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The Effects of Olprinone Hydrochloride on Hemodynamics Status in Patients with Moderate and Severe Preoperative Cardiac Function Under Cardiac Surgery

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SUMMARY

We compared the effects of olprinone hydrochloride in 22 patients undergoing coronary artery bypass grafting, to compare effectiveness and the relationship to hemodynamics. Patients were divided into 2 groups : Group M, with moderate preoperative cardiac function (Left ventricular ejection fraction 45 % and cardiac index >2.5 ; n = 10) ; and Group S, with severe (Left ventricular ejection fraction ≤45 % and cardiac index ≤2.5 ; n = 12) preoperative cardiac function. At time of weaning from cardiopulmonary bypass, both groups were administered 15 μg/kg olprinone hydrochloride as a bolus, then 0.1 μg/kg/min olprinone hydrochloride was infused continuously. In both groups, olprinone significantly increased cardiac index and stroke volume index. Rate of increase in cardiac index and stroke volume index after administration of olprinone was higher for Group S than that of Group M for an extended period of time. Ratio of increase in heart rate was significantly lower for Group S than that of M group. Thus, olprinone hydrochloride can effectively improve hemodynamics after emergence from cardiac bypass in cardiac surgical patients with severe preoperative cardiac function.

Key Words : olprinone hydrochloride ; coronary artery bypass grafting, cardiac function

INTRODUCTION

Phosphodiesterase (PDE)-III is present in the myocardium, vascular smooth muscle, bronchial smooth muscle and platelets, and metabolizes cAMP into 5'-AMP. Olprinone hydrochloride, a specific inhibitor of PDE-III, inhibits PDE-III activity without affecting b-adrenergic receptors, and increases intracellular concentrations of cAMP by inhibiting catabolism. This agent is therefore used to treat cardiac failure due to

potent positive inotropic effects on myocardium, and vasodilatory effects on vascular smooth muscle[1~3]. Compared to other PDE-III inhibitors, such as amrinone and milrinone, olprinone hydrochloride enhances myocardial contraction more strongly but does not dilate blood vessels to the same degree[4~6], and is less likely to induce thrombocytopenia, an adverse reaction associated with PDE-III inhibitors[7, 8].

In a previous study, we reported that 15 μg/kg of olprinone hydrochloride administration followed by 0.1 μg/kg/min of continuous infusion is useful in improving cardiac function at the time of weaning from cardiopulmonary bypass (CPB) without major adverse effects[8]. However, no studies have examined differences in the effects of this administration modality with respect to preoperative cardiac function. The present

study compared the effects of olprinone hydrochloride by dividing 22 patients undergoing coronary artery bypass grafting into moderate and severe preoperative cardiac function groups.

MATERIALS AND METHODS

Subjects comprised 22 patients (14 men, 8 women) who underwent coronary artery bypass grafting at our institution. Informed written consent was obtained from each patient by explaining the purpose of the study in the presence of a cardiovascular surgeon. In all patients, morphine and scopolamine were administered intramuscularly 30 min before entering the operating room. Anesthesia was induced using fentanyl, vecuronium and either propofol or diazepam. Anesthesia was maintained with oxygen, air and fentanyl. As a muscle relaxant, diazepam or inhalation anesthetic was administered as needed. Subjects were divided into 2 groups as follows : Group M, moderate preoperative cardiac function (Left ventricular ejection fraction 45 % and cardiac index > 2.5 ; n = 10) ; and Group S, severe preoperative cardiac function (Left ventricular ejection fraction ≤ 45 % and cardiac index ≤ 2.5 ; n = 12). In both groups, after aortic declamping, 15 μg/kg of olprinone hydrochloride was administered from the CPB reservoir over a 10-min period, then 0.1 μg/kg/min was infused continuously from the middle cardiac vein until 6 h after returning to intensive care unit (ICU).

