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High-dose Amrinone Is Required to Accelerate Rewarming from Deliberate Mild Intraoperative Hypothermia for Neurosurgical Procedures

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Background: **Since the time available to provide the cooling and rewarming is limited during deliberate mild hypothermia, the technique to accelerate the cooling and rewarming rate of core temperature has been studied. Amrinone has been reported to accelerate the cooling rate but not the rewarming rate of core temperature during deliberate mild hypothermia. The failure of amrinone effect on the rewarming rate might be due to an insufficient dose of amrinone during hypothermic conditions. The authors therefore tested whether higher doses of amrinone can accelerate the rewarming rate of core temperature during deliberate mild hypothermia for neurosurgery.**

Methods: **After institutional approval and informed consent, 30 patients were randomly assigned to one of three groups. Patients in the control group (n = 10) did not receive amrinone; patients in the AMR 15 group (n = 10) received 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ amrinone with a 1.0-mg/kg loading dose of amrinone at the beginning of cooling; and patients in the ReAMR group (n = 10) received 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ amrinone with 1.0-mg/kg loading and reloading doses of amrinone at the beginning of cooling and rewarming, respectively. Administration of amrinone was started just after the induction of cooling and continued until the end of anesthesia. Anesthesia was maintained with nitrous oxide in oxygen, propofol, and fentanyl. After induction of anesthesia, patients were cooled, and tympanic membrane temperature was maintained at 34.5°C. After completion of the main surgical procedures, patients were actively rewarmed and extubated in the operating room.**

Results: **The cooling and rewarming rates of core temperature were both significantly faster in both amrinone groups than in the control group. During the cooling and rewarming periods, forearm minus fingertip temperature gradient was significantly smaller in both amrinone groups than in the control group. During the rewarming period, heart rate and mean arterial pressure in the AMR 15 group were significantly faster and lower, respectively, than in the control group. Systemic vascular resistance in the AMR 15 group was smaller than in the control group throughout the study; on the other hand, only the value after the start of rewarming in the ReAMR group was smaller than in the control group.**

Conclusions: **Amrinone at an infusion rate of 15 or 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with a reloading at the beginning of rewarming accelerated the rewarming rate of core temperature during deliberate mild hypothermia. This suggests that high-dose amrinone is required to accelerate rewarming from deliberate mild intraoperative hypothermia for neurosurgical procedures.**

DELIBERATE mild hypothermia has been proposed as a means of providing cerebral protection during neurosurgical procedures complicated by cerebral ischemia, such as cerebral aneurysm clipping or arteriovenous malformation resection. Although the effects of mild hypothermia on neurologic outcome in such situations are still unknown,[1–3] research into techniques that allow safe management of deliberate mild intraoperative hypothermia seems warranted. This is particularly true because the time available to provide cooling and rewarming is limited.

Vasoconstriction due to hypothermia can decrease core-to-peripheral redistribution of body heat during cooling and peripheral-to-core heat transfer during rewarming, which makes intraoperative temperature management difficult. However, it has been suggested that only vasodilative therapy may not be efficient in counteracting the active vasoconstriction observed under mild hypothermic conditions.[4,5] In addition to vasoconstriction, hypothermia may reduce cardiac output,[6] resulting in a decrease in core-to-peripheral and peripheral-to-core heat flow coupled with blood flow. Therefore, intraoperative temperature management may need inotropic therapy as well as vasodilative therapy. Supplemental inotropic effect, besides a vasodilatory one, may improve peripheral circulatory insufficiency and cardiac depression due to hypothermia and may accelerate the cooling and rewarming rates of core temperature during deliberate mild hypothermia.

