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Nesiritide for treatment of perioperative low cardiac output syndromes in cardiac surgical patients: an initial experience

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Abstract
The physiologic properties of the b-type natriuretic peptide nesiritide include pulmonary, coronary, and renal arterial vasodilation and lusitropic effects on ventricular myocardium. These effects may be useful during cardiac surgery, particularly when myocardial function and cardiac output (CO) are compromised. Intraoperative hemodynamic data were collected retrospectively before and 5–15 min following completion of a nesiritide loading dose in 15 adult cardiac surgical patients with low CO associated with pulmonary hypertension, low left ventricular ejection fraction, diastolic dysfunction, or left ventricular assist device placement. In seven patients, prior alternative pharmacologic interventions had failed to improve CO, and fluid challenges were ineffective in six patients with diastolic dysfunction. Perioperative nesiritide administration (2 μg·kg^{-1} load, followed by 0.01 μg·kg^{-1}·min^{-1} for a maximum of 24 h) resulted in a statistically significant median increase in CO of 35% (P = 0.0006). In conclusion, nesiritide was associated with increased CO in patients with low CO syndromes undergoing cardiac surgery, when other measures failed. This novel agent may offer an additional option to inotropes and fluid challenges for these patients perioperatively. Randomized clinical trials are desirable to determine the risks and benefits of nesiritides and to elucidate its role for the cardiac anesthesiologist.

Key words Diastolic dysfunction · Pulmonary hypertension · Low cardiac output · Nesiritide · Natrecor

Introduction

Nesiritide, or b-type natriuretic peptide, is a human cardiac hormone available for pharmacologic therapy. It is approved by the United States Food and Drug Administration (FDA) for the treatment of systolic and diastolic congestive heart failure [1]. Nesiritide's physiologic effects include pulmonary, renal, and coronary arterial vasodilation [1], as well as lusitropic effects on ventricular myocardium [2,3]. These pharmacologic properties are often useful during cardiac surgery, especially in high-risk patients with low cardiac output syndromes (LCOS) associated with pulmonary hypertension, low left ventricular ejection fraction (LVEF), or diastolic dysfunction. However, the administration of nesiritide to treat LCOS perioperatively in cardiac surgery is not well studied. We present our initial experience in 15 adult cardiac surgical patients with LCOS treated with nesiritide to acutely improve their hemodynamic performance.

Methods

Following approval by the Institutional Review Board, we retrospectively collected and analyzed demographic and hemodynamic data of adult patients undergoing cardiac surgery. All patients presenting during an 18-month study period, clinically diagnosed with LCOS by the anesthesiologists (G.R.G. and M.R.E.) and subsequently treated with nesiritide perioperatively, were entered in the analysis. The clinical diagnosis of LCOS subgroups was based on transesophageal echocardiography data and values from a pulmonary artery catheter in each patient. Data collection included blood pressure (BP), heart rate (HR), pulmonary artery pressure (PAP), central venous pressure (CVP), and cardiac output (CO) 5–15 min before and 5–15 min following completion of a loading dose of nesiritide. Side effects that could have limited the use of nesiritide were noted. Nesiritide was administered intravenously as a 2 μg·kg^{-1} loading dose over 20 min, followed by an infusion of 0.01 mg·kg^{-1}·min^{-1} for a maximum of 24 h. All surgical procedures involved cardiopulmonary bypass. Routine

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Table 1. Patients with low cardiac output and diastolic dysfunction