Mean arterial pressure (MAP) was measured at the radial and femoral arteries. Using a pulmonary artery catheter (OptiQ, Dynabbot, Japan) and continuous cardiac output (CO) monitor (OX3CCO computer ; Dynabbot), CO, cardiac index (CI), pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP) and mixed venous oxygen saturation (SvO$_2$) were continuously monitored to determine stroke volume (SV), stroke volume index (SVI), systemic vascular resistance (SVR), systemic vascular resistance index (SVRI), pulmonary vascular resistance (PVR) and pulmonary vascular resistance index (PVRI). Arterial blood gas analysis was conducted to calculate anesthesia time, surgery time, total CPB time, aortic blockage time, cardiopulmonary bypass weaning time after declamping, total coadministered drug dosage, total fentanyl dos-

age, and total venous anesthetic dosage. While setting the point of reference at the time when hemodynamics were stabilized after median sternotomy, blood concentration of olprinone and hemodynamics were measured 5 and 60 min after weaning from CPB, upon returning to ICU and 3 and 6 h after returning to ICU. CPB was performed at a moderately low body temperature (rectal temperature) of 32–33°C. Weaning from CPB was performed if all the following conditions were fulfilled : femoral systolic pressure ≥ 80 mmHg ; heartbeat ≥ 80 beats/min ; rectal temperature $\geq 35$$^\circ$C ; and stable hemodynamics. After the heart resumed beating, 3 μg/kg/min of dopamine and dobutamine was administered, and dosage was adjusted to maintain femoral systolic pressure at > 90 mmHg. When necessary, phenylephrine was administered intravenously, or noradrenaline was infused. Patients were excluded when > 7 μg/kg/min of dopamine and dobutamine or > 0.2 μg/kg/min of noradrenaline were administered.

Results are expressed as mean $\pm$ SD. A t-test was used for comparing results between groups, and a Wilcoxon test was used to compare results within groups. Values of $P < 0.05$ and $P < 0.01$ were considered statistically significant.

RESULTS

No significant differences in age, sex, height, body weight, anesthesia time, surgery time, CPB time, aortic clamping time, CPB weaning time or number of grafts were noted between groups (Table 1). In addition, no significant differences in dosage of coadministered drugs and fentanyl were identified between the two groups. Intraaortic balloon pumping (IABP) was employed intraoperatively before olprinone administration in 5 patients in Group S, but not in any patients in Group M.

Preadministration CO and CI were significantly lower for Group S than for Group M ($p < 0.01$), and preadministration heart rate was significantly lower for Group M than for Group S ($p < 0.01$). Nonetheless, no significant differences were identified between groups after administration of olprinone hydrochloride (Table 2).

In both groups, blood concentrations of olprinone hydrochloride were > 20 ng/ml (effective concentration) at 5 min after weaning from CPB, and were main-

Table 1   Patient background

	S group	M group
Age (years)	66 ± 6	62 ± 8
Sex	men : 8 women : 4	men : 6 women : 4
Height (cm)	158.4 ± 7.8	159.1 ± 9.5
Body weight (kg)	61.3 ± 10	60.5 ± 11
Preoperative NYHA	III ~ IV	I ~ II
Anesthesia time (min)	411 ± 107	484 ± 73
Surgery time (min)	320 ± 94	381 ± 59
CPB time (min)	131 ± 34	151 ± 24
Aortic clamping time (min)	94 ± 33	108 ± 19
CPB weaning time (min)	23 ± 8	27 ± 7
Average number of grafts	3.0 ± 0.5	3.4 ± 0.7

NYHA : New York Heart Association

CPB : Cardiopulmonary bypass   MEAN ± S.D.

Table 2   Chronological changes in CI, SVI and HR

	CI ($1 \cdot min \cdot m^{-2}$)		SVI ($ml \cdot m^{-2}$)		HR (bpm)	
	S group	M group	S group	M group	S group	M group
Pre	2.44 ± 0.4[*]	3.22 ± 0.4	29 ± 3.8[*]	44.3 ± 6.5	85.8 ± 12.0[*]	73.3 ± 10.2
CPB 5 min	4.25 ± 1.0	4.72 ± 0.6	42.4 ± 8.9	46 ± 9.3	100.3 ± 12.0	104.8 ± 18.0
CPB 60 min	4.16 ± 0.8	4.34 ± 0.7	40.9 ± 8.4	41.3 ± 7.5	102.5 ± 13.3	106.2 ± 13.8
Return to ICU	3.79 ± 0.5	4.21 ± 0.5	38.8 ± 6.7	39.3 ± 6.8	98.8 ± 12.2	108.1 ± 10.3
3 hours after	3.48 ± 0.3	3.46 ± 0.4	36.8 ± 4.2	33.2 ± 4.0	95.4 ± 13.4	104.4 ± 7.7
6 hours after	3.7 ± 0.7	3.4 ± 0.6	37.3 ± 7.7	35.1 ± 6.2	100 ± 13.0	97.1 ± 10.0

[*] : P < 0.01   L group vs N group   (MEAN ± SD)

tained above this level for an extended period of time (Fig. 1). Rate of increase in CI before and after administration was significantly higher for Group S than for Group M at 3 and 6 h after returning to the ICU. Furthermore, in Group S, rate of increase in CI was maintained at approximately 150 % until 6 h after returning to the ICU (p < 0.01) (Fig. 2).

