Effects of Single Administration of a Phosphodiesterase III Inhibitor During Cardiopulmonary Bypass

— Comparison of Milrinone and Amrinone —

Yoshihiro Hamada, MD; Kanji Kawachi, MD; Tetsuya Yamamoto, MD; Tatsuhiro Nakata, MD;
Yasuaki Kashu, MD; Motomichi Sato, MD; Yuji Watanabe, MD

The effects of phosphodiesterase III (PDE III) inhibitors administered after aortic declamping during cardiopulmonary bypass (CPB) for open heart surgery were investigated. Ten patients (group M) were administered milrinone (50 µg/kg) after aortic declamping during CPB, 10 patients were administered amrinone (1 mg/kg) at the same time during their surgery (group A), and 10 patients served as controls with no drug administered (group C). Soon after bolus infusion of the PDE III inhibitor, perfusion pressure dropped significantly in groups M and A. However, after release of CPB and at the end of surgery, there was no difference in aortic pressure between the 3 groups. There were also no differences between the groups in heart rate, pulmonary artery pressure, and pulmonary capillary wedge pressure. After weaning from CPB, the cardiac index was high and systemic vascular resistance index was low in groups M and A. There were no significant differences in the need for additional catecholamines and time for rewarming between groups. No adverse reactions were observed. A single administration of a PDE III inhibitor during CPB was useful for post-CPB management of patients undergoing open heart surgery. Amrinone reduced perfusion pressures more than milrinone, but cardiac indices and aortic pressures after weaning from CPB showed no differences between group M and group A patients. (*Jpn Circ J* 1999; 63: 605–609)

Key Words: Amrinone; Cardiac surgery; Cardiopulmonary bypass; Milrinone; Phosphodiesterase III inhibitors

Phosphodiesterase (PDE) III inhibitors, such as milrinone and amrinone, are inotropic, vasodilatory agents that increase blood circulation by lowering vascular resistance and intense myocardial contractility. Their mechanisms of action are PDE inhibition and a consequent increase in intracellular cAMP. The higher concentration of cAMP in myocardial tissue increases its contractility, whereas in vascular smooth muscle an increase in cAMP produces a vasodilatory effect.^{1,2} PDE III inhibitors are widely used in Europe and North America to treat heart failure³ and low output syndrome after open heart surgery.⁴ They can be administered by single bolus infusion, continuous infusion, or both bolus and continuous infusion. However, few studies have reported the effects of these drugs during cardiopulmonary bypass (CPB) or their use in patients who are difficult to wean from CPB⁵ and at high risk for open heart surgery.⁶ No previous reports have compared amrinone and milrinone during open heart surgery. It has been reported that milrinone produces more intense myocardial contractility and less vasodilation than amrinone.⁷ During CPB, systemic blood flow can be easily adjusted to compensate for extreme hypotension or adverse reactions due to the vasodilatory effects of PDE III inhibitors. Therefore, in the present study, PDE III inhibitors were assessed for their usefulness during CPB

and whether any difference could be observed between milrinone and amrinone.

Methods

This study was conducted in 30 adult patients (19 men and 11 women) scheduled for elective cardiac surgery. Twenty-two patients underwent coronary artery bypass grafting (CABG) and 8 had prosthetic valve replacement. The patients ranged in age from 45 to 81 years. All patients gave informed consent and were allocated randomly to 3 groups. Ten patients received milrinone (group M), 10 received amrinone (group A), and 10 received no PDE III inhibitor (group C).

General anesthesia was established in accordance with routine clinical practice. Preparation for CPB consisted of ascending aortic cannulation and venous cannulation through the right atrial appendage for CABG and superior vena cava (SVC) and inferior vena cava (IVC) cannulation for valve replacement surgery. CPB flow was started at a perfusion index of $2.4 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ and decreased based on perfusion pressure. Mild hypothermia (rectal temperature, 32°C) was instituted immediately after the start of CPB. Myocardial protection, consisting of antegrade induction of cardioplegia, was conducted first time, crystalloid 10 ml/kg, and since second time, blood cardioplegia 5 ml/kg, was conducted every 30 min. Five minutes before ending the procedures, rewarming was started. After induction of terminal warm blood cardioplegia (1,000 ml), aortic declamping was performed, during which retrograde cardioplegia was induced continuously.

