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Natriuretic Peptides in the Perioperative Management of Cardiac Surgery Patients

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ABSTRACT

Both heart failure (HF) and cardiac surgery with cardiopulmonary bypass result in a release of neurohormones, with a variety of physiologic effects. Administration of exogenous B-type natriuretic peptide (BNP) has beneficial hemodynamic effects and reduces the level of several neurohormones in HF patients. BNP is currently being investigated in the perioperative management of cardiac surgery patients and may be especially beneficial for patients with ventricular dysfunction, pulmonary hypertension, or renal dysfunction. Using a neurohormonal approach to supportive therapy may enhance future strategies for patients undergoing cardiac surgery, especially those at greatest risk for complications.

INTRODUCTION

The number of hospitalizations related to heart failure (HF) in the United States continues to increase. Between 1979 and 2002, the number of hospital discharges due to HF rose by 157%, from 377,000 to 970,000 [American Heart Association 2005]. Currently, almost 5 million adults in the US have been diagnosed with HF, with approximately 550,000 new diagnoses made each year [American Heart Association 2005, Hunt 2001]. Because most patients affected by HF are over the age of 65 years, HF is the most common Medicare diagnosis-related group and is the source of more Medicare resource expenditures than any other disease [Hunt 2001].

This increasing population of HF patients has led to more patients with various degrees of ventricular dysfunction undergoing cardiac surgery. Consequently, new therapeutic strategies that minimize complications and improve outcomes in these patients are desirable. This article briefly describes the pathophysiology of chronic HF, compares the neurohormonal activation that occurs during HF with that which occurs during cardiopulmonary bypass (CPB), and discusses the potential use of natriuretic peptide administration as a perioperative supportive therapy in cardiac surgical patients.

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THE PHYSIOLOGIC RESPONSE TO HF

Systolic ventricular dysfunction is a well-known trigger for the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS). The physiologic manifestations of neurohormonal activation include peripheral vasoconstriction, an increase in the baseline heart rate, and fluid and sodium retention [Eichhorn 1996]. Although these changes initially result in hemodynamic stabilization and maintenance of systemic perfusion, chronic neurohormonal activation eventually leads to decreased cardiac output and fluid and salt retention.

Renal dysfunction is also a paramount feature of HF owing to decreased renal perfusion and a reduced glomerular filtration rate (GFR) [Brewster 2003, Volpe 2002]. Diuretic resistance, a hallmark of end-stage HF, is a significant complication that leads to increased morbidity and the need for additional monitoring and treatment [Krämer 1999]. In this setting, diuretic therapy with furosemide or other loop diuretics is associated with further decline in the GFR and can adversely affect renal function.

NATRIURETIC PEPTIDES

The natriuretic peptide system consists of 4 endogenous hormones (atrial natriuretic peptide [ANP], brain or B-type natriuretic peptide [BNP], C-type natriuretic peptide, and D-type natriuretic peptide) that regulate vascular and renal homeostasis [Abraham 1998, Hobbs 2003]. Of these, BNP, a 32-amino acid peptide chain originally isolated from porcine brain tissue, is a counter-regulatory hormone produced by the ventricles in response to pressure or volume overload [Hobbs 2003, Mills 2002]. Plasma BNP levels are negligible (<100 pg/mL) in healthy adults [Hobbs 2003], but ventricular overload induces cardiac myocytes to undergo rapid transcription and secrete this hormone, increasing these levels several fold [Boerrigter 2004, Nakagawa 1995, Yasue 1994]. In fact, plasma BNP levels of 1000 pg/mL are not uncommon in patients presenting to the emergency department with dyspnea resulting from HF [Hobbs 2003]. Plasma BNP levels reflect the ventricular secretion rate and are proportional to the severity of left ventricular dysfunction and increased wall tension [Yasue 1994].

Once produced and secreted, BNP binds to the natriuretic peptide-A receptor on endothelium and vascular smooth muscle cells [Boerrigter 2004]. This binding causes activation

of guanylate cyclase, with a subsequent increase in the intracellular second messenger, cyclic guanosine monophosphate (cGMP) [Boerrigter 2004]. This increase in cGMP activates a cGMP-dependent protein kinase, which then produces dephosphorylation of myosin light chains, ultimately leading to cellular relaxation [Murad 1986]. BNP is eventually cleared from the circulatory system via 3 mechanisms: binding to the natriuretic peptide-clearance receptor, enzymatic degradation by neutral endopeptidase-24.11, and glomerular filtration [Boerrigter 2004].