Rate of increase in SVI before and after administration was significantly higher for for Group S than for Group M at all measurement points (p < 0.01) (Fig. 3).

Rate of increase in heart rate before and after administration was significantly lower for Group S than for Group M at all measurement points (p < 0.01) (Fig. 4).

No significant differences in rate of change in SVRI were observed before and after administration between groups, and no significant differences in S-BP, MAP, MPAP, CVP or PVRI were seen throughout the measurement period between groups. Even though dopamine (2-5 μg/kg/ml) and dobutamine (3-5 μg/kg/

ml) were administered and represented drugs that could have affected hemodynamics, no significant differences in mean and total doses were seen between groups. Noradrenaline was continuously infused to 4 patients in Group S (0.1 μg/kg/min) and 3 patients in Group M (0.1 μg/kg/min) , but this drug was only administered for approximately 1 h in both groups, ensuring that administration was discontinued before the end of surgery.

Olprinone administration was not stopped in any subject due to onset of adverse reactions such as marked hypotension or arrhythmia.

DISCUSSION

Catecholamines, such as dopamine or dobutamine, have been used as required to manage circulatory conditions following weaning from cardiopulmonary bypass, although, higher doses of catecholamines may induce adverse reactions such as peripheral vasoconstriction, positive inotropic action, arrhythmia, in-
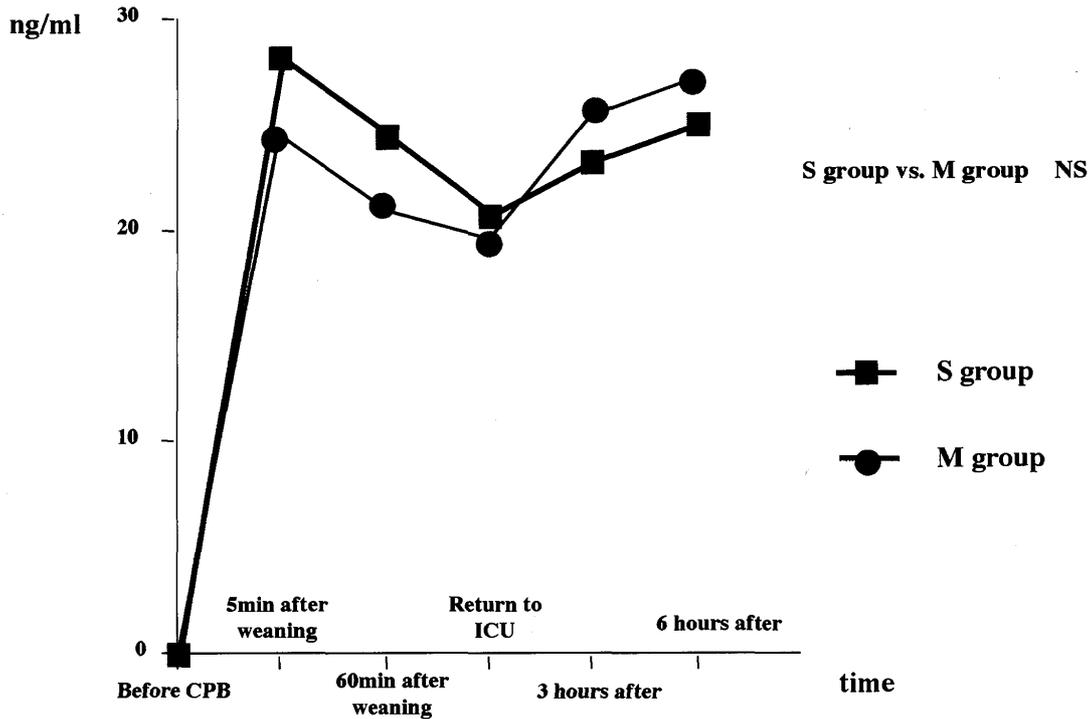
Fig. 1 Shifts in the blood concentration of olprinone hydrochloride