Amrinone is a phosphodiesterase inhibitor that has an inotropic effect in addition to a vasodilatory effect because of its dual mechanism of action.[7] In our previous study, we investigated whether 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ amrinone could affect temperature management during deliberate mild hypothermia for neurosurgery.[8] The results showed that amrinone could accelerate the cooling rate but not the rewarming rate of core temperature. The reasons for failure of amrinone effect on the rewarming rate were unknown. However, possible reasons could be that 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ amrinone may be not enough to improve thermoregulatory vasoconstriction or that the inotropic or vasodilatory effect of amrinone might be modified under mild hypothermic condition.[8] Thus, temperature management under mild hypothermic conditions might require higher-dose amrinone. In the previ-

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ous study,[8] we obtained the result of the rewarming rate of 0.7–0.8°C/h. We considered acceleration of the rewarming rate by 0.3–0.4°C/h to be clinically important because we could reduce a rewarming period of 2°C from about 3 h to 2. The present study was therefore conducted to investigate whether higher-dose amrinone can accelerate the rewarming rate of core temperature by 0.3–0.4°C/h during deliberate mild hypothermia for neurosurgery. To obtain a higher amrinone concentration during the rewarming period, we employed two methods in this study. One was a traditional high-dose method, the other was a new method, in brief, low dose and reloading at the beginning of rewarming. In this study, amrinone was administered at an infusion rate of 15 or 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with reloading at the beginning of rewarming.

Materials and Methods

After institutional approval and informed consent, 30 patients scheduled to undergo elective neurosurgical procedures while in the supine position were enrolled. The study population size was determined based on the previous study data of 10 patients.[8] We found a mean rewarming rate of 0.73°C/h (SD = 0.25). We assumed acceleration of the rewarming rate by 0.3–0.4°C/h to be clinically important. Based on the formula for normal theory and assuming a type I error protection of 0.05 and a power of 0.80, 7–12 patients in each of the three groups were required. Thus, we employed 10 patients in each group for the study population size. Patients with symptomatic ischemic heart disease, hepatic or renal disease, or coagulopathy were excluded. In addition, patients to whom vasodilators were administered were excluded. At the commencement of active cooling, patients with a tympanic temperature greater than 37.0°C or less than 36.0°C were excluded.

All patients were premedicated with 75 mg oral roxatidine (H2 blocker) 2 h preoperatively. Anesthesia was induced with 1.5–2.5 mg/kg propofol, 1–2 μg/kg fentanyl, and 0.15 mg/kg vecuronium. The trachea was intubated, and the lungs were mechanically ventilated. Anesthesia was maintained with 50–67% nitrous oxide in oxygen, 3–5 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol, and supplemented doses of fentanyl and vecuronium. Additional vecuronium was administered as required to maintain 1 to 2 mechanical twitches in response to supramaximal electrical stimulation of the ulnar nerve at the wrist. Routine monitoring included an electrocardiogram, a radial arterial catheter, a noninvasive blood pressure cuff, pulse oximetry, and a capnogram. A tympanic membrane probe was inserted in the external auditory meatus on the opposite side of surgery for temperature monitoring by using sterile copper–constantan thermocouple sensors (Mon-a-Therm thermocouples; Mallinkrodt Medical, St. Louis, MO). The probe was then taped in place, the aural canal was occluded with cotton, and the external ear was covered with a gauze pad. Skin temperature probes equipped with adhesive (Mon-a-Therm thermocouples) were placed on the surface of the thenar eminence and the index fingertip, respectively. These probes were connected to Mon-a-Therm thermometers (Mallinkrodt Medical).

A water blanket (BLANKETROL II Hyper-Hypothermia; Cincinnati Sub-Zero Products, Inc., Cincinnati, OH) was placed under each patient. A polyurethane-formed pad covered with a cotton sheet (S-K pad; Asahi Medical Co., Osaka, Japan) protected the patient from direct contact with the water blanket. A convective device blanket (Warm Touch; Mallinckrodt Medical) was applied directly to the ventral body surface. After induction of anesthesia, active cooling was started. The temperature of the water blanket was set at 5°C, and room-temperature air was circulated by the convective device. Active cooling was stopped at a tympanic membrane temperature of 35°C, and body temperature was then allowed to drift downward. Temperature settings on both the water blanket and the convective device were then adjusted to maintain a target of 34.5°C (passive cooling). After the completion of major surgical procedures, such as aneurysm clipping and tumor removal, active rewarming was instituted with the water blanket set at 41°C and the convective device at its highest setting (43°C). Active rewarming was stopped at a tympanic membrane temperature of 35.5°C, and body temperature was then allowed to drift upward. Temperature settings on both the water blanket and the convective device were then adjusted to maintain a target of 36°C (passive rewarming). After the operation, the patients were extubated in the operating room. The arm used to monitor skin temperature was excluded from the forced-air cover.