Procedure	Height Weight	Nesiritide	BP (mmHg)	HR (bpm)	PAP (mmHg)	CVP (mmHg)	CO ($l \cdot min^{-1}$)	Pharmacologic intervention
Redo CABG	58″[a]	Pre	105/53	90	42/30	19	2.7	Epinephrine
	52 kg	Post	108/48	90	48/29	18	3.5	
CABG	70″	Pre	135/52	90	46/24	14	3.3	Epinephrine
	77 kg	Post	105/45	90	41/24	14	4.4	
AVR, MAZE	66″	Pre	115/65	90	51/38	22	1.8	Epinephrine,
	98 kg	Post	105/55	90	44/30	18	2.8	amrinone
AVR, CABG	56″	Pre	103/60	91	23/15	11	2.3	Epinephrine
	53 kg	Post	109/61	91	24/12	10	4.1	
MVR, CABG	56″	Pre	102/52	100	35/22	16	3.8	None
aortic root	83 kg	Post	99/55	100	40/26	18	4.7	
CABG	60″	Pre	108/52	90	[b]/27	20	2.4	None
	60.1 kg	Post	125/60	90	[b]/20	13	4.3	

BP, blood pressure; PAP, pulmonary artery pressure; CVP, central venous pressure; CO, cardiac output; CABG, coronary artery bypass grafting; HR, heart rate; AVR, aortic valve replacement; MVR, mitral valve replacement; aortic root, aortic root replacement
[a] Inches
[b] Data not available

intraoperative care included the administration of 2 g magnesium sulfate after aortic crossclamp removal. When amrinone was used prior to nesiritide in an attempt to improve CO, it was administered as a bolus of 1 to 1.5 $mg \cdot kg^{-1}$ intravenously, followed by an infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Statistical analysis was performed using STATA statistical software, version 9.1 SE (College Station, TX, USA). Demographics are reported as means ± SD. We applied the nonparametric Wilcoxon test for paired data to detect a significant change in CO before and after nesiritide administration. $P < 0.05$ was considered statistically significant. The percent increase in CO in each subject was calculated, and we report the median increase and 95% confidence interval (CI).

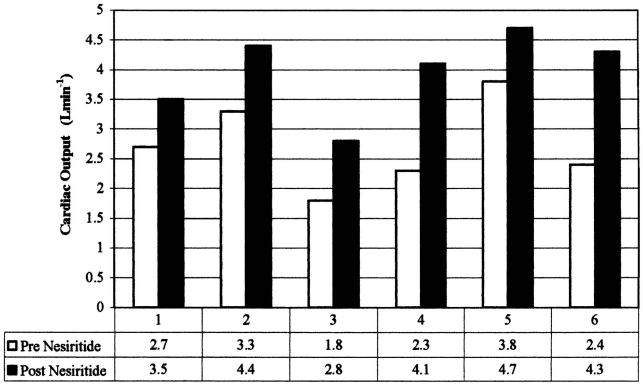

Fig. 1. Cardiac output pre- and post-nesiritide administration in six patients with diastolic dysfunction

Results

Nine male and six female patients between the ages of 45 and 84 years (69.8 ± 10.3; mean ± SD) with a body mass index of 29.3 ± 5.2 kg/m^2 (mean ± SD) received nesiritide for LCOS perioperatively. Low CO was associated with diastolic dysfunction in 6 patients, marked pulmonary hypertension in 5 patients, LVEF in 3 patients, and left ventricular assist device (LVAD) placement in 1 patient. Nesiritide treatment for the group of 15 patients resulted in a statistically significant median increase in CO of 35% (95% CI, 20%–49%; $P = 0.0006$) when comparing pre- and post-nesiritide values.

Diastolic dysfunction (n = 6)

Diastolic dysfunction was diagnosed using transesophageal echocardiography (TEE) and pulmonary artery catheter data. All patients had low CO and normal biventricular systolic function with a small left ventricular cavity. Pulmonary artery pressures were either normal ($n = 3$) or elevated ($n = 3$). None of the patients demonstrated an increase in CO with fluid challenge. Three patients were treated with epinephrine 1–2 $\mu g \cdot min^{-1}$ for 10–15 min and then had CO measured. One patient received epinephrine 2 $\mu g \cdot min^{-1}$ and amrinone prior to separation from cardiopulmonary bypass and for the subsequent 90 min continued to have low CO. Cardiac output was measured 5–15 min following completion of the loading dose of nesiritide and was associated with a clinically significant increase in CO in all patients. The median increase in CO was 44% (Fig. 1). Table 1 summarizes the hemodynamic profiles of these patients and their surgical procedures.

