CARDIOVASCULAR

High-Risk Mitral Valve Surgery: Perioperative Hemodynamic Optimization with Nesiritide (BNP)

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Background. **Nesiritide is a recombinant brain-type natriuretic peptide (BNP), which decreases pulmonary arterial (PA) pressures and myocardial oxygen consumption while increasing coronary flow and urine output. Mitral valve (MV) surgery in patients with severe mitral regurgitation (MR), impaired left ventricular function, and pulmonary hypertension is associated with a high operative mortality. We hypothesized that the perioperative use of Nesiritide is safe, and may improve surgical outcomes.**

Methods. **From May 2003 to August 2004, 14 patients (11 male, 3 female; mean age, 64 years [23–87 years]; mean systolic PA, 63 mm Hg [48–94 mm Hg]; mean ejection fraction, 36% [10–50%]), undergoing MV surgery (10 repairs, 2 replacements, and 2 rereplacements) for severe MR, were treated for a median of 24 hours (13–55 hours) preoperatively with intravenous Nesiritide. Expected mortality by EuroSCORE was 26% (7.8–59%) (5 reoperations). Concomitant procedures included tricuspid valve repair (n = 7), coronary artery bypass grafting (n = 5), and left atrial maze procedure (n = 3). Eleven patients received Nesiritide postoperatively during a mean duration of 22 hours (2–80 hours).**

Results. **Operative mortality was 0%. Prior to surgery after BNP treatment, mean systolic PA pressure dropped to 39 mm Hg ($p = 0.0003$), pulmonary capillary wedge pressure to 15 mm Hg ($p = 0.001$), central venous pressure to 6 mm Hg ($p = 0.002$), and weight by 3.7 kg ($p = 0.006$). Postoperative median ventilation time was 14 hours (4–48 hours). All other major hemodynamic parameters (systemic blood pressure, heart rate, and cardiac output) remained constant. The treatment was well-tolerated in all patients.**

Conclusions. **Perioperative use of Nesiritide is safe, and may contribute to improved early outcomes in high-risk patients undergoing MV surgery. This may be due to improved ventricular loading conditions (decreased PA pressures, more effective diuresis) and/or a direct myocardial effect of BNP. Further prospective evaluation of the role of BNP in cardiac surgery is warranted.**

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Endogenous B-type natriuretic peptide (BNP) was first discovered in pig brains in 1988 [1]. It has since become a sensitive marker for heart failure [2]. A 32-peptide amino acid, BNP is released by the cardiomyocytes after distension of the ventricles, as seen during volume overload in heart failure. The mechanisms are the same as for atrial natriuretic peptide (ANP) [1]. Endogenous BNP has several different mechanisms; it is a potent vasodilator and reduces pulmonary arterial (PA) pressures [3], leading to reduced pulmonary and systemic vascular resistance. It increases the glomerular filtration rate and stimulates urine output, especially the natriuretic component. It also decreases myocardial oxygen consumption through a still unknown mechanism, while increasing coronary blood flow [3–5].

The increased mortality risk associated with mitral valve surgery in the context of pulmonary hypertension has long been recognized [6, 7]. The euroSCORE group estimates that pulmonary hypertension increases the risk of perioperative mortality twofold [8]. The mechanisms are not completely understood but relate in part to increased right ventricular work, increased pulmonary vascular resistance, reduced pulmonary blood flow with consequent reduction in left ventricular filling, poorer oxygenation, and pulmonary endothelial dysfunction [9]. Most of the previous work directed at reducing the mortality risk of pulmonary hypertension has been focused on postoperative management with pulmonary vasodilators. The limited use or preoperative interventions may in part be because potent pulmonary vasodilators have either been inhalational (nitric oxide and prostacyclin) or cause considerable systemic hypotension (phosphodiesterase inhibitors), making them impractical for use in the ambulatory patient before cardiac surgery.

Recombinant BNP (Natrecor, Nesiritide, Scios Inc, Sunnyvale, CA) initially made its way into daily clinical practice for the treatment of congestive heart failure [10–14]. More recently, BNP has also been used in postoperative cardiac surgical care as an adjunct in the management of low cardiac output and pulmonary hypertension [11, 15, 16]; however, these have been small

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Table 1. Hemodynamic Measurements Before and After Infusion of BNP[a]

	Baseline BNP	Entry to OR	Before ICU discharge
Mean arterial pressure (mm Hg)	88 (84–92)	81 (76–85)	79 (76–82)
Cardiac index (L/m^2/min)	2.1 (1.9–2.3)	1.9 (1.7–2.2)	2.5 (2.3–2.7)
PA systolic (mm Hg)	63 (58–66)	38 (34–42)	44 (41–47)
PCWP (mm Hg)	30 (27–32)	15 (12–17)	16 (14–18)
CVP (mm Hg)	13 (11–15)	6 (5–8)	8 (7–9)
Heart rate (bpm)	86 (82–89)	81 (78–85)	83 (80–85)

[a] Values are means with 70% confidence interval (parentheses).