Animal data demonstrate that BNP plays several important physiologic roles, including balanced vasodilation, natriuresis and diuresis, neurohormonal blockade, lusitropy, and inhibition of cardiac remodeling [Mills 2002, Yoshimura 2001]. In isolated rat arterial rings, BNP produced a concentration-dependent relaxation that was independent of endothelium and associated with a sustained increase in cGMP [Zhou 1989]. In rat adrenal medulla slices, BNP inhibited both spontaneous and evoked release of norepinephrine [Vatta 1997]. In normal dogs, administration of BNP reduced blood pressure, decreased sodium resorption in the proximal and distal tubules in the kidney, and increased GFR, renal blood flow, and urinary sodium excretion [Clavell 1993]. Moreover, in a dog model of low-output HF, the systemic vasoactive effects of BNP administration were even greater than those seen in normal dogs [Clavell 1993]. In addition, in both normal and HF dogs, intracoronary infusion of BNP had a positive lusitropic effect, without any evidence of inotropy [Yamamoto 1997]. Finally, in normal anesthetized dogs, administration of BNP decreased renin secretion by 91% and inhibited the tubuloglomerular feedback response to hypertonic saline [Akabane 1991].

Initial human data are consistent with these animal findings. BNP induced concentration-dependent relaxation of arterial and venous tissues were obtained from individuals who underwent various types of cardiac surgery and preconstriction with either endothelin-1 or phenylephrine [Protter 1996]. In an evaluation of 8 control patients and 7 patients with HF, BNP significantly decreased pulmonary capillary wedge pressure (PCWP) and systemic vascular resistance and increased stroke volume index, urine volume, and urinary sodium and chloride excretion [Yoshimura 1991]. Moreover, these increases in sodium and chloride excretion were significantly higher in the HF patients than in the control subjects. In a randomized, double-blind, placebo-controlled evaluation of 16 patients with decompensated HF, BNP reduced right atrial pressure by 30%, PCWP by 40%, and systemic vascular resistance by 36% [Abraham 1998]; as a result, cardiac output increased by 28% without a change in the heart rate. Finally, in a prospective evaluation of 10 patients referred for cardiac angiography, BNP increased the coronary artery diameter by 15% (P = .007), peak coronary artery velocity by 14% (P = .015), and coronary artery blood flow by 35% (P = .007), while simultaneously decreasing myocardial oxygen uptake by 8% (P = .043) [Michaels 2003].

Human studies have also confirmed the favorable neurohormonal properties of BNP. Administration of BNP has been shown to suppress the secretion of renin [Yasue 1996], norepinephrine [Abraham 1998, Brunner-La Rocca 2001], and endothelin-1 [Aronson 2002]. It decreases plasma aldosterone concentrations both in healthy control subjects and in patients with HF [Abraham 1998, Yoshimura 1991], and inhibits the synthesis of aldosterone in both the adrenal cortex and cardiac tissue, reducing myocardial fibrosis and remodeling [Yoshimura 2001].

BNP ADMINISTRATION IN THE MANAGEMENT OF HF

The Vasodilation in the Management of Acute Congestive HF (VMAC) trial was a multicenter, double-blind evaluation of 489 patients admitted for decompensated HF, 246 of whom had undergone pulmonary artery catheterization. Patients were randomly assigned to receive intravenous nesiritide (a recombinant analog of human BNP), intravenous nitroglycerin, or placebo for an initial 3-hour "placebo-controlled" period, followed by randomization to nesiritide or nitroglycerin for the remainder of the study. In addition to the study medication, which was continued for a minimum of 24 hours, all patients received standard therapy, consisting of intravenous or oral diuretics, dobutamine, and/or dopamine, as deemed appropriate by their clinician [Publication Committee for the VMAC Investigators 2002]. Primary outcome measures were the change in PCWP in the subset of patients who had undergone pulmonary artery catheterization and self-assessment of dyspnea in all patients. Reductions in PCWP were greater with nesiritide than with nitroglycerin or placebo throughout the placebo-controlled period. At 3 hours, the mean change from baseline in PCWP was –5.8 mm Hg for nesiritide, –3.8 mm Hg for nitroglycerin (P = .03 versus nesiritide), and –2.0 mm Hg for placebo (P < .001 versus nesiritide; P = .09 versus nitroglycerin) [Publication Committee for the VMAC Investigators 2002]. Furthermore, there was no attenuation of this effect over time. At 24 hours the mean change in PCWP was –8.2 mm Hg for nesiritide compared to –6.3 mm Hg for nitroglycerin (P = .04) [Publication Committee for the VMAC Investigators 2002]. In addition, nesiritide significantly reduced dyspnea at 3 hours compared to placebo (P = .03); there were no significant differences in dyspnea between nesiritide and nitroglycerin at either 3 or 24 hours [Publication Committee for the VMAC Investigators 2002]. Headache was the most common adverse event during the initial 24 hours and occurred significantly more frequently with nitroglycerin (20%) than with nesiritide (8%; P < .001). There were no significant differences between nesiritide and nitroglycerin in the frequency or severity of ischemia, hypotension, or arrhythmia [Publication Committee for the VMAC Investigators 2002].

The Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy (PRECEDENT) trial was a multicenter, open-label, active-control evaluation of 255 acute decompensated HF patients, randomly assigned to therapy with nesiritide or dobutamine [Burger 2002]. Patients were monitored with 24-hour Holter recordings immediately before and during therapy, with the primary study end points being the change from baseline in mean heart rate, premature ventricular beats, and repetitive beats [Burger 2002]. Baseline Holter recordings were not signifi-

Table 1. Clinical Studies of Nesiritide in Heart Failure*

Author or Study Name	Patient Population	Study Setting	Major Findings
Colucci et al [Colucci 2000]	ADHF patients (n = 127)	Inpatient	Improved hemodynamic function and clinical status with nesiritide Comparable safety to nitroglycerin, more rapid symptomatic relief Decreased need for diuretic support
VMAC [Publication Committee for the VMAC Investigators 2002]	ADHF patients with class III/IV HF (n = 489)	Inpatient	Nesiritide was not proarrhythmic Comparable safety and efficacy to nitroglycerin Improved hemodynamic stabilization and symptoms compared with nitroglycerin
PRECEDENT [Burger 2002]	ADHF patients (n = 255)	Inpatient	No proarrhythmic effect compared with dobutamine, which caused proarrhythmia Reduced ventricular ectopy Superior safety profile versus dobutamine
PROACTION [Peacock 2003]	ADHF patients (n = 255)	ED	Decreased hospital admissions Decreased length of hospital stay Reduced hospital re-admissions at 30 days Did not require invasive monitoring Cost savings offset the acquisition cost of nesiritide therapy
FUSION [Yancy 2004]	ADHF patients with class III/IV HF (n = 210)	Outpatient	Compared to usual care, serial infusions of nesiritide resulted in: Similar frequency of adverse events Similar improvements in quality of life Acute reductions in aldosterone and endothelin-1 concentrations

*ADHF indicates acute decompensated heart failure; VMAC, Vasodilation in the Management of Acute Congestive heart failure; HF, heart failure; PRECEDENT, Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy; PROACTION, Prospective Randomized Outcomes Study of Acutely Decompensated Congestive heart failure Treated Initially in Outpatients With Natrecor; ED, emergency department; FUSION, Follow-Up Serial Infusions of Nesiritide.

cantly different between treatment groups. During therapy, dobutamine significantly increased the mean heart rate (+5.1 beats/minute; $P < .001$), premature ventricular beats (+69/hour; $P = .006$), repetitive ventricular beats (+15/hour; $P = .001$), and ventricular tachycardia events per 24 hours (+48, $P = .001$) [Burger 2002]. In contrast, nesiritide either had no effect on or significantly decreased these end points. Both drugs were similarly effective with respect to improving signs and symptoms of HF [Burger 2002]. The most common adverse events were hypotension in the nesiritide group and ventricular arrhythmias in the dobutamine group [Burger 2002].

Table 1 provides a summary of the clinical studies of nesiritide in patients with acute decompensated HF, as well as the experience with nesiritide in the emergency department and outpatient settings [Burger 2002, Colucci 2000, Peacock 2003, Publication Committee for the VMAC Investigators 2002, Yancy 2004].