Patients were randomly assigned to one of three groups. Patients in the control group did not receive amrinone; patients in the AMR 15 group received 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ amrinone with a 1.0-mg/kg loading dose of amrinone at the start of cooling; and patients in the ReAMR group received 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ amrinone with a 1.0-mg/kg loading dose of amrinone given twice, at the start of cooling and rewarming. The administration of amrinone was started just after the induction of cooling and continued until the end of anesthesia. Loading of amrinone was performed over approximately 5–10 min. Temperatures were recorded at 15-min intervals, starting immediately after induction of anesthesia when active cooling was started (initial values). Forearm minus fingertip skin surface temperature gradients (temperature gradient) were calculated. As in the previous study, we considered a temperature gradient less than 0°C to indicate vasodilation.[9] Arterial oxygen tension (Pa_{O_2}), arterial carbon dioxide tension (Pa_{CO_2}), pH, base excess, and hemoglobin, Na, K, glucose, and arterial lactate concentrations

Table 1. Patient Characteristics, Anesthesia and Surgery Times, and Balance

	Control	AMR15	ReAMR
n	10	10	10
Age (yr)	58 ± 11	55 ± 12	61 ± 10
Sex (F/M)	6/4	6/4	5/5
Weight (kg)	54 ± 7	55 ± 9	56 ± 7
Height (cm)	156 ± 7	156 ± 10	160 ± 7
Anesthesia time (min)	353 ± 101	317 ± 81	313 ± 103
Surgery time (min)	251 ± 100	245 ± 79	224 ± 101
Infusion + transfusion (ml)	2,497 ± 745	2,861 ± 1,238	2,386 ± 801
Blood loss + urinary output (ml)	1,590 ± 783	1,492 ± 662	1,495 ± 655

Data are expressed as mean ± SD. Comparisons among the three groups were carried out using analysis of variance or chi-square test.

Control = a group of patients who did not receive amrinone; AMR 15 = group of patients who received 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ amrinone with a 1.0-mg/kg loading dose of amrinone; ReAMR = group of patients who received 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ amrinone with a 1.0-mg/kg loading dose of amrinone twice, at the start of cooling and rewarming.

were determined in arterial blood samples, using a commercial blood gas analyzer (Bayer 860; Bayer Diagnostic Manufacturing Ltd., Suffolk, United Kingdom). Blood samples were collected at the initiation of the active cooling and around the target temperature and were analyzed immediately after collection.

We determined active cooling and rewarming rates of core temperature (tympanic membrane temperature) according to the following method because these plotted values changed in a linear fashion. Active cooling and rewarming rates (°C/h) were defined as the slopes of the simple regression lines calculated from plotted core temperature values over time from the beginning of cooling to the time when the temperature reached 35°C, and from the beginning of rewarming to the time when the temperature reached 35.5°C, respectively.[8]

Cardiac output were measured by dye dilution technique using indocyanine green (ICG) at the following time points: (1) 15 min after the start of active cooling; (2) 15 min after the start of active rewarming; and (3) at the end of surgery. The ICG blood concentrations were monitored by noninvasive pulse spectrophotometry (DDG2001; Nihon Kohden Inc., Tokyo, Japan). Twenty milligrams ICG was administered in an intravenous bolus dose within 1 s *via* a cannula placed in the peripheral vein, and the blood ICG concentration was monitored *via* pulse spectrophotometry using a probe fixed on the patient's thumb. Before injection of ICG, the hemoglobin concentration, which is necessary for calculating ICG blood concentration, was measured.[10,11] At each measurement, the value was corrected for body surface area, and systemic vascular resistance index (SVRI) was also calculated.