After aortic declamping, hearts started beating naturally

(Received February 22, 1999; revised manuscript received March 26, 1999; accepted April 16, 1999)

Department of Surgery II, Ehime University School of Medicine, Ehime, Japan

Mailing address: Yoshihiro Hamada, MD, Department of Surgery II, Ehime University School of Medicine Shitukawa, Sigenobu, Ehime 791-0295, Japan

Table 1 Demographic Data and Data From the Perioperative Period*

	Controls (n=10)	PDE III inhibitor	
		Milrinone (n=10)	Amrinone (n=10)
Age (years)	62.4±6.5	66.2±8.1	66.1±11
Sex (M/F)	6/4	6/4	7/3
BSA (m ²)	1.61±0.17	1.57±0.16	1.57±0.23
CPB time (min)	138±24	153±54	158±28
Aortic clamp time (min)	99.2±27	118±48	108±22
Procedure (N)			
CABG	7	6	9
AVR	1	2	1
MVR	2	1	0
AVR+MVR	0	1	0

*No intergroup differences were significant.

BSA, body surface area; CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; AVR, aortic valve replacement; MVR, mitral valve replacement.

Table 2 Effects of PDE III Inhibitors (Amrinone 1 mg/kg, Milrinone 50 µg/kg) on Hemodynamics

	Pre-CPB			Post-CPB			Post op		
	C	M	A	C	M	A	C	M	A
HR (beats/min)	70.5±8.3	71.6±21	70.5±19	105±6.8	105±3.5	111±13	104±4.2	106±8.8	106±11
MAP (mmHg)	77.6±13	79.4±13	75.4±13	78.0±15	68.6±17	64.7±10	83.9±9.4	86.5±19	84.8±14
PA (mmHg)	14.2±2.9	14.6±3.7	15.7±5.8	18.0±3.7	18.9±4.5	17.7±4.6	20.0±5.0	21.1±1.2	21.3±4.1
PCWP (mmHg)	8.60±2.1	9.20±3.4	9.00±5.5	9.70±2.5	10.5±2.0	10.9±5.5	10.4±1.3	10.5±1.1	11.4±5.1
CVP (mmHg)	7.20±1.5	7.70±2.9	7.60±4.9	8.00±1.9	8.80±1.6	9.10±4.6	8.80±0.79	8.60±0.9	9.60±4.3
CI (L·min ⁻¹ ·m ⁻²)	2.78±0.32	2.58±0.55	2.51±0.64	3.13±0.68	4.61±0.63	4.57±0.70	3.27±0.78	3.51±1.2	3.55±0.70
LVS WI (g·m/m ²)	36.8±5.8	37.2±14	33.9±8.7	28.1±11	33.7±9.2	29.9±9.2	31.9±10	32.6±7.0	33.0±9.8
SVRI (dynes·s·m ⁻⁵ ·m ²)	2080±610	2250±390	2250±570	1900±680	1080±440	989±270	2000±420	1990±820	1783±510
PVRI (dynes·s·m ⁻⁵ ·m ²)	164±45	166±94	208±74	226±83	154±82	116±67	285±190	265±71	228±67

Symbols denote significance (*p<0.05, **p<0.01) compared to the control group.