NEUROHORMONAL RESPONSE TO CPB

The neurohormonal activation that occurs during and after cardiac surgery, particularly with CPB, is similar to that which occurs in response to HF [Bond 2001, Downing 1992, Palazzuoli 2004, Sezai 2000]. CPB exposes blood to large areas of synthetic material, triggering a system-wide inflammatory response and the production and release of numerous vasoactive substances (Table 2) [Downing 1992]. Plasma concentrations of epinephrine and norepinephrine are increased 3- to 4-fold following CPB and do not return to baseline for 24 hours, increasing both the heart rate and the systemic vascular resistance while decreasing renal blood flow [Downing 1992]. Both β-receptor stimulation and decreased renal perfusion pressure stimulate the release of renin from the juxtaglomerular cells in the kidney, ultimately leading to production of the potent vasoconstrictor angiotensin II and the hormone aldosterone, which causes sodium and water retention [Downing 1992]. In addition, pain, visceral manipulation, changes in serum osmolality, and reductions in blood volume and blood pressure stimulate the release of vasopressin from the posterior pituitary [Downing 1992]. During the first 10 to 30 minutes of CPB, vasopressin levels increase from approximately 2 pg/mL to 16 to 80 pg/mL. These concentrations drop sharply with the cessation of CPB [Downing 1992]. Although vasopressin typically increases water resorption and, to a lesser extent, sodium resorption in the kidney, the supraphysiologic concentrations that occur during CPB have a paradoxic diuretic effect and serve as a potent systemic and coronary vasoconstrictor [Downing 1992]. In addition, patients undergoing CPB exhibit a disturbance of normal renal circulation dynamics, increased renal vascular resistance, and decreases both in renal blood flow and GFR [Mangano 1998].

RATIONALE FOR THE USE OF BNP IN CARDIAC SURGERY

Supportive management of patients before, during, and after cardiac surgery involves strategies aimed at improving end-organ perfusion. Attenuation of the neurohormonal and

Table 2. Physiologic Effects of Cardiac Surgery*

Event	Response	Physiologic Effect
Reduced cardiac output	RAAS activation	↑ SVR
		↑ Fluid retention
		↑ Sodium retention
	ANP/BNP release	↑ Sodium retention
		↓ SVR activity
		↓ RAAS activity
RAAS activation	Epinephrine release	↑ HR
		↑ Muscle BF
		↓ Renal BF
	Norepinephrine release	↑ SV
		↑ SVR
		↑ BP
	Vasopressin release	↑ Fluid retention
		↑ Sodium retention
RAAS activation/endothelial cell activation	Endothelin-1 release	↑ SVR
		↑ PVR
Circulatory system/synthetic surfaces interface	Complement cascade activation	↑ Vascular permeability
		↑ Histamine release
		↑ Hypotension
		↑ Coronary vasoconstriction
		↓ Contractility
Neutrophil release	Adhesion molecule stimulation	Vasoconstriction
Neutrophil activation and system-wide inflammatory response	Cytotoxic release of hydrogen peroxide and other oxygenated molecules	Oxidative stress

Adapted with permission from Downing and Edmunds [Downing 1992].

*RAAS indicates renin-angiotensin-aldosterone system; SVR, systemic vascular resistance; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; HR, heart rate; BF, blood flow; SV, systolic volume; BP, blood pressure; PVR, pulmonary vascular resistance.

inflammatory responses may significantly improve outcomes, specifically in the high-risk group of patients with ventricular dysfunction. Increased tissue oxygen delivery based on hemodynamic goals have led to beneficial effects in postsurgical CPB patients, including improvements in end-organ perfusion accomplished through pulmonary vasodilation, afterload reduction, and diuresis [Pölönen 2000]. The pharmacologic profile of BNP is favorable for achieving a similar goal. In addition to offering significant hemodynamic benefits [Abraham 1998, Colucci 2000, Publication Committee for the VMAC Investigators 2002, Yoshimura 1991] because of its pulmonary, systemic, and coronary vasodilative properties, BNP may attenuate the negative effects of CPB by reducing cytokine and neurohormonal activation [Asimakopoulos 1998, Carlucci 2002]. In addition, exogenous BNP can potentially preserve renal function by maintaining the GFR and renal blood flow despite an increase in natriuresis and diuresis, and decreases in the mean arterial pressure and systemic vascular resistance [Abraham 1998, Butler 2004, Jensen 1998, Jensen 1999, Yoshimura 1991]. Unlike inotropic therapy, BNP reverses the deleterious activation of neurohormones caused by cardiac stress [Abraham 1998, Aronson 2002, Brunner-La Rocca 2001, Burger 2001, Yoshimura 1991], and has demonstrated a superior safety and efficacy profile compared with inotropes in recent HF trials [Burger 2002, Colucci 2000, Publication Committee for the VMAC Investigators 2002]. Based on these comparative data in patients with HF, BNP may be a beneficial perioperative adjunct to inotropic therapy for the management of low cardiac output, pulmonary hypertension, and compromised renal function. Normalization of renal function can be particularly critical, as compromised renal function is a common and substantial clinical problem that extends coronary care unit stay, and is predictive of in-hospital mortality as well as discharge to a long-term care or skilled nursing facility [Mangano 1998].

