery) trial found that perioperative use of nesiritide in patients with left ventricular dysfunction undergoing coronary artery bypass grafting *protected* against renal dysfunction and was notable for the fact that a bolus dose was not included in the protocol (37). The patients in the NAPA trial were very different from those evaluated in our trial, most notably because the NAPA trial cohort did not evaluate patients with ADHF (for whom nesiritide is Food and Drug Administration approved). Although only 1 of the 5 subjects in our study who had the nesiritide infusion discontinued due to hypotension received a bolus, this is likely a reflection of the fact that the group who received the bolus had significantly higher baseline blood pressure than the group who had the bolus withheld. Receiving a nesiritide bolus was associated with a trend toward developing a larger drop in systolic blood pressure at 1 h in our study.

A second difference between our trial and other studies is the dose of nesiritide infusion used. In our trial, all patients randomized to the nesiritide arm received the recommended starting dose of 0.01 μg/kg/min, a dose that retrospective analyses have found to be more consistent with a neutral or positive effect on renal function (38,39). Past studies have used doses between 0.01 and 0.06 μg/kg/min, with higher doses leading to more hypotension and more reports of worsened renal function (31,36,39).

Another possible difference between the results of our trial and observations from previous trials is the timing when the nesiritide infusion was initiated. In our study, all patients were started within 12 h of hospitalization, before they might have otherwise been aggressively diuresed with loop diuretics. This earlier administration may have contributed to a lower incidence of hypotension, and may have also prevented up-regulation of the renin-angiotensin-aldosterone system otherwise associated with loop diuretic administration (14–16,19,20).

A final important difference between our study and earlier trials is the makeup of the study population. Our trial design, which targeted all consecutive patients who met entry criteria, was intended to yield a patient population representative of admissions for heart failure in the general population—and not surprisingly included many patients of advanced age (48% of patients were >79 years of age) and many patients with heart failure with preserved systolic function (42%). This is opposed to a mean age of 61 years and only 15% of patients with a left ventricular ejection fraction >40% in the VMAC trial (36). Importantly, older average age and higher prevalence of preserved systolic function are both characteristics of the "cardiorenal" patient (3,6,7,11).

Patients in the nesiritide group did develop significantly lower systolic and diastolic blood pressure, with a trend toward the infusion needing to be discontinued for hypotension more frequently. Despite this lower blood pressure, patients in the nesiritide group did not develop worsened renal dysfunction. A possible explanation may be the balance of "direct" and "indirect" effects of natriuretic peptides on renal function. Direct effects of natriuretic peptides serve to increase GFR by relaxing renal mesangial cells, dilating the afferent renal arteriole, and constricting the efferent renal arteriole; indirect effects serve to decrease GFR by inhibiting the renin-angiotensin-aldosterone and sympathetic axes and by lowering systemic blood pressures and circulating blood volume (21,40–43). It is likely the balance of these direct and indirect effects that causes GFR to increase, decrease, or stay the same in individual patients. In our cohort of patients with nesiritide administered per our protocol, the net effect on GFR was neutral.

There were several important limitations to this study. Although this represents the largest randomized trial to prospectively evaluate the effect of nesiritide on renal function in ADHF, the number of participants still could allow for a type II error. A large treatment effect on the primary end points is unlikely given the lack of even a trend in either direction, but a smaller and potentially clinically relevant effect is still possible. Another limitation to this trial was the exclusion of important subgroups of ADHF patients, including those needing intensive care and those requiring IV vasodilator therapy; the results of this trial certainly do not exclude a potentially important effect of nesiritide (positive or negative) on renal function in those patients. Finally, although our trial was not powered to evaluate mortality and hospital readmission, there were nonsignificant trends observed in favor of placebo. Due to the relatively small sample size, the lack of statistical significance does not rule out differences in these outcomes.

Conclusions

The results of this prospective, randomized, double-blind, placebo-controlled clinical trial indicate that nesiritide therapy does not cause or prevent worsened renal function in patients with ADHF and pre-existing renal dysfunction. Data regarding the renal effects of nesiritide therapy in other patient populations, and effects on other clinical end points, await the result of other randomized trials.

