

The Efficacy of Intravenous Milrinone in Left Ventricular Restoration

Atsushi Yamaguchi, MD, Masashi Tanaka, MD, Kazuhiro Naito, MD, Chieri Kimura, MD,
Toshiyuki Kobinata, MD, Homare Okamura, MD, Takashi Ino, MD, and Hideo Adachi, MD

Purpose: The aim of this study was to clarify the efficacy of intravenous milrinone in postoperative care for patients following left ventricular (LV) restoration (LVR).

Methods: Fourteen patients who had ischemic cardiomyopathy with an LV ejection fraction (LVEF) of less than 0.30 and an LV end-systolic volume index of more than 100 ml/m² underwent coronary artery bypass grafting and concomitant LVR. The patients received perioperative management with continuous infusions of 0.5 µg/kg/min milrinone that were started at the induction of a cardiopulmonary bypass (CPB). The perioperative course and outcome of these patients were retrospectively compared with those of matched LVR patients (n = 14) without milrinone administration during perioperative management.

Results: The preoperative LV end-diastolic pressure (26.3 mmHg vs. 15.4 mmHg) and early diastolic filling velocity/atrial filling velocity ratio (4.1 vs. 2.1) in the milrinone patients were significantly worse than those in the control. Even though the preoperative LV function in each patient demonstrated to be extremely poor, the perioperative hemodynamic variables were stable. The administered doses of dobutamine (4.01 vs. 5.81 µg/kg/min) and epinephrine (0.017 vs. 0.038 µg/kg/min) at the end of CPB were significantly lower in the milrinone patients compared to control.

Conclusion: In those patients who underwent LVR because of ischemic cardiomyopathy, the administration of milrinone achieved safe perioperative management for stable hemodynamics and reduced the postoperative doses of dobutamine and epinephrine. (*Ann Thorac Cardiovasc Surg* 2009; 15: 233–238)

Key words: left ventricular restoration, coronary artery bypass grafting, cardiopulmonary bypass, inotropic agent

Introduction

Phosphodiesterase enzymes (PDE) are ubiquitous in the cardiovascular system and have characteristic substrate

From Department of Cardiovascular Surgery, Saitama Medical Center, Jichi Medical University, Saitama, Japan

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Address reprint requests to Atsushi Yamaguchi, MD: Department of Cardiovascular Surgery, Saitama Medical Center, Jichi Medical University, 1–847 Amanuma, Omiya-ku, Saitama 330–8503, Japan.
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specificities, kinetic characteristics, and responses to pharmacological agents.^{1,2} Phosphodiesterases terminate the actions of cyclic 3', 5'-nucleotides (e.g., adenosine 3', 5'-cyclic monophosphate [cAMP]) by catalyzing their hydrolyses. Milrinone (MilrilaTMK; Astellas Pharma Co., Tokyo, Japan) is a selective inhibitor of cAMP—specific PDE III isoenzyme in myocardium and vascular smooth muscle. By increasing cAMP concentrations in both myocardium and vascular smooth muscle, milrinone causes an increase in cardiac output (CO) through combined positive inotropic and vasodilative effects, and a decrease in systemic blood pressure and cardiac filling

Table 1. Preoperative variables

	Group M	Group C	<i>p</i> value
No. of patients	14	14	–
Mean age	64.1 ± 8.0	65.2 ± 8.5	ns
Male:Female	13:1	13:1	ns
History of CHF	14	14	ns
BNP (pg/mL)	504 ± 380	426 ± 505	ns
LVEF	0.23 ± 0.07	0.25 ± 0.09	ns
LVESVI (mL/m ²)	132 ± 24	135 ± 25	ns
LVEDVI (mL/m ²)	187 ± 41	173 ± 36	ns
E/A ratio	4.1 ± 1.5	2.1 ± 1.7	<0.05
LVDd (mm)	66.2 ± 5.5	63.2 ± 10.4	ns
PAP (mmHg)	51.6 ± 19.3	34.0 ± 13.9	<0.05
LVEDP (mmHg)	26.3 ± 7.7	15.4 ± 7.9	<0.05
Use of intra-aortic balloon	9	9	ns
Grafted vessels	2.6 ± 1.2	2.5 ± 1.0	ns

BNP, brain natriuretic peptide; CHF, congestive heart failure; E/A, early diastolic filling velocity/atrial filling velocity; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; PAP, pulmonary artery systolic pressure.