BNP = brain-type natriuretic peptide (Nesiritide); bpm = beats per minute; CVP = central venous pressure; ICU = intensive care unit; OR = operating room; PA = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure.

series with limited patient numbers. Encouraged by our initial experience with the use of this drug in the postoperative setting (unpublished data), we sought to explore whether this drug could also be usefully applied to preoperative hemodynamic optimization and postoperative use in high-risk mitral valve patients with pulmonary hypertension.

Patients and Methods

We conducted a prospective noncontrolled study of patients undergoing high-risk mitral valve surgery at the Mount Sinai Medical Center from May 2003 to August 2004. This research was done in accordance with the Institutional Review Board. Inclusion criteria for this study were severe mitral regurgitation (grade MR >3), impaired left ventricular function (EF < 50%), and pulmonary hypertension measured by cardiac catheterization (PA systolic > 45 mm Hg).

Drug Administration Protocol

Patients were admitted to the cardiac surgery intensive care unit (ICU) a day prior to surgery. A pulmonary artery catheter was placed and if pulmonary hypertension was confirmed the patients proceeded with the study. At this point all baseline values were recorded (Table 1).

After a loading dose of 2 mcg/kg, BNP was started at 0.01 mcg/kg/min intravenous on a continuous infusion as described per drug label. Continuous hemodynamic monitoring was maintained during the infusion period and arterial, central venous, and pulmonary artery pressures, and urine was collected every hour. If a hemodynamic response was not achieved after 3 hours, the infusion rate was increased at increments of 0.005 mcg/kg/min to a maximum of 0.03 mcg/kg/min until a significant decrease in PA pressures was achieved. The infusion was discontinued if persistent systemic hypotension occurred, or no decrease in PA pressures was seen after dose increase. Otherwise infusion was continued until hemodynamic response was obtained. No other drug was administered during the preoperative study period.

A decrease of 25% or more of systolic PA pressures was set an arbitrary preoperative goal, and was considered a sufficient therapeutic effect which in turn led to the decision to take the patients to the operating room for their surgical procedure. In patients in whom the response was minimal, we assumed that no further hemodynamic response would be obtained after 48 hours of maximal dosage and proceeded with surgery. The drug was discontinued immediately prior to taking these patients to the OR. Postoperatively BNP was administered upon arrival in the ICU at 0.01 mcg/kg/min intravenous on a continuous infusion, identical to the preoperative rate in 11 patients. No patients received any BNP during surgery while on cardiopulmonary bypass.

Patient Population

Fourteen patients were included (11 male, 3 female). The median age was 71 years (range, 23 to 87 years). All patients had severe mitral regurgitation, mechanism of MR according to Carpentier's functional classification was type I (n = 1), type II (n = 3), type IIIa (2), and type IIIb (n = 8). Etiology of MR was degenerative (n = 4), dilated cardiomyopathy (n = 3), rheumatic (n = 3), ischemic (3), and endocarditis (n = 1). The mean ejection

Table 2. Patient Demographics

N	14
Gender	11M/3F
Median age (years)	71 (R:23–87)
Heart rhythm:	
Sinus	11
Atrial fibrillation	3
MR etiology:	
Degenerative	4
Rheumatic	3
Ischemic CMP	3
Dilated CMP	3
Endocarditis	1
NYHA IV	11
Ejection fraction (%)	37 (10–50)
Reoperation	5
Predicted mortality (%) (EuroSCORE)	26 (R: 7–59)

CMP = cardiomyopathy; MR = mitral regurgitation; NYHA = New York Heart Association.

