Human B-Natriuretic Peptide Improves Hemodynamics and Renal Function in Heart Transplant Patients Immediately After Surgery

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ABSTRACT

Background: B-natriuretic peptide (BNP) is effective in the treatment of decompensated heart failure, but has not specifically been evaluated in the immediate postoperative cardiac transplant population.

Objective: To determine if BNP can favorably alter hemodynamics in the perioperative setting after heart transplantation.

Methods and Results: We administered $_{human}$BNP ($_{h}$BNP, Nesiritide) to 10 consecutive patients with preexisting renal insufficiency and elevated filling pressures. All patients had failed to respond to inotropes and escalating doses of diuretics. BNP was started 48 hours after transplantation, and continued for 48 to 72 hours. Intravascular hemodynamics were measured. With $_{h}$BNP therapy, the pulmonary capillary wedge pressure, central venous pressure, and mean pulmonary artery pressure were all attenuated, whereas the cardiac output was significantly increased. The mean urine output increased significantly in the first 24 hours of therapy with no increase in diuretics. Implementation of BNP therapy allowed for a reduction of patients' inotropes and diuretics, while decreasing serum BNP levels.

Conclusion: An improvement in cardiac hemodynamics and renal function was observed with administration of $_{h}$BNP in these postsurgical patients with elevated filling pressures and acute on chronic renal insufficiency. This study demonstrates that posttransplant patients retain the capacity to respond to exogenous BNP immediately after surgery.

Key Words: Congestive heart failure, Filling pressures, Renal failure, Volume overload.

Postoperative heart transplant patients frequently have elevated cardiac filling pressures, refractory volume overload, and acute renal insufficiency. Registry data suggest that right ventricular dysfunction accounts for 50% of all postoperative complications after heart transplantation.[1] Posttransplant patients are typically managed with various combinations of vasodilators, diuretics, and inotropes. Many of these therapeutic interventions are potentially deleterious to these patients, despite acute hemodynamic improvement. In this study, the investigators provide evidence that human B-natriuretic peptide ($_{h}$BNP) is an effective treatment strategy in posttransplant patients with acute volume overload.

Methods

This study was conducted in 10 consecutive patients who underwent orthotopic heart transplant and had elevated filling pressures with a serum creatinine greater than 2.5 mg/dL two days after surgery. Demographic data are provided in Table 1. Before surgery all patients had a serum creatinine less than 1.8 mg/dL and a serum creatinine clearance greater than 45 mL/min. Invasive hemodynamic monitoring was performed with pulmonary artery catheters. Urine collection was standardized using a Foley catheter to quantify hourly urine output. When available, serum BNP levels were determined using radioimmunoassay (Assay, Biosite, San Diego, CA). Given the small number and uncommon pathology of the patients involved in this study, each patient served as his or her own control.

Before initiation of nesiritide therapy, doses of vasoactive drugs and diuretics were titrated at the discretion of the treating physician based on the patients' clinical status. The drug therapies for each patient before initiation of nesiritide are reviewed in Table 2. Refractoriness to this type of conventional therapy was defined as

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Table 1. Baseline Characteristics

Characteristic	Mean +/− SEM
Pre-OHT LVEF	19.4 +/− 3.65
Pre-OHT NYHA class	IIIB
Ischemic vs. idiopathic cardiomyopathy	70% vs. 30%
UNOS status 1B	30%
UNOS status 2	70%
Redo sternotomy	40%
Donor ischemic time	253.4 +/− 25.4 min
Coagulopathy	50%
Total bypass time	274 +/− 69.6 min
Delayed graft function intraopt	50%
Duration of BNP therapy	64.8 +/− 15.1 hrs
Male vs. female	60% vs. 40%
% African American	40%
% patients with DM	30%

OHT, Orthotopic Heart Transplant; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; UNOS, United Network for Organ Sharing; BNP, B-natriuretic peptide; DM, diabetes mellitus.