To confirm whether the two administration methods could produce a high concentration as we expected, in five patients in the AMR 15 group and five patients in the ReAMR group, amrinone concentrations were measured at the following time points: (1) 15 min after the start of active cooling; (2) around the mild hypothermia at the target temperature; (3) 15 min after the start of active rewarming; (4) at the end of surgery; and (5) at the end of anesthesia. Each 5.0 ml of blood was drawn into a heparinized syringe, collected into a glass tube, and centrifuged for 10 min at 3,000 rpm, and 2.0 ml of each plasma sample was stored immediately at −20°C for amrinone analysis. Plasma concentrations of amrinone were determined by high-performance liquid chromatography as described by Kullberg *et al.*[12]

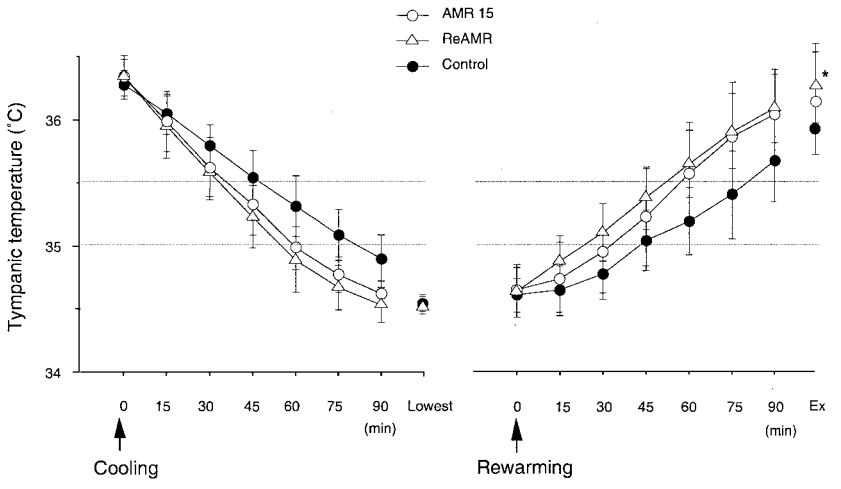

Fig. 1. Intraoperative changes in tympanic membrane temperature. Data are expressed as mean ± SD. Comparisons at Lowest and Ex among the three groups were performed using analysis of variance followed by the Dunnett test. *$P < 0.05$ *versus* the control group. AMR 15 (open circle) = a group of patients who received 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ amrinone with a 1.0-mg/kg loading dose of amrinone; ReAMR (open triangle) = a group of patients who received 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ amrinone with a 1.0-mg/kg loading dose of amrinone twice, at the start of cooling and rewarming; Control (solid circle) = a group of patients who received no amrinone; Cooling = at the start of active cooling; Rewarming = at the start of active rewarming; Lowest = at the time when tympanic temperature reached the lowest temperature; Ex = at extubation.

Table 2. Active Cooling Rate and Rewarming Rate

	Control	AMR15	ReAMR
Cooling rate (°C/h)	−0.96 ± 0.12	−1.36 ± 0.23*	−1.45 ± 0.22*
r^2 of cooling rate	0.98 ± 0.02	0.98 ± 0.01	0.99 ± 0.01
Rewarming rate (°C/h)	0.73 ± 0.31	1.02 ± 0.27*	1.04 ± 0.20*
r^2 of rewarming rate	0.91 ± 0.06	0.93 ± 0.09	0.97 ± 0.02

Data are expressed as mean ± SD. Comparisons among the three groups were carried out using analysis of variance followed by the Dunnett test.

* $P < 0.05$ *versus* the control group.

r^2 = Coefficient of determination.

Statistical Analysis

To reduce the number of tests, tympanic temperature changes during the cooling and rewarming periods were compared using a simple slope (cooling rate or rewarming rate), and changes of temperature gradient, heart rate, and mean arterial pressure were compared at defined temperature points (at the start of cooling, 35.5°C, and 35.0°C for the cooling period, and at the start of rewarming, 35.0°C, and 35.5°C for the rewarming period). Comparisons among the groups were carried out using analysis of variance (ANOVA) or ANOVA for repeated measures followed by the Dunnett test for continuous variables, and the chi-square test for nominal data. The data are expressed as mean ± SD; differences were considered significant when *P* was less than 0.05.