In both group, the blood concentration of olprinone hydrochloride was above 20 ng/ml (effective concentration) five minute after wearing from cardiopulmonary bypass, and was maintained above this level for an extended priod of time.
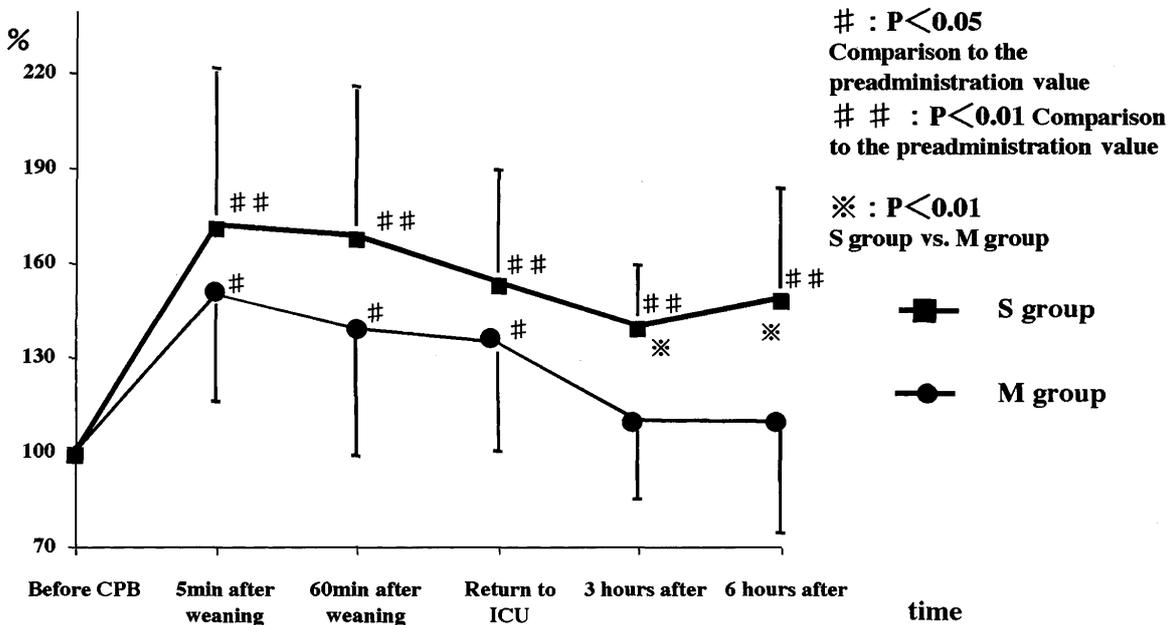

Fig. 2 Chronological shifts in the rate of change in CI （%）

The rate of increase in Cl before and after administration for S group was significantly higher than for for M group 3 and 6 hours after returning to ICU. Also, in S group, the rate of increase in Cl was maintained at approximately 150 % until 6 hours after returning to ICU.
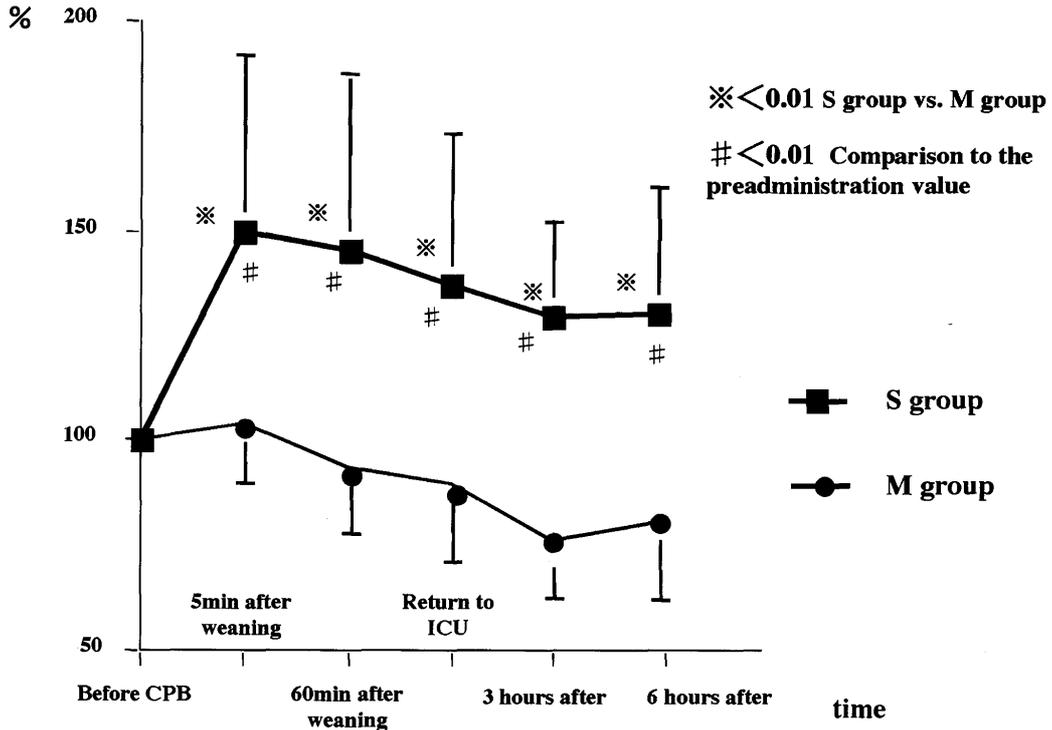
%   **200**