persistently elevated cardiac filling pressures (central venous pressure >15, pulmonary capillary wedge pressure >22), and suboptimal urine output (<60 cc/hr) on escalating doses of diuretic therapy. Nesiritide was started approximately 48 hours after transplantation with a bolus of 2 mcg/kg, followed by an infusion of 0.010 mcg·kg·min. If systemic hypotension (defined as systolic blood pressure <90 mm Hg or mean arterial pressure <60 mm Hg on 2 consecutive blood pressure measurements) was present or initial systemic vascular resistance was less than 850 dynes.s.m^2/cm^3, the bolus dose was reduced to 1 mcg/kg, and the infusion was initiated at 0.005 mcg·kg·min. After 3 to 6 hours, the infusion was increased as needed to "normalize" right atrial (<7 mm Hg) and pulmonary capillary wedge pressures (<16 mm Hg). The maximum dose used in the study was 0.025 mcg·kg·min. The following parameters were measured: central venous pressure (CVP), pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), cardiac output (CO) and index, systemic vascular resistance (SVR), blood pressure, heart rate, serum creatinine, and urine output (UOP). Duration of the nesiritide therapy was determined by the treating physician based on the patients' clinical response, but was uniformly greater than 24 hours. The mean time of drug infusion was 64.8 hours (±15 hours).

Ethical conduct was observed throughout all stages of patient care, data interpretation, and reporting of significant results. Internal review board approval was obtained for the reporting of data in these post transplant patients (on file). All patients in this study

Table 2. Pharmacologic Management

	1 h Before Nesiritide	24 h of Treatment	On Discontinuation (mean 75.4 h)
Patient 1	Dobutamine 6 mcg·kg·min Dopamine 5 mcg·kg·min	Dobutamine 3 mcg·kg·min Dopamine 3 mcg·kg·min	None
Patient 2	Nitroglycerin 10 mcg/min Dobutamine 5 mcg·kg·min Fenoldopam 0.05 mcg·kg·min Furosemide 120 mg IV q8h Metolazone 10 mg po q8h	Nitroglycerin 5 mcg/min	None
Patient 3	Dobutamine 3 mcg·kg·min Nitroglycerin 10 mcg/min Lasix 40 mg IV q12h	Dobutamine 1 mcg·kg·min	Milrinone 0.20 mcg·kg·min
Patient 4	Dopamine 5 mcg·kg·min Lasix 200 mg IV q8h Metolazone 10 mg po q8h Chlorothiazide 500 mg IV q8h × 2 doses	Dopamine 3 mcg·kg·min	Dobutamine 1 mcg·kg·min
Patient 5	Norepinephrine 3 mcg·kg·min Epinephrine 0.03 mcg·kg·min Dopamine 5 mcg·kg·min Nitroglycerin 100 mcg/min Lasix IV drip at 20 mg/h	Nitroglycerin 10 mcg/min Dopamine 3 mcg·kg·min	Dopamine 5 mcg·kg·min
Patient 6	Vasopressin 0.01-0.1 U/min Epinephrine 0.03 mcg·kg·min Milrinone 0.375 mcg·kg·min Dopamine 10 mcg·kg·min Lasix 60 mg IV q 8h	Dopamine 5 mcg·kg·min Milrinone 0.20 mcg·kg·min Lasix 40 mg IV q12h	Dopamine 3 mcg·kg·min Lasix 40 mg IV q12h
Patient 7	Dopamine 3 mcg·kg·min Nitroglycerin 20 mcg/min Lasix 80 mg IV q 12 h	Dopamine 2 mcg·kg·min Lasix 80 mg IV q12h	Lasix 80 mg IV q12h
Patient 8	Epinephrine 0.02 mcg·kg·min Nitroglycerin 10 mcg/min Dopamine 5 mcg·kg·min Lasix 80 mg IV q12h	Dobutamine 3 mcg·kg·min Dopamine 3 mcg·kg·min	Dobutamine 2 mcg·kg·min
Patient 9	Dopamine 5 mcg·kg·min Dobutamine 3 mcg·kg·min Nitroglycerin 15 mcg/min Lasix 80 mg IV q12h	Dopamine 3 mcg·kg·min Nitroglycerin 10 mcg/min Lasix 80 mg IV q12h	Dobutamine 2 mcg·kg·min Nitroglycerin 10 mcg/min
Patient 10	Epinephrine 0.02 mcg·kg·min Norepinephrine 5 mcg·kg·min Dopamine 10 mcg·kg·min Milrinone 0.375 mcg·kg·min Lasix 40 mg IV q12h	Dopamine 5 mcg·kg·min Milrinone 0.375 mcg·kg·min Lasix 40 mg IV q12h	Dopamine 3 mcg·kg·min Milrinone 0.20 mcg·kg·min

received care in accordance with standards, which met or exceeded institutional, International Society of Heart and Lung Transplant, and American Heart Association guidelines for posttransplant care. Throughout the study, the acting physician had the option of discontinuing therapy with nesiritide for any reasons of medical prudence. Statistical significance was determined using a Student's *t*-test (2-tailed distribution, homoscedastic) with $P < .05$ considered statistically significant. Differences were assessed as a change in hemodynamics before and after drug therapy, as each patient served as its own control.