Each *p* value was obtained by a Student's *t*-test or a χ^2 test to determine differences between the two groups.

pressures.^{3,4)} This drug has been used effectively during separation from cardiopulmonary bypass (CPB) and for the treatment of low output syndrome after cardiac operations.^{5–7)} Its pharmacokinetics are more prolonged than those of the catecholamines commonly used for inotropic support after cardiac surgical procedures. Milrinone has been demonstrated to be particularly efficacious in patients who are at risk for β -receptor down-regulation, such as those with congestive heart failure (CHF), prior to operation.^{8,9)}

In this study, intravenous milrinone was used on patients who had undergone left ventricular (LV) restoration (LVR) for the treatment of ischemic cardiomyopathy. Patients with this ailment develop LV dysfunction because of reiterative myocardial infarction associated with high incidence of postoperative low output syndrome, sometimes leading to in-hospital mortality. The Japanese association for thoracic surgery reported 8.4% of in-hospital mortality following LV infarctectomy or aneurysmectomy.¹⁰⁾ The aim of this study was to clarify the efficacy of intravenous milrinone in postoperative care for patients following LVR surgery.

Patients and Methods

From September 2004 to December 2007, 14 patients underwent elective coronary artery bypass grafting (CABG) and concomitant LVR at Saitama Medical Center, Jichi Medical University. All patients had LV dysfunction with a left ventricular ejection fraction (LVEF) of less than 0.30 and a left ventricular end-systolic volume index (LVESVI) of more than 100 ml/m² as a result of ischemic-dilated cardiomyopathy. The clinical data and cardiac risk factors for the 14 patients in this series are shown in Table 1. Preoperative coronary angiography (CAG) was performed in every patient, and the LVEF and LVESVI were calculated using the data of biplane left ventriculography (LVG). Preoperative hemodynamic variables were assessed using a flow-directed balloon-tipped thermodilution catheter (Edwards Laboratory, Santa Ana, CA) in the catheter laboratory. Myocardial wall motion and physiological evaluation were preoperatively performed using transthoracic echocardiography. The ratio of early diastolic filling velocity/atrial filling velocity (E/A) as an index of restrictive diastolic dysfunction was calculated using the data from echocardiography. When a patient developed pulmonary hypertension

resulting from CHF or unstable myocardial ischemia refractory to medical therapy, intra-aortic balloon pumping (IABP), used in nine patients, was applied preoperatively for stabilization of cardiac performance. All patients were free of significant primary renal or hepatic disease. No patient had a serious hematological abnormality or an abnormal platelet count.

Perioperative monitoring

Every patient received routine sedative anesthetic premedication, and general anesthesia was established in accordance with routine practice. At the induction of anesthesia, each patient was monitored by a continuous display of the electrocardiogram (ECG) and invasive systemic arterial blood pressure (ABP), which was obtained by intra-arterial catheter in the right radial artery. Also, right atrial pressure (RAP), pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure (PCWP) measurements were made by means of a balloon-tipped, flow-directed, pulmonary artery catheter. And the cardiac index (CI) was measured by the bolus thermodilution technique in accordance with standard practice; intermittent blood gas analysis was also carried out. Multiple measurements were made each time and the mean was calculated.

Surgical procedures

Every patient underwent CABG and LVR concomitantly. Patients who underwent mitral valve annuloplasty for treatment of ischemic mitral insufficiency were not included in this study. The operation was performed by means of CPB with a roller pump (Stöckert 53; Munich, Germany) under a mean pressure of 60 mmHg and a flow rate of 2.5 L/min/m², a membrane oxygenator (CapiioxTM RX25; Terumo Corp., Tokyo, Japan), and a 40- μ m arterial blood filter (AutoventTM; Pall Corp., East Hills, NY). Intermittent antegrade and retrograde delivery of cold blood cardioplegia were used under moderate hypothermia (28°C). Heparin (3.0 mg/kg) was administered intravenously after sternotomy to maintain an activated clotting time (ACT) of more than 400 seconds, and it was neutralized at the end of the procedure by using protamine sulfate (3.0 mg/kg).

CABG was performed first using single or double internal thoracic arteries and saphenous vein grafts, and the LVR portion of the operation was then carried out. The principle of the LVR procedure was the surgical anterior ventricular endocardial restoration (SAVER) procedure¹¹⁾ as a modification of endoventricular circular

patch plasty by Dor et al.¹²⁾ The LV was opened parallel to the left anterior descending artery at the center of the myocardial scar, and the endocardial scar was resected. A Dacron hemircular patch was then anchored to the fibrotic tissue to close the orifice and reconstruct the internal cavity, resulting in an exclusion of the LV scar. The excluded external tissue was then folded over the patch to reinforce the suture line and provide additional hemostasis.