※<0.01 S group vs. M group

#<0.01 Comparison to the preadministration value

■ S group

● M group

5min after weaning

Return to ICU

50

Before CPB   60min after weaning   3 hours after   6 hours after   **time**

Fig. 3   Chronological shifts in the rate of change in SVI （%）
The rate of increase in SVI before and after administration for S group was significantly higher than that for M group at al measurement points.
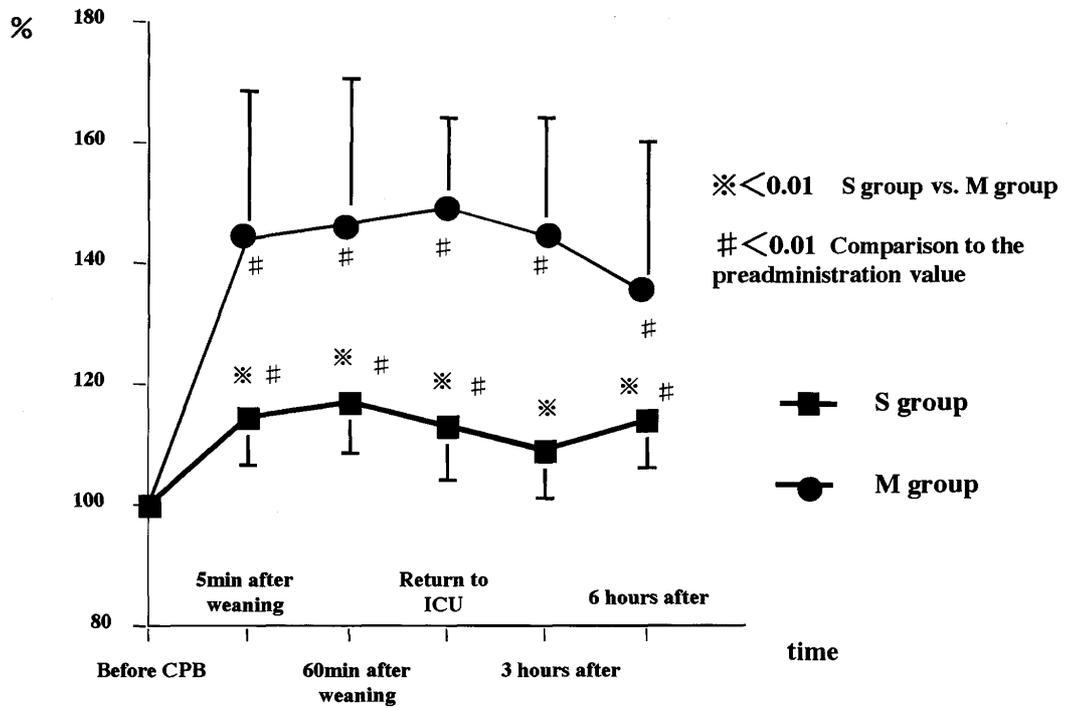
%   **180**