All patients received standard triple therapy immunosuppression with steroids, mycophenolate mofetil, and a calcineurin inhibitor in the form of cyclosporine or tacrolimus. Cytolytic induction in the form of Thymoglobulin was used in only 1 patient.

Results

Use of Nesiritide ($_h$BNP); Effect on Hemodynamics

To determine the hemodynamic and neurohumoral effect of nesiritide on a recently transplanted heart, we selected a group of posttransplanted patients who had elevated filling pressures and significant renal insufficiency 48 hours after implantation. Initial studies were designed to determine if nesiritide would be physiologically active in an explanted (and then reimplanted) heart. Hemodynamic data before and after nesiritide therapy is summarized in Table 3. An initial bolus followed by a continuous infusion of nesiritide revealed a significant decrease of right-sided filling pressures (Fig. 1, $P < .001$). CVP and mean pulmonary artery pressure was lowered, whereas there was no significant change in either mean arterial blood pressure or transpulmonary gradient.

Indirect left-sided hemodynamics were measured using PCWP and SVR. A significant reduction in the PCWP (Fig. 2, $P < .001$) was observed after initiating nesiritide. Although analysis did not reveal statistical significance, a strong trend in reduction of SVR was seen ($P = .07$). In addition, an increase in CO was observed (Fig. 3, $P < .001$) with the decrease in filling pressures. In a few patients (n = 4), we followed serum BNP levels immediately after surgery and 72 hours later. In this limited group, we saw BNP levels decrease by approximately 45% (568, 136, 396, 1220 to 250, 38, 150, and 856 mg/dL, respectively). Improvement in hemodynamics with the addition of nesiritide allowed for reduction in pharmacologic support (Table 2).

Table 3. Hemodynamics

	1 h Before BNP Initiation	12 Hours After Therapy Initiated	*P* Value
CVP (mm Hg)	21.1 +/− 1.61	8.7 +/− 0.88	<.001
MPAP (mm Hg)	30.7 +/− 1.22	17.9 +/− 1.06	<.001
PCWP (mm Hg)	25.2 +/− 0.62	12.8 +/− 0.2	<.001
CO (L/min)	4.44 +/− 0.29	5.96 +/− 0.28	<.001
MAP (mm Hg)	89.9 +/− 5.5	82 +/− 2.8	.21
SVR (dynes.s.m^2/cm^3)	1160 +/− 155.7	946 +/− 48.8	.07
Serum Cr (mg/dL)	2.82 +/− 0.52	2.31 +/− .45	.05

BNP, B-natriuretic peptide; CVP, central venous pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; MAP, mean arterial pressure; SVR, systemic vascular resistance; Cr, creatinine.

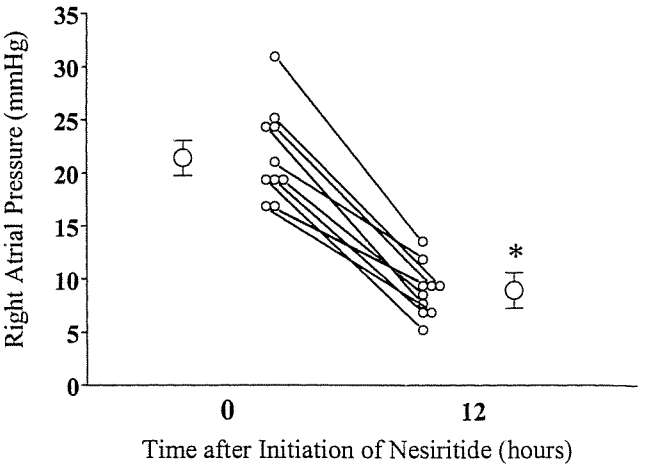

Fig. 1. Right atrial pressure before (time 0) and 12 hours after institution of nesiritide therapy. Individual data points for each patient and the mean ± SEM are shown. There was a significant decrease in right atrial pressure with use of nesiritide (*$P < .001$ vs. time 0).