USE OF NATRIURETIC PEPTIDES IN CARDIAC SURGERY

Several natriuretic peptide therapies, including human ANP and BNP, have been investigated for use in cardiac surgical patients. An investigation of 40 patients undergoing elective coronary artery bypass grafting (CABG) found that patients who were administered human ANP demonstrated lower renin and angiotensin II levels and increased urinary volume, and were able to maintain their GFR when compared with patients who received a placebo. In addition, the ANP-treated patients experienced a reduction in the need for furosemide; reductions in mean pulmonary artery pressure, central venous pressure, systemic vascular resistance index, and pulmonary vascular resistance index; a higher respiratory

index; and reduced pleural effusions [Sezai 2000]. These data are promising and have led to ongoing studies to further characterize the utility of ANP in cardiac surgery.

Few studies have examined the perioperative use of BNP in cardiac surgical patients, but preliminary reports have been positive [Feldman 2004, Radovancevic 2003, Sanyal 2005, Witteles 2003]. Intravenous BNP has demonstrated an initial benefit when used in maintenance therapy for patients with severe HF who are awaiting transplantation [Witteles 2003], in patients receiving the drug perioperatively during implantation of a left ventricular assist device [Radovancevic 2003], and following explantation of a left ventricular assist device [Entwistle, III 2004].

Samuels evaluated the effect of BNP in 12 patients with advanced HF following cardiac surgery [Samuels 2004]. Other cardiac medications, such as milrinone to augment cardiac output, norepinephrine to increase blood pressure, and amiodarone for arrhythmia control, were administered as needed. Administration of BNP resulted in a 38% reduction in mean pulmonary artery pressure, a 39% reduction in mean central venous pressure, and a 47% increase in mean cardiac index compared to preinfusion values, without any significant change in the systolic blood pressure (pre-BNP: 116 mm Hg; post-BNP: 114 mm Hg).

A recently published abstract describes the largest evaluation to date of BNP use following cardiac surgery [Sanyal 2005]. In this evaluation, 50 consecutive postoperative patients with HF refractory to conventional therapy received intravenous nesiritide a mean of 2.8 days following surgery. The mean age of the patients was 68 years; 39 patients had undergone isolated CABG, 5 had undergone isolated valve procedures, and 6 had undergone combined CABG/valve procedures. Within 8 hours of instituting nesiritide, there were significant reductions in systemic vascular resistance (from 1115 ± 232 to 1024 ± 220 Woods units; $P = .038$), pulmonary artery diastolic pressure (from 25.8 ± 2.9 to 19.2 ± 2.8 mm Hg; $P < .001$), central venous pressure (from 15.5 ± 3.0 to 13.4 ± 2.9 mm Hg; $P = .004$), and oxygen requirements (from 46.2 ± 13.2 to 37.2 ± 17.3 percent inspired oxygen; $P < .001$), and significant increases in cardiac index (from 2.35 ± 0.27 to 2.49 ± 0.19 L/min/m^2; $P = .002$) and urine output (from 46.6 ± 26.9 to 91.7 ± 47.0 mL/hr; $P < .0001$) relative to preinfusion values. Nesiritide was well tolerated, with only one discontinuation due to hypotension. It did not increase serum creatinine levels.