Pulmonary hypertension (n = 5)

Severe pulmonary hypertension, diagnosed by severely elevated pulmonary artery pressures, was encountered

Table 2. Patients with pulmonary hypertension and low cardiac output

Procedure	Height Weight	Nesiritide	BP (mmHg)	HR (bpm)	PAP (mmHg)	CVP (mmHg)	CO ($l \cdot min^{-1}$)	Pharmacologic intervention	TEE
CABG, AVR, MAZE	72″[a] 106 kg	Pre	95/55	120	80/45	21	3.0	Amrinone	LVEF 25%
		Post	95/55	120	55/36	20	4.0		
CABG	74″	Pre	105/55	115	82–	15	5.3	Amrinone	LVEF 20%
	94 kg	Post	95/52	115	93/46 75/41	13	6.3		Moderate low RV function
AVR, MV ring	66″	Pre	147/67	100	74/46	18	2.9		LVEF 55%
	64 kg	Post	120/53	100	50/30	14	4.5		
AVR, MVR, CABG	71″	Pre	120/79	60	73/29	20	2.8		LVEF 35%
	80 kg	Post	105/48	60	66/27	17	4.4		
MVR	61″	Pre	130/82	112	78/38	24	2.1		Severe mitral stenosis
	72 kg	Post	105/72	112	77/41	28	2.5		

BP, blood pressure; HR, heart rate; PAP, pulmonary artery pressure; CVP, central venous pressure; CO, cardiac output; TEE, transesophageal echocardiography; CABG, coronary artery bypass grafting; AVR, aortic valve replacement; MV, mitral valve; MVR, mitral valve replacement; LVEF, left ventricular ejection fraction

[a] Inches

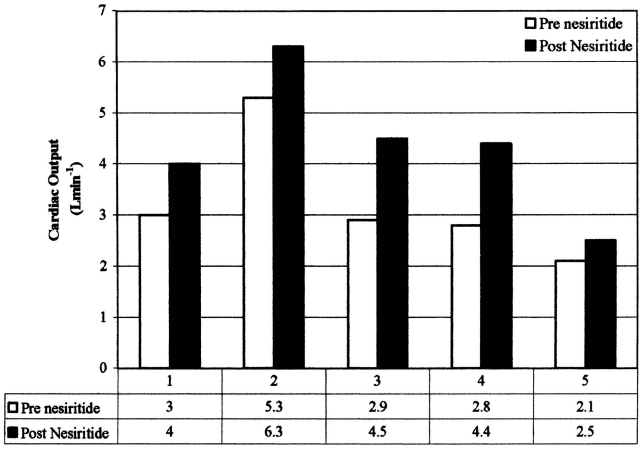

Fig. 2. Cardiac output pre- and post-nesiritide administration in five patients with pulmonary hypertension

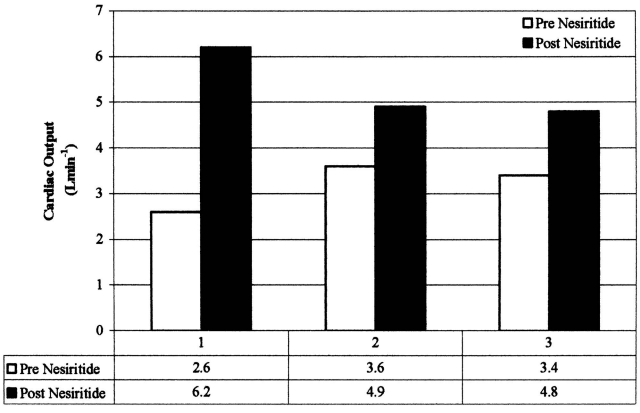

Fig. 3. Cardiac output pre- and post-nesiritide administration in three patients with low left ventricular ejection fraction and low cardiac output syndrome

in five patients, one of whom was diagnosed post-cardiopulmonary bypass. Four patients were treated prior to cardiopulmonary bypass. Two patients were unsuccessfully treated with amrinone prior to receiving nesiritide, resulting in unchanged CO or PAP. With the exception of one patient with severe mitral stenosis who did not respond, all four patients experienced a decrease in PAP and an increase in CO following nesiritide administration. The median increase in CO was 33% (Fig. 2). Details of the hemodynamic parameters of these patients and their procedures are shown in Table 2.