Perioperative management

The patients received perioperative hemodynamic management with continuous infusions of 0.5 μ g/kg/min milrinone. The infusion started after the induction of CPB and was maintained for at least 48 hours after surgery. The patients were weaned from CPB with nicorandil 1.0 μ g/kg/min (SigmartTM; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) and diltiazem 1.0 μ g/kg/min (HerbesserTM; Mitsubishi Tanabe Pharma Corp., Osaka, Japan). When CI was defined as less than 2.5 L/min/m², or when mean arterial pressure was defined as less than 60 mmHg, dobutamine (DobupomTM; Terumo Corp., Tokyo, Japan) and/or norepinephrine (Nor-Adrenaline; Daiichi Sankyo Co. Ltd., Tokyo, Japan) were also loaded to stabilize hemodynamics. The hemodynamic measurements, including heart rate (HR), ABP, RAP, PAP, PCWP, and CI, had to be made within 60 minutes of receiving treatment following the administration of such inotropic agents.

Following the surgery, the patients were transferred to the intensive care unit and treated using the same protocol for hemodynamic stability. Hemodynamic measurements, including HR, ABP, RAP, PAP, and CI, were monitored by continuous display.

Retrospective matched study

All 14 patients (group M) received perioperative hemodynamic management using continuous infusions of 0.5 μ g/kg/min milrinone from September 2004 to December 2007. Another 14 patients underwent the same surgical treatment of elective CABG and concomitant LVR from September 2000 to August 2004 (group C). These patients underwent CABG and LVR under the same criteria of the LVEF of less than 0.30 and the LVESVI of more than 100 ml/m² as a result of ischemic-dilated cardiomyopathy. The 14 patients who received the same perioperative management, except for the administration of milrinone, were analyzed as a matched control group. The clinical data and cardiac risk factors for group C patients are shown in Table 1. The perioperative data and

Table 2. Hemodynamic variables

	End of CPB	12 hr after surgery	24 hr after surgery
ABP (mmHg)			
Group M	118 ± 11	108 ± 11	115 ± 12
Group C	112 ± 14	115 ± 13	115 ± 12
PAP (mmHg)			
Group M	31.2 ± 6.7	29.3 ± 7.2	33.1 ± 8.9
Group C	27.8 ± 6.1	27.3 ± 6.3	30.6 ± 8.6
PCWP (mmHg)			
Group M	13.2 ± 4.2	13.1 ± 4.7	14.9 ± 4.0
Group C	11.0 ± 5.1	11.6 ± 4.3	13.5 ± 4.8
CI (L/min/m ²)			
Group M	3.42 ± 0.93	3.80 ± 1.43	3.66 ± 0.81
Group C	3.63 ± 1.05	4.19 ± 0.96	3.85 ± 0.94

ABP, arterial blood pressure (systolic phase); CI, cardiac index; CPB, cardiopulmonary bypass; PAP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure.

Table 3. Perioperative administration of inotropic agents

	End of CPB	12 hr after surgery	24 hr after surgery
Dobutamine (µg/kg/min)			
Group M	4.01 ± 2.14*	4.66 ± 2.09	4.55 ± 2.15
Group C	5.81 ± 2.61*	5.63 ± 2.27	5.31 ± 2.37
Norepinephrine (µg/kg/min)			
Group M	0.017 ± 0.017*	0.022 ± 0.031	0.023 ± 0.033
Group C	0.038 ± 0.035*	0.034 ± 0.035	0.032 ± 0.032
Milrinone (µg/kg/min)			
Group M	0.51 ± 0.17	0.39 ± 0.21	0.38 ± 0.20
Group C	0	0	0

CPB, cardiopulmonary bypass.

*A *p* value of less than 0.05 in comparison between two treatment groups.

Each *p* value was obtained by a Student's *t*-test to determine differences between the two groups.

outcome were retrospectively compared between group M and group C, even though the design of this study was not a case-controlled study, but a retrospective matched study.

Statistical analysis

Continuous variables are expressed as the mean plus or minus standard deviation. Continuous data were analyzed using the Student's *t*-test. A value of *p* less than 0.05 was considered statistically significant.

Results

Table 1 shows the preoperative and operative variables in each group, and neither group experienced a hospital mortality. The mean value of plasma B-type natriuretic peptide (BNP) level was significantly higher than the

standard level in both groups. The preoperative PAP (51.6 mmHg vs. 34.0 mmHg), LVEDP (26.3 mmHg vs. 15.4 mmHg), and the E/A ratio (4.1 vs. 2.1) in group M was significantly greater (*p* < 0.05) than those in group C, though there were no significant differences in the preoperative LVEF, LVEDVI, and LVESVI between the two groups. These preoperative variables demonstrate that both groups of patients had poor preoperative LV function. Some preoperative data of the LV function, including E/A ratio and LVEDP, were quite likely to be much worse in group M, compared to group C.