Results

Patient characteristics, anesthesia and surgery times, and balance are shown in table 1. Intraoperative changes in tympanic membrane temperature and the active cooling and rewarming rates are shown in figure 1 and table 2. The active cooling and rewarming rates of core temperature were both significantly faster in both amrinone groups than in the control group. Tympanic temperature at extubation was significantly higher in the ReAMR group than in the control group, although the lowest tympanic temperature was similar among the three groups.

Table 3 shows the changes in skin surface temperature gradient (forearm minus fingertip), heart rate, and mean arterial blood pressure at the defined temperature points. Temperature gradients at 35.0°C during the cooling period and at 35.0°C and 35.5°C during the rewarming period were significantly smaller in both amrinone groups than in the control group. Heart rate at the start of rewarming and at 35.0°C was significantly faster and mean arterial pressure at 35.5°C during the rewarming period was significantly lower in the AMR 15 group in than the control group.

Figure 2 shows the intraoperative changes in cardiac index and SVRI. There was no significant difference in cardiac index among the three groups. SVRIs at the all measurement points in the AMR 15 group were smaller than in the control group; on the other hand, only the value 15 min after the start of active rewarming in the ReAMR group was smaller than in the control group.

Figure 3 shows plasma amrinone concentrations in the AMR 15 and ReAMR groups. The values in the AMR 15 group kept increasing during the study and reached approximately 2.5 μg/ml at the last stage. The values in

Table 3. Changes in Forearm Minus Fingertip Skin Surface Temperature Gradient (temp grad), Heart Rate (HR), and Mean Arterial Blood Pressure (MAP) during the Cooling and Rewarming Periods

	Control	AMR15	ReAMR
Cooling			
Temp grad at cooling start	−0.58 ± 0.51	−0.71 ± 0.82	−0.80 ± 0.46
Temp grad at 35.5°C	−0.05 ± 0.80	−0.48 ± 0.52	−0.49 ± 0.70
Temp grad at 35.0°C	0.35 ± 0.05	−0.71 ± 0.55*	−0.43 ± 0.67*
HR at cooling start	71 ± 11	71 ± 12	66 ± 10
HR at 35.5°C	66 ± 13	70 ± 16	72 ± 12
HR at 35.0°C	67 ± 13	75 ± 13	71 ± 12
MAP at cooling start	77 ± 10	75 ± 5	77 ± 10
MAP at 35.5°C	83 ± 9	75 ± 5	81 ± 8
MAP at 35.0°C	84 ± 10	78 ± 9	82 ± 9
Rewarming			
Temp grad at rewarm start	0.21 ± 0.91	−0.27 ± 0.62	0.24 ± 0.85
Temp gradient at 35.0°C	0.61 ± 0.56	−0.15 ± 0.91*	−0.47 ± 0.65*
Temp gradient at 35.5°C	1.06 ± 1.19	−0.01 ± 0.51*	−0.03 ± 0.48*
HR at rewarm start	66 ± 9	72 ± 10*	66 ± 9
HR at 35.0°C	62 ± 10	74 ± 12*	69 ± 10
HR at 35.5°C	67 ± 10	72 ± 9	71 ± 8
MAP at rewarm start	84 ± 7	75 ± 11	79 ± 12
MAP at 35.0°C	85 ± 6	75 ± 11	78 ± 11
MAP at 35.5°C	87 ± 8	75 ± 7*	79 ± 7

Data are expressed as mean ± SD. Comparisons among the three groups were performed by using analysis of variance for repeated measures followed by the Dunnett test.

* $P < 0.05$ *versus* the control group.