Use of Nesiritide ($_h$BNP); Effect on Renal Function

To determine the effect of $_h$BNP on renal function, we examined 2 parameters easily followed after transplant (urinary output and serum creatinine). Those enrolled in this study did not receive induction agents (with 1 exception), and developed their acute renal insufficiency after transplantation. We subselected this unique group of patients to look for discrete changes in renal function over a brief period. Analysis revealed a 285% increase in UOP (1625 ± 318 to 4641 ± 692, $P < .001$) with the initiation of nesiritide in the first 24 hours (Fig. 4, $P < .001$). A similar diuresis persisted throughout nesiritide drug therapy to a lesser

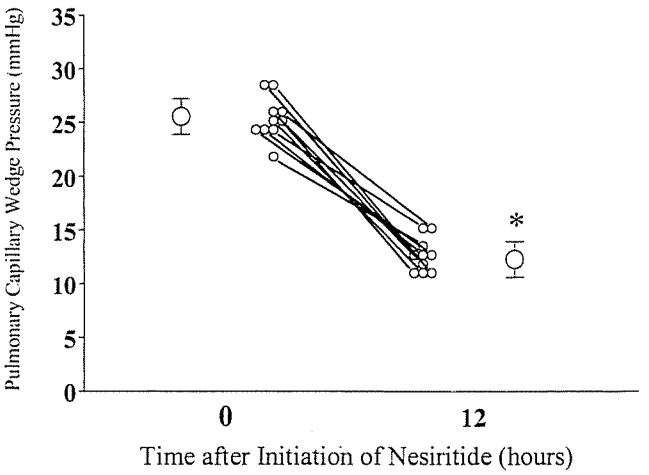

Fig. 2. Pulmonary capillary wedge pressure before (time 0) and 12 hours after institution of nesiritide therapy. Individual data points for each patient and the mean ± SEM are shown. There was a significant decrease in pulmonary capillary wedge pressure with use of nesiritide (*$P < .001$ vs. time 0).

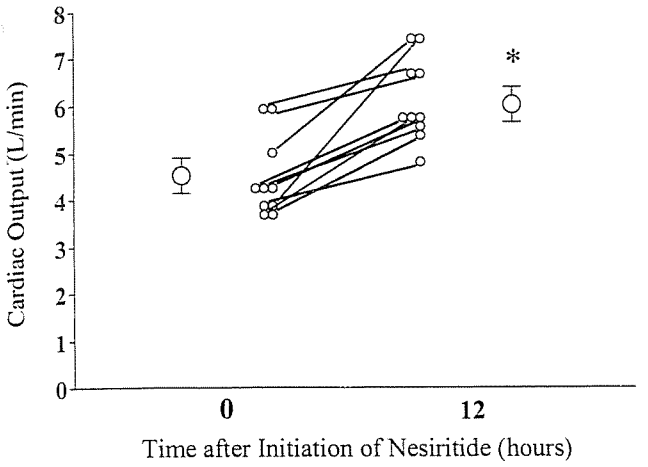

Fig. 3. Cardiac output before (time 0) and 12 hours after institution of nesiritide therapy. Individual data points for each patient and the mean ± SEM are shown. There was a significant increase in cardiac output with use of nesiritide (*$P < .001$ vs. time 0).

degree. In addition, loop diuretics did not have to be increased at any time during the study in our patient population. Additional analysis revealed a similar decrease in serum creatinine ($P < .05$) with increased UOP and an attenuation in cardiac filling pressures.

Discussion

After heart transplantation, there is an increase in both endogenous (patient-produced) and exogenous (iatrogenic administration) catecholamines. This increase in catecholamines increases levels of endothelin, angiotensin II, and other humoral regulators. The upregulation of these counterregulatory mechanisms antagonizes the receptor activation

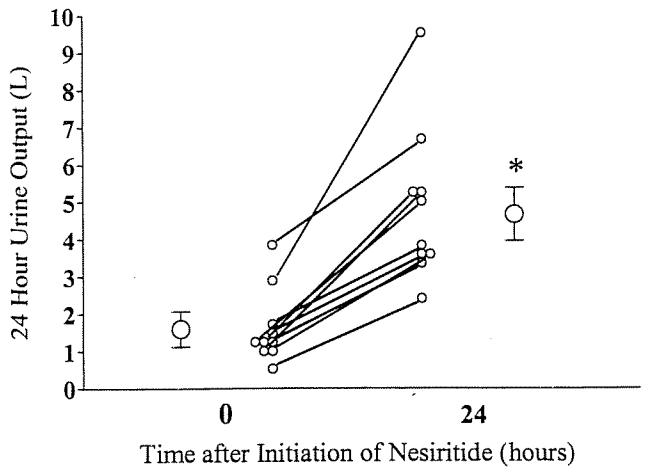

Fig. 4. Urine output over 24 hours before (time 0) and 24 hours after institution of nesiritide therapy. Individual data points for each patient and the mean ± SEM are shown. There was a significant increase in urine output with use of nesiritide (*$P < .001$ vs. time 0).