Poor systolic function (n = 3)

Three patients presented with low LVEF by transesophageal echocardiography, mild to moderately elevated PAP, and low CO in the pre-bypass period. Treatment with nesiritide and no additional inotropes was associated with an increase in CO and minimal changes in PAPs in all patients. The median increase in CO was 41% (Fig. 3). Hemodynamic details are shown in Table 3.

Left ventricular assist device (LVAD) placement (n = 1)

A patient with severe pulmonary hypertension and poor LVEF underwent LVAD placement. Upon chest closure, his LVAD flow remained in the range of $3.3 l \cdot min^{-1}$, despite treatment with amrinone and isoproterenol $2 \mu g \cdot min^{-1}$, as well as volume loading. Nesiritide administration improved the LVAD flow to $4 l \cdot min^{-1}$ (21%) consistently.

Table 3. Patients with low left ventricular ejection fraction and low cardiac output

Procedure	Height Weight	Nesiritide	CO ($l \cdot min^{-1}$)	BP (mmHg)	HR (bpm)	PAP (mmHg)	CVP (mmHg)	TEE/LVEF
Redo CABG,	6″[a]	Pre	2.6	105/60	70	45/26	14	20%, 3+
MV repair	91 kg	Post	6.2	107/60	76	54/30	18	MR
CABG 15%	74″	Pre	3.6	102/49	62	47/19	9	15%
	95 kg	Post	4.9	95/43	58	45/18	10	
CABG 15%	67″	Pre	3.4	115/65	58	58/25	12	15%
	73 kg	Post	4.8	102/48	60	41/18	11	

CO, cardiac output; BP, blood pressure; HR, heart rate; PAP, pulmonary artery pressure; CVP, central venous pressure; CABG, coronary artery bypass grafting; MV, mitral valve; MR, mitral regurgitation; LVEF, left ventricular ejection fraction
[a] Inches

Discussion

Low CO syndromes are common during the perioperative period in patients undergoing cardiac surgery. Options for the treatment of low CO include optimizing preload with appropriate volume administration, pharmacologic therapy aimed at increasing contractility with catecholamines and phosphodiesterase inhibitors, and mechanical support. These treatments may be ineffective in the presence of diastolic dysfunction, or may be limited by side effects such as tachyarrhythmias and systemic vasodilation. Hence, a novel pharmacologic agent that is effective when standard therapy is unsuccessful or limited by side effects is desirable and may be useful.

Nesiritide, a human cardiac hormone, is FDA-approved for the treatment of acute congestive heart failure. When contemplating the "off-label" use of any new pharmacologic agent, two important considerations must be addressed. First, does the agent's putative pharmacologic property provide a reasonable clinical basis to believe it will be effective in a specific patient population and clinical setting? Second, does the new treatment offer results that cannot be achieved by established and accepted therapies? Both questions influenced our clinical decision to use nesiritide in cardiac surgical patients with LCOS. Because of its physiologic role in humans and its known pharmacologic properties, we hypothesized that nesiritide may be effective in acutely treating low CO via mechanisms that are distinctly different from those of other available medications. The anesthesiologists' (G.R.G and M.R.E.) rationale for the use of b-type natriuretic peptide in these patients included failure of more established pharmacologic treatments of specific LCOS intraoperatively, or comorbidities, such as renal insufficiency, that would suggest additional benefits to the patients from the use of this agent.