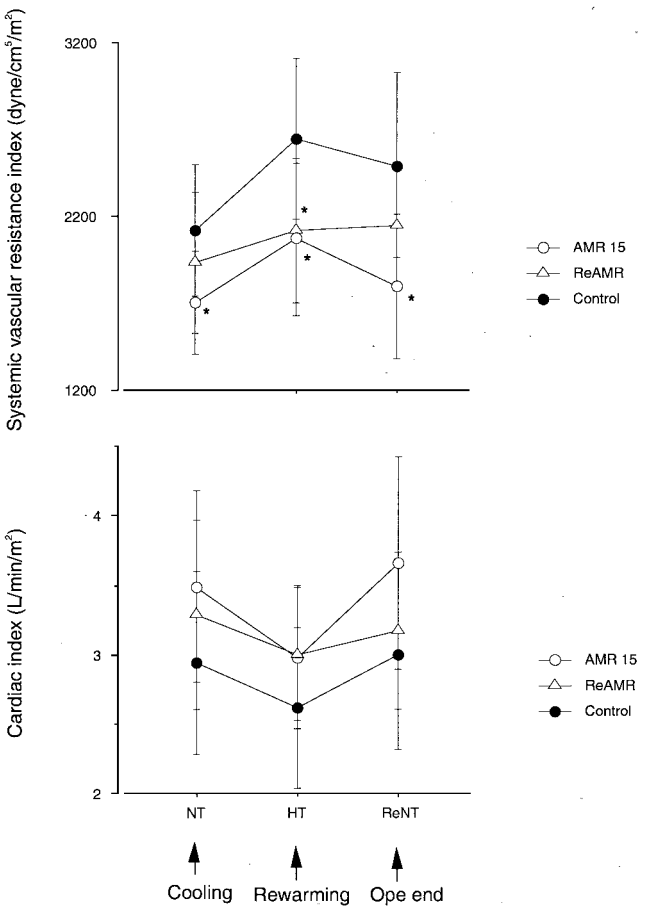

Fig. 2. Intraoperative changes in cardiac index and systemic vascular resistance index. Data are expressed as mean ± SD. Comparisons among the three groups were performed using analysis of variance for repeated measures followed by the Dunnett test. *$P < 0.05$ *versus* the control group. NT = normothermia at early phase of cooling; HT = hypothermia around target temperature; ReNT = normothermia at late phase of rewarming; Ope end = at the end of surgery. Other abbreviations are the same as for figure 1.

the ReAMR group were between 1.0 and 2.0 μg/ml during the cooling period; however, they showed manifest elevation after the start of active rewarming. After that, the values in the ReAMR group gradually decreased.

In regard to intraoperative data of arterial blood analysis, there were no significant differences among the three groups in pH, $Paco_2$, Pao_2, base excess, hemoglobin, Na, K, glucose, and lactate before or during mild hypothermia (data are not shown).

Discussion

The results in the present study revealed that intraoperative administration of 5 and 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ amrinone with a 1.0-mg/kg loading dose of amrinone accelerated the cooling rate of core temperature and successfully demonstrated that 15 and 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ amrinone with a supplemental 1.0-mg/kg reloading dose of amrinone accelerated the rewarming rate by 0.3–0.4°C/h during deliberate mild intraoperative hypothermia. These results suggest that a high dose of amrinone is required to accelerate the rewarming rate of core temperature during mild hypothermic conditions.

Previous investigators have tested the hypothesis that thermoregulatory vasoconstriction decreases cutaneous transfer of applied heat and restricts peripheral-to-core flow of heat, thereby delaying and reducing the increase in core temperature.[4,13] However, rewarming of core temperature was not affected by vasodilation by anesthetics and prostaglandin E1. We hypothesized that a supplemental inotropic effect in addition to the vasodilatory effect of amrinone would maintain peripheral circulation and cardiac output well, thereby enhancing peripheral heat gain and peripheral-to-core flow of heat, resulting in an acceleration of the rewarming rate. However, a low dose of amrinone could not affect the rewarming rate in the previous study.[8] According to the results obtained in the previous study, we hypothesized that a low dose of amrinone may be not enough to attenuate thermoregulatory vasoconstriction, or the inotropic or vasodilatory effect of amrinone might be modified under mild hypothermic conditions, which might result in rewarming from mild hypothermic condition requiring higher doses of amrinone.[8] Just as we had expected, high doses of amrinone induced by two methods applied in the present study accelerated the rewarming rates of core temperature.