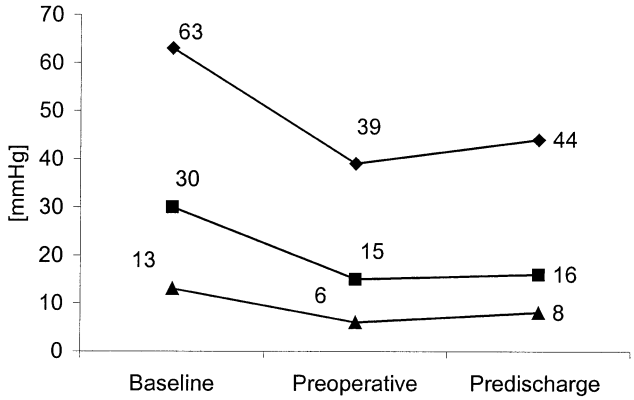

Fig 1. Changes in pulmonary artery pressures and central venous pressure during treatment with brain-type natriuretic peptide (n = 14). ♦ = pulmonary arterial; ■ = pulmonary capillary wedge pressures; ▲ = central venous pressure.

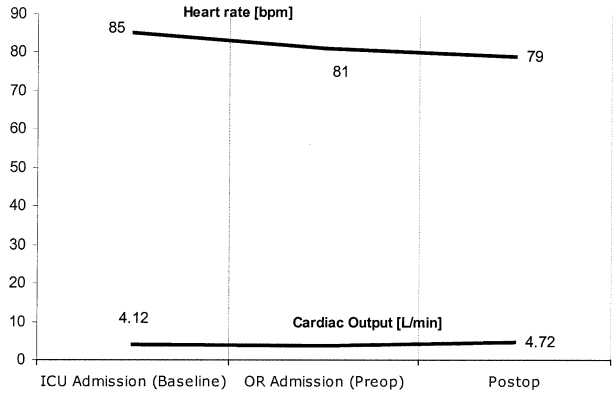

Fig 2. Hemodynamic recordings, heart rate, and cardiac output. (bpm = *beats per minute;* ICU = *intensive care unit;* OR = *operating room.)*

fraction (EF) was 36% (range, 10 to 50%). Five patients (36%) had undergone prior cardiac surgery. Table 2 summarizes patient demographics. Preoperative calculation of the expected mortality in this cohort by logistic EuroSCORE was 26% (R: 7–59).

Surgical Techniques

After a median sternotomy, cardiopulmonary bypass was instituted between the ascending aorta and superior and inferior vena cava with moderate hypothermia. Myocardial protection was achieved with antegrade, or combined antegrade and retrograde cold blood high potassium cardioplegia. Ten patients underwent mitral valve repair with a remodeling annuloplasty (mean prosthetic ring size, 28 mm), and in three patients leaflet resections (quadrangular posterior [n = 3] and triangular anterior [n = 1]) and chordal transfers were done. In 4 patients chordal sparing mitral valve replacement was performed (2 rereplacements). Concomitant procedures were tricuspid valve repairs in 8, coronary artery bypass grafting (CABG) in 4, left atrial cryoablation maze procedure in 3, and aortic valve replacement in one patient.

Endpoints

Pulmonary arterial pressures, pulmonary wedge pressure, central venous pressure, arterial pressure, and heart rate were measured every 6 hours (Table 1). Body weight was measured on the same scale every morning. Primary study endpoints were changes in PA pressures and level of diuresis prior to surgery. Secondary endpoints were operative mortality and postoperative morbidity.

Statistical Analysis

Hemodynamic data are presented as means with 70% confidence intervals. Group means were compared using the paired t test. The p value was considered significant when it was less than 0.05.

Results

BNP Infusion

The median duration of therapy before surgery was 24 hours (range, 13 to 55 hours). Long duration of therapy (> 24 hours) was necessary in 5 patients to effectively decrease the PA pressure (> 25% decrease) and body weight. After surgery 11 patients received BNP for a median duration of 22 hours (range, 2 to 80 hours).

The pulmonary artery catheterization and intravenous BNP therapy was well-tolerated in 11 patients, no patients suffered from hypotension or arrhythmias and there were no complications related to the pulmonary artery catheterization. Discontinuation or dose decrease due to hypotension, or low cardiac output was not necessary in any patient and the mean arterial pressure prior to surgery was not significantly reduced by the BNP infusion (Table 1).

No adverse effects were observed. No changes in the anesthetic management, surgical procedure, and intraoperative course could be attributed to the preoperative BNP therapy; this is, however, a subjective observation as this series was not controlled.