Table 2 shows perioperative changes of hemodynamic measurements. Hemodynamic variables of ABP, PAP, PCWP, and CI were maintained within a favorable range in both groups. Table 3 shows the administered doses of dobutamine and epinephrine during perioperative periods. The administered doses of dobutamine (4.01 vs. 5.81

$\mu\text{g}/\text{kg}/\text{min}$) and epinephrine (0.017 vs. 0.038 $\mu\text{g}/\text{kg}/\text{min}$) at the end of CPB were significantly lower ($p < 0.05$) in patients treated with milrinone (group M) compared to those treated without it (group C).

Twenty-six patients of the two groups underwent postoperative evaluation using CAG and LVG. The CAG demonstrated every bypassed graft patent in each patient. The LVG demonstrated perioperative changes of left ventricular dimension. The mean values of postoperative LVEF (0.36 ± 0.09 in group M and 0.38 ± 0.07 in group C) significantly improved in both groups compared to the preoperative LVEF; however, there was no significant difference between the groups. Nor was there any significant difference between postoperative LVEDVI (128 ± 34 ml/m^2 in group M vs. 120 ± 30 ml/m^2 in group C) and LVESVI (84 ± 22 ml/m^2 in group M vs. 78 ± 20 ml/m^2 in group C) following LVR between the two groups. The LVR procedure achieved approximately a 40% reduction of LVEDVI and LVESVI in both groups, compared to the preoperative value.

Discussion

Milrinone has been shown to increase CO and improve hemodynamics in a variety of cardiac surgical and CHF patients. For the treatment of cardiac surgical patients who had deteriorating ventricular function, Bailey et al.⁵ and Butterworth et al.⁷ recommended a loading dose of 50 $\mu\text{g}/\text{kg}$ intravenous milrinone followed by a continuous infusion of 0.5 $\mu\text{g}/\text{kg}/\text{min}$ to maintain therapeutic plasma concentrations, leading to hemodynamic stability after separation from CPB. Feneck⁸ also studied 99 adult patients after elective cardiac operation with a low CO. In his study, milrinone treatment resulted in a rapid, well-sustained, and highly significant increase in CI and significant reductions in systemic vascular resistance and pulmonary vascular resistance (PVR). Further analysis revealed that a low CI (1.59 $\text{L}/\text{min}/\text{m}^2$), high-resting PVR (> 200 $\text{dynes s}/\text{cm}^5$), and low mean arterial pressure (64 mmHg) prior to treatment were predictors of a good therapeutic response to milrinone.⁹ The other placebo-controlled study⁶ and double-blind study¹³ demonstrated the benefits of milrinone in facilitating the weaning of high-risk patients from CPB. These clinical reports concluded that intravenous milrinone was an effective therapy for treatment in cardiac surgery, leading to successful

withdrawal from CPB despite low output states.

Using both standard hemodynamic measures and echocardiography, Kikura et al.¹⁴ studied the effects of milrinone in cardiac surgical patients immediately after separation from CPB. The results of the study also indicated that milrinone improved LV function and hemodynamics in patients who were undergoing treatment with catecholamines, vasodilators, or both under constant loading conditions maintained by volume reinfusion from the CPB reservoir. Milrinone administration significantly increased CI, stroke volume index, and velocity of circumferential fiber shortening. The increase in the velocity of circumferential fiber shortening indicated a positive inotropic effect of milrinone in cardiac surgical patients.

Low output syndrome has been demonstrated to be common among patients with larger hearts during postoperative periods. Postinfarction LV aneurysm, as a result of ischemic cardiomyopathy, is an extreme example of adverse remodeling that leads to a progressive deterioration of function with symptoms and signs of CHF.^{15,16} The progressive deterioration of cardiac function in patients with ischemic cardiomyopathy has been demonstrated to be associated with a down-regulation of β_1 -adrenergic receptors.^{17,18} Although the mechanism of action of catecholamines is a stimulation of cAMP production, milrinone potentiates action of these agents by inhibiting the breakdown of cAMP.³ This may be particularly important in patients who experienced CHF during postoperative periods, because β_1 -adrenergic receptors can be down-regulated in this population. Therefore when LVR surgery is performed in patients with impaired LV, milrinone, in addition to catecholamine therapy, can provide effective inotropic support.