C, control group; M, milrinone group; A, amrinone group; CPB, cardiopulmonary bypass; MAP, mean arterial pressure; PA, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure.

without defibrillating in all patients. PDE III inhibitors (milrinone 50 µg/kg or amrinone 1 mg/kg, which are the dosages recommended by the manufacturers) were infused into the venous reservoir. During and after infusion of PDE III inhibitors, perfusion flow was kept constant at a rate of 2.3 L·min⁻¹·m⁻² and did not change. Heart rate and perfusion pressure were recorded before infusion and at 5 and 10 min after infusion. When the perfusion pressure could not be maintained above 40 mmHg, metaraminol bitartrate 1 mg was infused. However, we did not change the perfusion index. About 5 min before weaning from CPB, dopamine 5 µg·kg⁻¹·min⁻¹ and nitroglycerin 0.4 µg·kg⁻¹·min⁻¹ were routinely administered as a continuous infusion. Thirty minutes after aortic declamping, when patients had a rectal temperature of at least 34°C, separation from CPB was initiated. Upon successful separation from CPB, patients were transfused from the reservoir of the pump-oxygenator until the pulmonary capillary wedge pressure (PCWP) exceeded 8 mmHg to maintain adequate arterial pressure. Dopamine doses were titrated to achieve systolic blood pressure >90 mmHg. PDE III inhibitors were infused as a single administration, not as a continuous infusion.

Mean arterial pressure, heart rate, mean pulmonary artery pressure, pulmonary capillary wedge pressure and central venous pressure were recorded before starting CPB, soon after weaning from CPB, and after the end of surgery. Cardiac output (CO) was measured using a Swan-Ganz catheter. The following hemodynamic data were calculated

from these measurements.

- (1) Cardiac index (CI) = CO/BSA (L·min⁻¹·m⁻²)
- (2) Left ventricular stroke work index (LVS WI) = (Ao-LA)·SVI·0.0136 (g·m/m²)
- (3) Systemic vascular resistance index (SVRI) = {(Ao-RA)/CI}·79.92 (dynes·s·cm⁻⁵·m²)
- (4) Pulmonary vascular resistance index (PVRI) = {(PA-LA)/CI}·79.92 (dynes·s·cm⁻⁵·m²)

where BSA is body surface area (m²), SVI is CI/heart rate (ml/m²·beats), Ao is mean aortic pressure (mmHg), LA is left atrial pressure (mmHg), and RA is right atrial pressure (mmHg).

The amounts of catecholamine needed at the end of surgery and the time for rewarming (the peripheral temperature reading 36.5°C) were compared between groups. The following data on respiratory function were obtained immediately after the end of surgery (under an inspired oxygen fraction of 1.0): arterial oxygen pressure (PaO₂); arterial carbon dioxide pressure (PaCO₂); central venous oxygen pressure (PvCO₂); arterial oxygen saturation (SaO₂); central venous oxygen saturation (SvO₂); and hemoglobin (Hb). Using these data and applying the following formulas, the respiratory index (RI) and intrapulmonary shunt (Qs/Qt) were calculated.

Fig 1. Effects of PDE III inhibitors (amrinone 1 mg/kg, milrinone 50 µg/kg) on perfusion pressure. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

$$RI = (\text{alveolar-arterial oxygen gradient}/PaO_2) = (713 - PaCO_2 - PaO_2)/PaO_2$$

$$Qs/Qt = [1.39 \cdot Hb \cdot (1 - SaO_2)] \div (1.39 \cdot Hb + 0.003 \cdot PaO_2 - 0.003 \cdot PvO_2 - 1.39 \cdot Hb \cdot SvO_2)$$

Statistical Analysis

All data are expressed as mean $\pm$ SD. Statistical analyses were performed using a multivariate analysis of variance for repeated measures and Scheffe's test. Values were considered statistically significant when $p<0.05$.

Results

The 3 groups were comparable in terms of age, sex, BSA, duration of CPB, and aortic clamp time (Table 1). After aortic declamping, hearts started beating normally (normal sinus rhythm) in all patients with no arrhythmias. The first attempt at weaning from CPB was successful in all patients. No patients required intraaortic balloon pumping (IABP) or experienced perioperative myocardial infarction (PMI).