160

※<0.01   S group vs. M group

#<0.01   Comparison to the preadministration value

■ S group

● M group

140

120

100

5min after weaning

Return to ICU

6 hours after

80

Before CPB   60min after weaning   3 hours after   **time**

Fig. 4   Chronological shifts in the rate of change in Heart Rate （%）
The rate of increase in heart rate before and after administration for S group was significantly lower than that for M group at all measurement poits.

creased myocardial oxygen consumption, and resistance due to long-term administration[11~14]. Conversely, olprinone hydrochloride does not increase myocardial oxygen consumption, and is often used in the field of cardiac anesthesia when irritability of the myocardium is high, particularly during weaning from cardiopulmonary bypass and soon after surgery[15]. Olprinone hydrochloride efficiently improves ventricular function, and is used clinically to treat severe cardiac insufficiency, or in cases in which catecholamines are ineffective. We therefore investigated whether the effectiveness of olprinone hydrochloride differs with respect to preoperative cardiac function. The present results indicate that the effectiveness of this drug was more marked in Group S. After administration of olprinone hydrochloride in Group M, increases in CO were caused by increases in heart rate. However, increases in CO in Group S were caused by increases in SV, and this effect was maintained for an extended period of time after surgery.

In Group S, preoperative IABP was employed in 5 patients, all of whom underwent emergency surgery. However, levels of CO and CI before olprinone hydrochloride administration were significantly lower for Group S. Significant increases in CO and CI in Group S are thus unlikely to be attributable to IABP. Nevertheless, we do not deny a possible influence of IABP on our results. Transient reductions in cardiac function following weaning from CPB may contribute to low CO when left ventricular ejection fraction rate is 45% or less or in the presence of inappropriate myocardial wall movement (as in S group). Nonetheless, the present results show that olprinone hydrochloride maintained high CI levels following weaning, preventing low CO.

Preoperative β1-blockers were administered to 1 patient in Group M and 5 patients in Group S. Even though the effectiveness of catecholamines was attenuated, reactivity to olprinone hydrochloride may have been maintained. β1-adrenergic receptor down-regulation may contribute to difficulty in weaning from CPB with catecholamines and vasodilators. Since the PDE III inhibitor can bypass β1-adrenergic receptors to increase cAMP and potentiate the effects of catecholamine, the concomitant use of the PDE III inhibitor with catecholamines may provide optional treatment

for weaning from CPB. In any case, no study concerning the effectiveness of olprinone hydrochloride in relation to preoperative cardiac function has been reported previously and the present results were unable to identify the causes of significant differences in drug effectiveness.

Adrenomedullin is a hypotensive peptide that plays a role as a circulatory hormone involved in regulation of the cardiovascular system. A positive correlation exists between adrenomedullin and the concentration of compounds such as endogenous norepinephrine and c-AMP[15]. In patients with heart failure, plasma levels of adrenomedullin are known to increase have reported that when preoperative left ventricular ejection fraction is low, rate of increase in cAMP level during surgery is high[15] To explain why severe cases responded to olprinone hydrochloride, further investigation is warranted. Increased c-AMP levels in Group S may have caused differences in sensitivity to olprinone.

Hypotension must be avoided during coronary artery reconstruction, particularly when artery bypass grafts are used. MAP was maintained at >65 mmHg during the administration period, suggesting that blood flow was maintained in the major organs, and the coronary arteries in particular. In fact, no subjects suffered intraoperative myocardial ischemia as evaluated by ECG and echocardiography. Likewise, no subjects experienced S-G catheter postoperative renal insufficiency or dysfunction of other major organs. Hypotension caused by the vasodilatation effect of olprinone hydrochloride was properly treated by ensuring a sufficient volume of circulating blood or by coadministering a cardiac vasoactive agent. Preventive continuous low-dose infusion of dopamine or noradrenaline seemed effective. In the present study, olprinone hydrochloride did not cause adverse reactions such as hypotension or arrhythmia, while reduced platelets did not cause any problems with postoperative hemorrhage in any patients. These findings suggest that olprinone hydrochloride can be safely administered when irritability of the myocardium is high.

In conclusion, olprinone hydrochloride can effectively improve hemodynamics after emergence from cardiac bypass in cardiac surgical patients with severe preoperative cardiac function.

Whether similar phenomenon can be seen for the ef-

fects of other PDE-III inhibitors is unclear, but this property of olprinone appears likely to prove beneficial for patient with low cardiac function undergoing open heart surgery.

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