In this study, although the preoperative variables demonstrated that both groups of patients had extremely poor preoperative LV function, perioperative hemodynamic variables were maintained within a favorable range in both groups. Some preoperative data of LV functions, including E/A ratio and LVEDP, were very likely to be much worse in patients having postoperative treatment of milrinone, compared to the control patients. However, the administration of milrinone could avoid the postoperative doses of dobutamine and epinephrine and could maintain stable postoperative hemodynamics.

References

1. Silver PJ. Biochemical aspects of inhibition of cardiovascular low (Km) cyclic adenosine monophosphate phosphodiesterase. *Am J Cardiol* 1989; **63**: 2–8A.
2. Rocci ML Jr, Wilson H. The pharmacokinetics and pharmacodynamics of newer inotropic agents. *Clin Pharmacokinet* 1987; **13**: 91–109.
3. Levy JH, Ramsay J, Bailey JM Jr. Pharmacokinetics and pharmacodynamics of phosphodiesterase-III inhibitors. *J Cardiothorac Anesth* 1990; **4** (Suppl 5): 7–11.
4. Harrison SA, Chang ML, Beavo JA. Differential inhibition of cardiac cyclic nucleotide phosphodiesterase isozymes by cardiotonic drugs. *Circulation* 1986; **73** (3 Pt 2): III109–16.
5. Bailey JM, Levy JH, Kikura M, Szlam F, Hug CC Jr. Pharmacokinetics of intravenous milrinone in patients undergoing cardiac surgery. *Anesthesiology* 1994; **81**: 616–22.
6. Doolan LA, Jones EF, Kalman J, Buxton BF, Tonkin AM. A placebo-controlled trial verifying the efficacy of milrinone in weaning high-risk patients from cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1997; **11**: 37–41.
7. Butterworth JF IV, Hines RL, Royster RL, James RL. A pharmacokinetic and pharmacodynamic evaluation of milrinone in adults undergoing cardiac surgery. *Anesth Analg* 1995; **81**: 783–92.
8. Feneck RO. Effects of variable dose milrinone in patients with low cardiac output after cardiac surgery. European Multicenter Trial Group. *Am Heart J* 1991; **121** (6 Pt 2): 1995–9.
9. Feneck RO. Intravenous milrinone following cardiac surgery: II. Influence of baseline hemodynamics and patient factors on therapeutic response. The European Milrinone Multicentre Trial Group. *J Cardiothorac Vasc Anesth* 1992; **6**: 563–7.
10. Kazui T, Osada H, Fujita H; Japanese Association for Thoracic Surgery Committee for Scientific Affairs. Thoracic and cardiovascular surgery in Japan during 2004. *Jpn J Thorac Cardiovasc Surg* 2006; **54**: 363–5.
11. Athanasuleas CL, Stanley AW, Buckberg GD, Dor V, Di Donato M, et al.; RESTORE Group. Surgical anterior ventricular endocardial restoration (SAVER) for dilated ischemic cardiomyopathy. *Semin Thorac Cardiovasc Surg* 2001; **13**: 448–58.
12. Dor V, Di Donato M, Sabatier M, Montiglio F, Civaia F; RESTORE Group. Left ventricular reconstruction by endoventricular circular patch plasty repair: a 17-year experience. *Semin Thorac Cardiovasc Surg* 2001; **13**: 435–47.
13. Möllhoff T, Schmidt C, Van Aken H, Berendes E, Buerkle H, et al. Myocardial ischemia in patients with impaired left ventricular function undergoing coronary artery bypass grafting—milrinone versus nifedipine. *Eur J Anesthesiol* 2002; **19**: 796–802.
14. Kikura M, Levy JH, Michelsen LG., Shanewise JS, Bailey JM, et al. The effect of milrinone on hemodynamics and left ventricular function after emergence from cardiopulmonary bypass. *Anesth Analg* 1997; **85**: 16–22.
15. Braunwald E, Pfeffer MA. Ventricular enlargement and remodeling following acute myocardial infarction: mechanism and management. *Am J Cardiol* 1991; **68**: 1–6D.
16. Gaudron P, Eilles C, Kugler I, Ertl G. Progressive left ventricular dysfunction and remodeling after myocardial infarction. Potential mechanisms and early predictors. *Circulation* 1993; **87**: 755–63.
17. Feldman AM, Bristow MR. The β -adrenergic pathway in the failing heart: Implications for inotropic therapy. *Cardiology* 1990; **77** (Suppl): 1–32.
18. Weber KT, Janicki JS, Jain MC. Enoximone (MDL 17,043) for stable, chronic heart failure secondary to ischemic or idiopathic cardiomyopathy. *Am J Cardiol* 1986; **58**: 589–95.