Changes in major hemodynamic variables in each group before CPB, soon after weaning, and after the end of surgery are summarized in Table 2. Perfusion pressures before and after infusion of PDE III inhibitors are illustrated in Fig 1. Perfusion pressures decreased significantly 5 min after infusion of drugs in groups A and M, but group A showed a greater decrease than group M (group A vs M; $p=0.031$, group A vs C; $p<0.0001$, group M vs C $p=0.010$). Five minutes after infusion of amrinone, 3 patients in group A required administration of metaraminol bitartrate in order to maintain perfusion pressure above 40 mmHg. However, even 10 min after infusion the perfusion pressures were lower in group A than in group M (group A vs M; $p=0.0051$). After weaning from CPB and soon after the end of surgery, no significant change in mean arterial pressure (MAP) was observed in any group (Table 2).

The amount of dopamine needed immediately after

Fig 2. Effects of PDE III inhibitors (amrinone 1 mg/kg, milrinone 50 µg/kg) on heart rate. No intergroup differences were significant.

surgery was $6.10 \pm 2.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in group C, $6.26 \pm 1.8 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in group M, and $6.71 \pm 1.9 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in group A, with no significant difference between groups. There was no need for noradrenaline or adrenaline in any group.

CI increased significantly after weaning from CPB in groups A and M, but there was no difference in CI between the 2 groups. Similarly, no differences in CI between groups A, M, and C were observed at the end of surgery. The SVRI was lower in groups A and M than in group C soon after weaning from CPB, but at the end of surgery that difference disappeared (Table 2). The PVRI was lower in group A than in group C soon after weaning from CPB, but at the end of surgery that difference also disappeared. There was no difference in LVSWI between any group during the perioperative period.

There were no differences between groups in rewarming time (145 ± 33 min in group C, 157 ± 48 min in group M, and 122 ± 29 min in group A). Respiratory indices were 0.502 ± 0.13 in group C, 0.921 ± 0.73 in group M, and 1.00 ± 0.47 in group A (before CPB: group C, 0.465 ± 0.23 ; group M, 0.339 ± 0.13 ; group A, 0.418 ± 0.20), and there were no differences ($p=0.319$). Qs/Qt was $9.96 \pm 1.8\%$ in group C, $12.5 \pm 4.2\%$ in group M, and $20.5 \pm 3.9\%$ in group A (before CPB: group C, $8.77 \pm 2.8\%$; group M, $7.68 \pm 2.4\%$; group A, $12.6 \pm 4.1\%$), and there were differences between group A and M ($p=0.0011$) and between group C and A ($p=0.0007$). After surgery, platelet counts decreased due to the influence of CPB, but there were no differences between groups (before operation: group C, $23.0 \pm 3.4 \cdot 10^4/\mu\text{l}$; group M, $21.3 \pm 4.7 \cdot 10^4/\mu\text{l}$; group A, $24.2 \pm 7.1 \cdot 10^4/\mu\text{l}$; after operation: group C, $8.85 \pm 2.3 \cdot 10^4/\mu\text{l}$; group M, $7.01 \pm 1.8 \cdot 10^4/\mu\text{l}$; group A, $8.01 \pm 1.9 \cdot 10^4/\mu\text{l}$).

Discussion

Recently, cardiac surgery has been performed without CPB in cases such as minimally invasive direct CABG (MIDCAB)⁸ However, almost all other surgeries require

CPB and induction of cardiac arrest. Cardiac surgery can be followed by the development of acute myocardial dysfunction due to cardiac ischemia and reperfusion after weaning from CPB, and therefore the length of CPB is very important. In patients with preoperative left ventricular dysfunction, there is a greater decrease in cardiac function after weaning from CPB, and in some instances this results in low CO syndrome or multiple organ failure. Therefore during open heart surgery in patients with left ventricular dysfunction, the most important problem occurs in the period immediately before and after weaning from CPB. Inotropic agents have traditionally been administered during this period, but positive inotropic agents such as dopamine and norepinephrine increase not only myocardial contractility but also vascular resistance. Therefore use of these agents may increase afterload and contribute to increased burden on the heart.