Hemodynamic Response to BNP Infusion

Hemodynamic data before and after BNP infusion, and also immediately after surgery, are shown in Table 1. A significant decrease of pulmonary artery pressures was observed after a very short duration of therapy in all patients (< 3 hours). The mean systolic PA pressures dropped from 63 to 39 mm Hg ($p = 0.0003$). Pulmonary capillary wedge pressure decreased from a mean of 30 to 15 mm Hg ($p = 0.001$), and central venous pressure from 13 to 6 mm Hg ($p = 0.002$) (Fig 1). There was no change in cardiac output and mean aortic pressures (Fig 2). Diuresis increased in 11 patients and mean body weight decreased by 3.7 kg ($p = 0.006$). Postoperatively all patients received BNP upon arrival in the ICU.

Surgical Outcomes

After surgery, median time on the ventilator was 14 hours (range, from 4 to 48 hours). All patients required minimal

inotropic (epinephrine < 50 ng/kg/min, or milrinone < 0.375 mcg/kg/min) support in the immediate postoperative period and all but one patient had a stable postoperative course. This was a 68-year-old patient who underwent multivalve and concomitant CABG procedure, with a postoperative low output who required an intraaortic balloon pump and moderate inotropic support (epinephrine > 50 ng/kg/min, and milrinone > 0.375 mcg/kg/min). The intraaortic balloon pump was successfully weaned after 4 days; the patient did not exhibit any signs of perioperative myocardial infarction. No strokes, deep sternal infections, renal failure requiring hemofiltration, or major bleeding problems were observed. There were no in-hospital deaths. All patients were discharged home. No patients required postoperative use of inhaled nitric oxide.

Comment

In this small series of 14 patients we have demonstrated the feasibility of using BNP for preoperative optimization of high-risk patients undergoing mitral valve surgery. We have also shown that this agent successfully lowers the pulmonary artery pressures in this setting. Our data showed reduction in pulmonary pressures in the majority of patients. We have also shown excellent clinical outcomes in a high-risk group of patients above that which we would normally expect (no mortality observed against EuroSCORE predicted mortality of 26%). Furthermore these early results suggest that the use of BNP is safe in the postoperative setting. It appears that BNP may have played a role in achieving these favorable clinical outcomes, and we expect this will be further confirmed in future studies.

Pathophysiologically there are several plausible explanations for a clinical benefit from BNP in these patients. The potent vasodilator effect of BNP through the decrease of pulmonary pressures leads to improved left ventricular loading conditions. Improved ventricular loading conditions as seen in this patient group may be partly the cause of increased myocardial efficiency. Additionally, by decreasing right and left ventricular afterload through decreased PA pressures and increased diuresis, the vicious circle as seen in congestive heart failure can be broken. As seen in Figure 1, the slope under the curves, ie the rate of decrease, is much bigger for the pulmonary artery pressures than for the central venous pressures. This leads to the conclusion that the primary effect observed in this patient population is more due to the vasodilator effect than to the diuretic effect.

Perioperative RV failure is a leading cause of postoperative death in pulmonary hypertensive patients and we believe that the BNP infusion makes the right ventricle more able to cope with the inevitable insult from ischemic myocardial arrest. The BNP also improves coronary perfusion and may therefore have a potential myocardial protective effect although the significance of this effect in this setting is unclear and warrants further investigation.

Our study is limited by the small study size and the lack of a control group. We did not use a control group as our study was primarily designed to look at the feasibility, safety, and hemodynamic effectiveness of perioperative BNP infusion. We are unable to make definitive statements on benefits and harms of therapy, as we do not have comparative data from a control arm. While a randomized study would be ideal, the practicalities (small patient group, ethical considerations, and strong physician bias) are such that one may never be performed. Supporting data from the literature are also sparse because preoperative hemodynamic optimization in cardiac surgery has not previously been widely applied nor studied. There is, however, a large body of evidence from noncardiac patients showing that preoperative hemodynamic optimization does improve outcomes in high-risk surgery, and we anticipate that the same will be shown in cardiac surgery [17].

We believe that hemodynamic optimization plays an important role in high-risk mitral valve surgery. Encouraged by the above reported findings, we now use BNP for preoperative hemodynamic optimization as the standard of care in high-risk patients for mitral valve surgery with documented pulmonary hypertension. Our protocol is admission to the regular ward and peripheral venous administration of BNP at the same dosage as mentioned above. An additional 13 patients have so far been treated in this fashion with excellent outcomes (unpublished data).