In addition, the favorable renal protective properties of BNP in the setting of CPB make this a theoretically promising agent for heart transplant patients. Transient renal dysfunction is common in cardiac transplant recipients because of the additive effects of nephrotoxic calcineurin inhibitors, CPB, and pre-existing renal insufficiency. Although calcineurin inhibitors exert direct renal toxicity, at least part of their deleterious effect may be related to increases in serum endothelin levels, an effect that can be antagonized by BNP. Nesiritide significantly reduced PCWP, mean pulmonary artery pressure, and central venous pressure, and significantly increased cardiac output and 24-hour urine output in 10 consecutive heart transplant patients with pre-existing renal insufficiency and elevated filling pressures who had failed to respond to inotropes and escalating doses of diuretics [Feldman 2004]. Moreover, there was a trend for a reduction in serum creatinine levels from 2.8 ± 0.5 mg/dL 1 hour prior to initiation of nesiritide to 2.3 ± 0.5 mg/dL 12 hours following initiation of nesiritide ($P = .05$).

These findings, however, are limited by small patient numbers, non-randomized design, and the absence of a control group. Moreover, the relationship among pulmonary, renal, and outcome parameters in these patients is unknown. Consequently, the exact role of BNP in the management of postoperative HF remains an unresolved issue. Given the theoretical rationale for the use of BNP in patients undergoing cardiac surgery and these preliminary findings, a multicenter, randomized, double-blind, placebo-controlled pilot evaluation, the Natrecor Administered Peri-Anesthesia in patients undergoing CardioThoracic surgery (NAPA-CT Surgery) study, has been initiated to investigate the utility of perioperative nesiritide in patients with left ventricular systolic dysfunction who are undergoing CABG requiring CPB. The specific objectives of this study are to determine the effects of nesiritide on neurohormones, hemodynamics, renal function, requirement for intervention, and clinical outcomes. This study should help in clarifying the role of BNP in these patients.

ALTERNATIVE APPROACHES TO NEUROHORMONAL MODIFICATION DURING CARDIAC SURGERY

Several other pharmacologic approaches have been investigated to counteract the neurohormonal activation and complications that occur during cardiac surgery. The antidiuretic vasopressin has been administered with success in CPB patients experiencing postsurgical vasodilatory shock as a result of low levels of endogenous vasopressin [Albright 2002, Zimmerman 2002]. Endothelin receptor antagonists have been investigated in animal and cellular studies and may attenuate ischemia-reperfusion injury incurred during surgery, especially in diabetic patients, since hyperglycemia stimulates endothelin-1 production [Verma 2002]. Inhaled prostacycline has been evaluated as a selective pulmonary vasodilator in postoperative patients with pulmonary hypertension, hypoxemia, or right heart dysfunction [De Wet 2004]. Postoperative angiotensin-converting enzyme inhibition and β-blockade are useful in patients because of the ability of these agents to inhibit activation of the RAAS and their proven benefits in patients with HF. Finally, adenosine antagonists may prove useful because of their ability to attenuate cardiac hypertrophy and myocardial dysfunction in animal and cellular models, but clinical studies are needed to confirm their utility in surgical patients [Cohen 1998, Liao 2003].

WHEN PHARMACOTHERAPY IS NOT ENOUGH: INNOVATIVE STRATEGIES AND SUPPORTIVE DEVICES

Despite an improved understanding of the neurohormonal processes that surround HF and heart surgery, patients with

inadequate left ventricular function to support basic metabolism will require more aggressive therapies with mechanical support. Understanding when this threshold is met remains an important area of clinical research. Left ventricular assist devices are being used in a limited number of patients as a supportive bridge to transplantation and in patients with end-stage cardiac disease who are ineligible for transplantation [Frazier 2003, Rose 2001]. As technology advances, earlier insertion of these devices will become the norm. However, the therapeutic goal in these patients cannot be limited to mechanical augmentation of cardiac function and must include preservation, to the extent possible, of all remaining ventricular function. Consequently, these patients require a comprehensive approach, potentially including neurohormonal modulation.

CONCLUSIONS

Despite constant improvements in cardiac surgical techniques and resulting outcomes, the risks associated with these procedures are still high. Efforts to improve the risk/benefit profile of cardiac surgery should include consideration of the neurohormonal activation that occurs during and after cardiac surgery. This neurohormonal activation is similar to that seen in patients with HF. Consequently, effective HF therapies, especially those that counteract this deleterious response, might prove beneficial in patients undergoing cardiac surgery. Nesiritide blunts neurohormonal activation and has demonstrated significant efficacy in patients with HF. Preliminary data on the use of nesiritide in patients following cardiac surgery are promising, and a randomized, double-blind, placebo-controlled trial is currently evaluating the role of this agent in the postoperative management of cardiac surgery patients.

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