PDE III inhibitors such as milrinone and amrinone have inotropic and vasodilatory action without affecting beta receptors. Consequently their use is expected to increase CO and dilate peripheral vessels, without increasing oxygen demand in myocardial tissue.⁹⁻¹¹ However, if these agents are used after weaning from CPB, aortic pressure may drop under the influence of their vasodilatory action. Therefore their use after weaning from CPB requires skill and caution. Numerous studies have reported their use after weaning from CPB^{4,12-17} but few have reported the effects of these drugs during CPB¹⁸ or their use in patients who were difficult to wean from CPB⁵ or were at high risk for open heart surgery.⁶ To the authors' knowledge, there have been no previous reports comparing amrinone and milrinone in patients undergoing cardiac surgery. In the present study, PDE III inhibitors were used under conditions in which systemic blood flow could be controlled. When the systemic flow is fixed, perfusion pressure drops due to vasodilation. However, if the perfusion index of CPB is increased, perfusion pressure can be easily raised in response to hypotension. Therefore we used PDE III inhibitors during CPB.

After weaning from CPB, there were no differences in MAP between the 3 groups. The peripheral vascular resistance could be decreased with an accompanying rise in CO. This is beneficial in patients with left ventricular dysfunction. At the end of surgery, intergroup differences in CI and SVRI disappeared. The reason for this is thought to be that the half-life of milrinone is 1.7 h¹⁹ and that of amrinone 2.6 h²⁰.

When cardiac surgery is performed in patients with left ventricular dysfunction, CO must be maintained at a high level for a long time after CPB. Therefore PDE III inhibitors should be administered continuously, not given in a single administration. However, during continuous administration, vasoconstrictive agents must also be used.³ In our study, no patients had left ventricular dysfunction, and thus we gave PDE III inhibitors as a single bolus administration. The dosage of milrinone was that recommended by the manufacturer and supported by other investigators. Butterworth et al reported that 50 µg/kg and 75 µg/kg doses of milrinone produced significantly larger increases in CI than a 25 µg/kg dose; however, a 75 µg/kg dose did not produce a significantly larger increase in CI than did the 50 µg/kg dose.¹⁶ However, the amrinone dose differs in the literature,^{4,11,19} and therefore we used that recommended by the manufacturer.

The reason why there was no difference in rewarming

time between the 3 groups is that during CPB the body temperature was not lowered excessively. Vasodilatory agents such as nitroglycerine increase intrapulmonary shunt and reduce pulmonary function. Qs/Qt was higher in group A than group M and C because of the vasodilatory action of PDE III inhibitors. But RI had no differences, so it was not a problem for clinical use. The platelet count decrease that has been observed with amrinone use²¹ was not seen in any of the present groups, and complications such as arrhythmia were not observed. These findings suggest that PDE III inhibitors administered during CPB may be useful in managing weaning. PDE III inhibitors may be particularly useful in treating patients with left ventricular dysfunction when administered continuously. The infusion of 1 mg/kg amrinone decreased perfusion pressure more than did 50 µg/kg milrinone, requiring a higher dose of metaraminol bitartrate. After weaning from CPB and after surgery, the CI was the same in the A and M groups, and patients in group M were more easily managed after infusion than patients in group A.