Further prospective evaluation of the role of BNP in several areas of cardiac surgery is under way and should yield interesting results and open the door to novel therapeutic strategies. Obviously data from further studies are required to confirm our impressions and identify the optimal treatment regimen, but as BNP was easy to use, with no major adverse effects or toxicity to the patient, we believe that the probability of significant benefit in a very high-risk group justifies its use in this setting. Indeed, BNP does not need to be administered in an intensive care environment as pulmonary artery pressure monitoring is not mandatory. The majority of patients respond to the standard 0.01 mcg/kg/min, which may be administered through a peripheral vein without need for invasive monitoring. We have shown that preoperative administration of BNP is a feasible technique with possible benefit and no clear deleterious effects. We recommend its consideration by surgeons faced with the high-risk pulmonary hypertensive patient requiring mitral valve surgery.

References

1. Sudoh T, Kangawa K, Minamino N, Matsuo H. A new natriuretic peptide in porcine brain. Nature 1988;332:78–81.
2. Rodeheffer RJ. Measuring plasma B-type natriuretic peptide in heart failure: good to go in 2004? J Am Coll Cardiol 2004;44:740–9.
3. Bobadilla RV, Oppelt TF, Hirshy TC. Nesiritide treatment of noncardiogenic pulmonary edema. Ann Pharmacother 2003; 37:530–3.
4. Michaels AD, Klein A, Madden JA, Chatterjee K. Effects of intravenous nesiritide on human coronary vasomotor regu-

lation and myocardial oxygen uptake. Circulation 2003; 107:2697–701.
5. Rayburn BK, Bourge RC. Nesiritide: a unique therapeutic cardiac peptide. Rev Cardiovasc Med 2001;2(suppl 2):S25–31.
6. Bolling SF. Mitral reconstruction in cardiomyopathy. J Heart Valve Dis 2002;11(suppl 1):S26–31.
7. Bishay ES, McCarthy PM, Cosgrove DM, et al. Mitral valve surgery in patients with severe left ventricular dysfunction. Eur J Cardiothorac Surg 2000;17:213–21.
8. Roques F, Nashef SA, Michel P, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 1999;15:816–22; discussion 822-3.
9. Riedel B. The pathophysiology and management of perioperative pulmonary hypertension with specific emphasis on the period following cardiac surgery. Int Anesthesiol Clin 1999;37: 55–79.
10. Smith AL, Brown CS. New advances and novel treatments in heart failure. Crit Care Nurse 2003;23(suppl):11–8.
11. Moazami N, Damiano RJ, Bailey MS, et al. Nesiritide (BNP) in the management of postoperative cardiac patients. Ann Thorac Surg 2003;75:1974–6.
12. Mills RM, Hobbs RE, Young JB. "BNP" for heart failure: role of nesiritide in cardiovascular therapeutics. Congest Heart Fail 2002;8:270–3.
13. Maisel AS. Nesiritide: a new therapy for the treatment of heart failure. Cardiovasc Toxicol 2003;3:37–42.
14. Colbert K, Greene MH. Nesiritide (Natrecor): a new treatment for acutely decompensated congestive heart failure. Crit Care Nurs Q 2003;26:40–4.
15. Entwistle JW, McLoughlin DE, Baghelai K. Postoperative Nesiritide use following high-risk mitral valve replacement. Heart Surg Forum 2004;7:E189–90.
16. Simsic JM, Reddy VS, Kanter KR, Kirshbom PM, Forbess JM. Use of Nesiritide (human B-type natriuretic peptide) in infants following cardiac surgery. Pediatr Cardiol 2004.
17. Davies SJ, Wilson RJ. Preoperative optimization of the high-risk surgical patient. Br J Anaesth 2004;93:121–8.

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Southern Thoracic Surgical Association: Fifty-Second Annual Meeting

The Fifty-Second Annual Meeting of the Southern Thoracic Surgical Association (STSA) will be held November 10–12, 2005, in Orlando, Florida.

The Postgraduate Course will be held the morning of Thursday, November 10, 2005, and will provide in-depth coverage of cardiothoracic surgical topics selected primarily as a means to enhance and broaden the knowledge of practicing thoracic and cardiac surgeons.

Manuscripts accepted for the Resident Competition must be submitted to the STSA headquarters office no later than September 16, 2005. The Resident Award will be based on abstract, presentation, and manuscript.

Applications for membership should be completed by September 15, 2005, and forwarded to Richard L. Prager, MD, Membership Committee Chairman, Southern Thoracic Surgical Association, 633 N Saint Clair St, Suite 2320, Chicago, IL 60611-3658.

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