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REFERENCES

1. van Kimmenade RR, Januzzi JL, Baggish AL, et al. Amino-terminal pro-brain natriuretic peptide, renal function, and outcomes in acute heart failure: redefining the cardiorenal interaction? J Am Coll Cardiol 2006;48:1621–7.
2. Mahan NG, Blackstone EH, Francis GS, Starling RC III, Young JB, Lauer MS. The prognostic value of estimated creatinine clearance alongside functional capacity in patients with chronic congestive heart failure. J Am Coll Cardiol 2002;40:1106–13.
3. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.
4. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000;35:681–9.
5. Hillege HL, Girbes AR, de Kam PJ, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation 2000;102:203–10.
6. Shlipak MG, Massie BM. The clinical challenge of cardiorenal syndrome. Circulation 2004;110:1514–7.
7. Krumholz HM, Chen YT, Vaccarino V, et al. Correlates and impact on outcomes of worsening renal function in patients ≥65 years of age with heart failure. Am J Cardiol 2000;85:1110–3.
8. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol 2004;43:61–7.
9. Hillege HL, Nitsch D, Pfeffer MA, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 2006;113:671–8.
10. Smith GL, Vaccarino V, Kosiborod M, et al. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? J Card Fail 2003;9:13–25.
11. Gheorghiade M, Filippatos G. Reassessing treatment of acute heart failure syndromes: the ADHERE registry. Eur Heart J 2005;7 Suppl B:B13–9.
12. Gheorghiade M, Zannad F, Sopko G, et al. Acute heart failure syndromes: current state and framework for future research. Circulation 2005;112:3958–68.
13. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. Am J Cardiol 2006;97:1759–64.
14. McCurley JM, Hanlon SU, Wei SK, Wedam EF, Michalski M, Haigney MC. Furosemide and the progression of left ventricular dysfunction in experimental heart failure. J Am Coll Cardiol 2004;44:1301–7.
15. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced heart failure. Am Heart J 1999;138:285–90.
16. Knight EL, Glynn RJ, McIntyre KM, Mogun H, Avon J. Predictors of decreased renal function in patients with heart failure during angiotensin-converting enzyme inhibitor therapy: results from the Studies of Left Ventricular Dysfunction (SOLVD). Am Heart J 1999;138:849–55.
17. Philbin EF, Cotto M, Rocco TA Jr., Jenkins PL. Association between diuretic use, clinical response and death in acute heart failure. Am J Cardiol 1997;80:519–23.
18. Neuberg GW, Miller AB, O'Connor CM, et al. Diuretic resistance predicts mortality in patients with advanced heart failure. Am Heart J 2002;144:31–8.
19. Butler J, Forman DE, Abraham WT, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. Am Heart J 2004;147:331–8.
20. NHLBI Working Group. Cardio-Renal Connections in Heart Failure and Cardiovascular Disease. August 20, 2004. Available at: http://www.nhlbi.nih.gov/meetings/workshops/cardiorenal-hf-hd.htm. Accessed September 20, 2007.
21. 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. Circulation 1996;94:3184–9.
22. De Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003;362:316–22.
23. Aronson D, Burger AJ, Cleland JG, et al. Nesiritide: a review of its use in acute decompensated heart failure. Drugs 2003;63:47–70.
24. La Villa G, Fronzaroli C, Lazzeri C, et al. Cardiovascular and renal effects of low dose brain natriuretic peptide infusion in man. J Clin Endocrinol Metab 1994;78:1166–71.
25. van der Zander K, Houben AJ, Hofstra L, Kroon AA, de Leeuw PW. Hemodynamic and renal effects of low-dose brain natriuretic peptide infusion in humans: a randomized, placebo-controlled crossover study. Am J Physiol 2003;285:H1206–12.
26. Cataliotti A, Boerrigter G, Costello-Boerrigter LC, et al. Brain natriuretic peptide enhances renal actions of furosemide and suppresses furosemide-induced aldosterone activation in experimental heart failure. Circulation 2004;109:1680–5.
27. Jensen KT, Carstens J, Pedersen EB. Effect of BNP on renal hemodynamics, tubular function, and vasoactive hormones in humans. Am J Physiol 1998;274:F63–72.
28. Chen HH, Grantham JA, Schirger JA, Jougasaki M, Redfield MM, Burnett JC Jr. Subcutaneous administration of brain natriuretic peptide in experimental heart failure. J Am Coll Cardiol 2000;36:1706–12.
29. Lazzeri C, Franchi F, Porciani C, et al. Systemic hemodynamics and renal function during brain natriuretic peptide infusion in patients with essential hypertension. Am J Hypertens 1995;8:799–807.
30. Jensen K, Eiskjaer H, Carstens J, Pedersen EB. Renal effects of brain natriuretic peptide in patients with congestive heart failure. Clin Sci (Lond) 1999;96:5–15.
31. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation 2005;111:1487–91.

32. Hauptman PJ, Schnitzler MA, Swindle J, Burroughs TE. Use of nesiritide before and after publications suggesting drug-related risks in patients with acute decompensated heart failure. JAMA 2006;296: 1877–84.
33. Wang DJ, Dowling TC, Meadows D, et al. Nesiritide does not improve renal function in patients with chronic heart failure and worsening serum creatinine. Circulation 2004;110:1620–5.
34. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
35. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:81–266.
36. Publication Committee for the VMAC Investigators. Intravenous nesiritide vs. nitroglycerin for treatment of decompensated congestive heart failure. JAMA 2002;287:1531–40.
37. Mentzer RM, Oz MC, Sladen RN, et al. Effects of perioperative nesiritide in patients with left ventricular dysfunction undergoing cardiac surgery. J Am Coll Cardiol 2007;49:716–26.
38. Riter HG, Redfield MM, Burnett JC, Chen HH. Nonhypotensive low-dose nesiritide has differential renal effects compared with standard-dose nesiritide in patients with acute decompensated heart failure and renal dysfunction. J Am Coll Cardiol 2006;47:2334–5.
39. Burger AJ, Horton DP, LeJemtel T, et al. Effect of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias in the treatment of patients with acutely decompensated congestive heart failure: the PRECEDENT study. Am Heart J 2002;144:1102–8.
40. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med 1998;339:321–8.
41. Holmes SJ, Espiner EA, Richards AM, Yandle TG, Frampton C. Renal, endocrine, and hemodynamic effects of human brain natriuretic peptide in normal man. J Clin Endocrinol Metab 1993;76: 91–6.
42. Brunner-La Rocca HP, Kaye DM, Woods RL, Hastings J, Esler MD. Effects of intravenous brain natriuretic peptide on regional sympathetic activity in patients with chronic heart failure as compared with healthy control subjects. J Am Coll Cardiol 2001; 37:1221–7.
43. Molina CR, Fowler MB, McCrory S, et al. Hemodynamic, renal and endocrine effects of atrial natriuretic peptide infusion in severe heart failure. J Am Coll Cardiol 1988;12:175–86.