References

- Endo M, Yamashita S, Taira N: Positive inotropic effect of amrinone in relation to cyclic nucleotide metabolism in the canine ventricular muscle. *J Pharmacol Exp Ther* 1982; **221**: 775-783
- Endo M, Yanagisawa T, Taira N, Blinks CR: Effects of new inotropic agents on cyclic nucleotide metabolism and calcium transients in canine ventricular muscle. *Circulation* 1986; **73**(Suppl III): III-117-III-133
- Anderson JL: Hemodynamic and clinical benefits with intravenous milrinone in severe chronic heart failure: Results of a multicenter study in the United States. *Am Heart J* 1991; **121**: 1956-1964
- Goenen M, Pedemonte O, Baele P, Col J: Amrinone in the management of low cardiac output after open heart surgery. *Am J Cardiol* 1985; **56**: 33B-38B
- De Hert S, Moens MM, Jorens PG, Delrue GL, De Paep RJ, Vermeyen KM: Comparison of two different loading doses of milrinone for weaning from cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1995; **9**: 264-271
- Doolan LA, Jones EF, Kalman J, Buxton B, Tonkin M: 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
- Alousi AA, Stankus GP, Stuart JC, Walton LH: Characterization of the cardiotonic effects of milrinone, a new and potent cardiac pyridine, on isolated tissues from several animal species. *J Cardiovasc Pharmacol* 1983; **5**: 804-811
- Calafiore AM, Angelini GD, Bergsland J, Salerno TA: Minimally invasive coronary artery bypass grafting. *Ann Thorac Surg* 1996; **62**: 1545-1548
- Monrad ES, Donald SB, Smith HS, Lanoue A, Braunwald E, Grossman W: Effects of milrinone on coronary hemodynamics and myocardial energetics in patients with congestive heart failure. *Circulation* 1985; **75**: 972-979
- Jentzer JH, Lejemtel TH, Sonnenblick EF, Kirk ES: Beneficial effect of amrinone on myocardial oxygen consumption during acute left ventricular failure in dogs. *Am J Cardiol* 1981; **48**: 75-83
- Monrad ES, Baim DS, Smith HS, Lanoue AS: Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. *Circulation* 1986; **73**(Suppl III): III-168-III-174
- Feneck RO: Intravenous milrinone following cardiac surgery. I. Effects of bolus infusion followed by variable dose maintenance infusion. *J Cardiothorac Vasc Anesth* 1992; **6**: 554-562
- Feneck RO: Intravenous milrinone following cardiac surgery. II. Influence of baseline hemodynamics and patient factors on therapeutic response. *J Cardiothorac Vasc Anesth* 1992; **6**: 563-567
- Das PA, Skoyles JR, Sherry KM, Peacock JE, Fox PA, Woolfrey SG: Disposition of milrinone in patients after cardiac surgery. *Br J Anaesth* 1994; **72**: 426-429
- Chang AC, Atz AM, Wernovsky G, Burke RP, Wessel DL: Milrinone: Systemic and pulmonary hemodynamic effects in neonates after cardiac surgery. *Crit Care Med* 1995; **23**: 1907-1914
- Butterworth JF IV, Hines RL, Royster RL, James RL: A pharmaco-

- kinetic and pharmacodynamic evaluation of milrinone in adults undergoing cardiac surgery. *Anesth Analg* 1995; **81**: 783–792
17. Kikura M, Levy JH, Michelsen LG, Shanewise JS, Bailey JM, Sadel SM, et al: The effects of milrinone on hemodynamics and left ventricular function after emergence from cardiopulmonary bypass. *Anesth Analg* 1997; **85**: 16–22
 18. Bailey JM, Levy JH, Rogers HG, Sziam F, Hug CC Jr: Pharmacokinetics of amrinone during cardiac surgery. *Anesthesiology* 1991; **75**: 961–968
 19. Benotti JR, Lesko LJ, McCue JE, Alpert JS: Pharmacokinetics and pharmacodynamics of milrinone in chronic congestive heart failure. *Am J Cardiol* 1985; **56**: 685–689
 20. Kullberg MP, Freeman GB, Biddlecome C, Alousi AA, Edelson J: Amrinone metabolism. *Clin Pharmacol Ther* 1981; **29**: 394–401
 21. Goldstein RA: Clinical effects of intravenous amrinone in patients with congestive heart failure. *Circulation* 1986; **73**(Suppl III): III-191–III-195