and associated signaling physiology of the guanylyl cyclase A receptor (endogenous receptor for $_h$BNP).[2,3] This reduction in guanylyl cyclase A receptor (GCA receptor) activity is more than just a theoretical concern. Newly transplanted hearts often develop significant myocardial edema and decreased myocardial compliance secondary to ischemic injury and surgical manipulation. These patients subsequently require large amounts of colloid and crystalloid in the perioperative period to maintain hemodynamics. In addition, immunosuppressive agents are initiated in the perioperative period, which cause intense renal vasoconstriction and reduction in glomerular filtration rate (GFR).[4] Taken together, these factors often produce a scenario of refractory volume overload, elevated cardiac filling pressures, and relative oliguria. In fact, 19% of first-year deaths (after transplant) are directly related to volume overload complications.[5]

$_h$BNP and Posttransplant Heart Failure

In both animal and human studies of acute decompensated heart failure, BNP has been demonstrated to alter hemodynamics.[6] The current data suggest that increasing doses of nesiritide decreased PCWP (and CVP, mean pulmonary artery pressure, and so on) in a dose-dependent manner (maximum study dose used was 0.025 mcg·kg·min).[4,7,8] These findings are further supported by studies that demonstrate that patients with acute heart failure have a subjective improvement in symptoms (dyspnea, fatigue, and global functional status) with nesiritide as quickly as 1 hour after administration, and show no signs of tolerance up to 7 days of continued therapy. This study demonstrates that the newly implanted heart continues to respond to $_h$BNP. Perhaps the transplanted heart does not have the ability to adequately increase endogenous levels of BNP to therapeutic levels to counteract the activated neurohumoral system of the recipient. This may be overcome by the administration of exogenous BNP to decrease symptoms of volume overload.[4,9] This theory is supported by previous studies in animals and heart failure patients that had acute decompensated heart failure.[2,3,8] Although nesiritide has been demonstrated to be efficacious in acute volume overload states compared with conventional medical therapy (eg, nitroglycerin), this study is one of the first to look at hemodynamics of recently transplanted hearts. As in previous studies, attenuation of right heart and PCWP was observed in patients with volume overload.[3,8,10] The decrease in cardiac filling pressures in the current study was accompanied by an increase in CO. One possible explanation for this phenomenon may be attributed to an alteration of ventricular loading conditions and a decrement in SVR.

$_h$BNP and Posttransplant Renal Insufficiency

Guanylyl cyclase activity in the glomerulus is decreased in patients who receive calcineurin inhibitors. With initiation of calcineurin inhibitors, there is a reduction of GCA receptors or a direct antagonism of the receptor.[4] In addition, elevation in renin and endothelin levels exacerbates the decline in renal tubular function and GFR in these patients.[9]

These data demonstrate that short-term administration of $_h$BNP has a favorable effect on renal function (decreasing creatinine and increased urinary output) in patients after heart transplantation. The supplementation of endogenous BNP may in part be responsible for the renoprotective effect observed in this small group of patients. Previous studies have shown that $_h$BNP increased urine volume, excretion of sodium, and GFR in the kidney.[3,8,10] The data in this study support these previous findings. An upregulation of renal cGMP levels (via $_h$BNP) may exert a renoprotective effect in these posttransplant patients who are exposed to numerous nephrotoxic agents and potentially facilitate recovery of normal renal function.

Study Limitations

This study is limited by it being a nonrandomized, observational study on a small but unique set of patients. Further, larger scale, prospective randomized trials in postsurgical patients would be warranted to confirm these findings.

Conclusion

$_h$BNP is both safe and effective in treating acute decompensated heart failure immediately after cardiac transplantation. This agent may offer an improved therapeutic strategy for treating acute decompensated heart failure in this unique patient population by providing reduction of cardiac filling pressures. These decreased pulmonary pressures, an increased CO, improved renal capacity, and an increase in systemic perfusion may lead to increased GFR and diuresis with lower doses of loop diuretics. Further, nesiritide may be helpful in weaning inotropes and facilitating normalization of patients' hemodynamics. These investigators advocate that early implementation of nesiritide may lower health care cost and be safer than traditional inotropes in posttransplant patients. As suggested in previous studies, this may decrease 6-month mortality.[7–10]

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