Awareness of diastolic dysfunction as a cause for low CO and pulmonary congestion is increasing, and most cardiac surgical patients with this condition can be adequately managed by fluid loading, inotropic pharmacologic support, including catecholamines, phosphodiesterase inhibitors, and magnesium sulfate. The latter two have lusitropic properties [4–6] and should be beneficial in this setting. However, some patients do not respond to these standard therapies, and additional pharmacologic treatment options are desirable. During a period of 18 months, only 6 patients presented with this severe form of diastolic dysfunction. Nesiritide was associated with improved CO perioperatively when other therapies were not.

Five patients with low CO associated with pulmonary hypertension were treated with nesiritide. Two of the patients received amrinone and showed no increase in CO or decrease in PAP. Following nesiritide administration, both patients showed an increase in CO and also a decrease in PAP. Two patients received nesiritide in the absence of additional inotropes and experienced an increase in CO and decrease in PAP.

In the patient with severe mitral stenosis, the CO and PAP remained unchanged following nesiritide administration. This lack of response to nesiritide could be an illustration of, and may be explained by the drug's mechanism that is responsible for improving CO. While its pulmonary vasodilating properties may contribute to a rise in CO, its lusitropic effects on the ventricular myocardium may be the predominant and far more important mechanism. If lusitropy is, in fact, the eminent mechanism for nesiritide's effect on CO, then improved ventricular relaxation would not be expected to lower PAP or increase CO in the presence of tight mitral stenosis.

Patients with poor systolic function and low CO will usually respond to the administration of standard inotropes. However, catecholamines are sometimes ineffective, due to beta receptor downregulation and the desensitization [7], and the administration of phosphodiesterase inhibitors may occasionally result in unwanted vasodilation or tachyarrythmias. In addition, it is increasingly appreciated that patients with poor systolic function may also have abnormal diastolic function

[8]. All three of our patients in this group demonstrated an increase in CO without changes in HR or systemic BP.

Our patient with an LVAD illustrates the pulmonary vasodilating properties of nesiritide, as well as its lusitropy, thereby increasing right ventricular CO, resulting in increased LVAD flow. Nesiritide may prove to be useful in minimizing low-flow states in this group of patients if given before LVAD placement.

Our results are limited by the small number of patients and the retrospective study design, reflected by a diversity of intraoperative treatments for LCOS prior to nesiritide use. However, nesiritide was administered in a standard manner to those patients thought by the anesthesiologists to most likely benefit from its pharmacologic effect; namely, patients with difficult-to-treat LCOS undergoing cardiac surgery. Although our findings consistently demonstrate an association of nesiritide with increased CO in a variety of intraoperative circumstances, other factors may have contributed to this increase. It would be desirable to determine, in future studies, whether the acute increase in CO shown in our patients following nesiritide administration continues throughout their perioperative course.

Two recent metaanalyses revealed a risk of worsening renal function and suggested the possibility of an increased short-term risk of death in patients receiving nesiritide [9,10]. Our study did not track intermediate or long-term renal outcome or mortality. However, in contrast to the studies by Sackner-Bernstein at al. [9,10], in our clinical practice, nesiritide was only used acutely intra- and perioperatively, and in patients without decompensated heart failure. Hence, we believe our clinical indications for the use of b-type natriuretic peptide to be sufficiently different to justify its use in this setting and in further studies to confirm or reject its potential benefits in short-term clinical circumstances.

In conclusion, this retrospective analysis of our initial clinical experience suggests that nesiritide was associated with acutely increased CO in LCOS in patients with diastolic dysfunction, pulmonary hypertension, decreased LVEF, and LVAD. Nesiritide appears to provide a novel pharmacologic mechanism that may be effective in improving CO and PAP in cardiac surgical patients, when standard inotropic medications have failed. Although its pulmonary vasodilating properties contribute to a rise in CO, we believe its lusitropic effects may be the predominant mechanism. Systematic evaluation of nesiritide in randomized clinical trials is desirable to determine its risks and benefits in cardiac surgery and anesthesia, and to elucidate its role in the cardiac anesthesiologist's armamentarium.

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