Findings that support our hypothesis were found in the present study. Temperature gradient at some defined points during the rewarming were significantly lower in both amrinone groups than in the control group. Temperature gradient is considered to evaluate peripheral thermoregulatory vasoconstriction.[9,14,15] Generally, it is thought that the more a temperature gradient increases, the more vasoconstriction develops; on the other hand, the less a temperature gradient decreases, the more vasodilation develops. Besides that, SVRIs in both

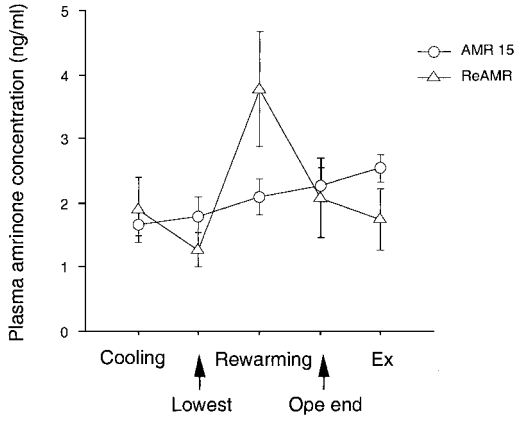

Fig. 3. Intraoperative changes in plasma amrinone concentration. Data are expressed as mean ± SD. The abbreviations are the same as for figure 1.

groups, especially in the AMR 15 group, tended to be lower compared with the control group. Thus, it seems reasonable to think that this well-maintained peripheral circulation enhanced peripheral heat gain. In regard to cardiac index, in both amrinone groups, the values tended to be larger compared with the control group, although the differences were not significant. Plattner *et al.*[16] reported that there is little restriction of heat flow between peripheral and core tissues in the case of vasodilated, anesthetized subjects. Likewise, in the vasodilated condition during the rewarming period, we could understand that peripheral-to-core heat flow would depend on cardiac output. Therefore, it is reasonable to suppose that the increasing tendency of cardiac output in both amrinone groups at least in a supplementary manner affected the rewarming period in addition to peripheral vasodilation. However, we have to add that it is uncertain whether the inotropic or the vasodilatory effect of amrinone mainly contributed to the increasing tendency of cardiac output because we did not directly assess cardiac contractility.

During the cooling period, the cooling rates in both amrinone groups were also significantly faster than in the control group. Temperature gradients were significantly lower in both amrinone groups at some defined points during the cooling period than in the control group. In addition, SVRIs in both groups, especially in the AMR 15 group, tended to be lower compared with the control group. These findings are compatible with the results obtained in the previous study.[8] Vassilieff *et al.*[17] also demonstrated that vasodilation induced by nifedipine immediately before induction of anesthesia aggravated redistribution hypothermia. Besides that, we could say that the increasing tendency of cardiac output in both amrinone groups at least in a supplementary manner affected the cooling period as well as the rewarming one.[16] Shitara *et al.*[18] have demonstrated that dobutamine accelerated the decline of core temperature in volunteers anesthetized with isoflurane. They explained that the observed phenomenon was attributed to the inotropic and vasodilatory effects by dobutamine, suggesting that the inotropic effect enhanced core-to-peripheral redistribution of heat coupled with blood flow and the vasodilatory effect enhanced cutaneous heat loss during anesthesia.[19–21] It appears that their explanation also serves as an understanding of the acceleration of the cooling rate by amrinone in the present study.

The optimal therapeutic range of plasma amrinone concentration is known to be approximately 1.0–2.0 ng/ml.[22–24] The plasma amrinone concentrations during the cooling period (before reloading for the ReAMR group) in both amrinone groups were in the optimal range. On the other hand, the values during rewarming (after reloading for the ReAMR group) were over the therapeutic range. According to our previous results using the low-dose method (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ without reloading),[8] which could maintain the optimal therapeutic range of plasma amrinone concentration, the range might be insufficient in counteracting the active vasoconstriction or improving depression of left ventricular contractility under completed mild hypothermic conditions. The early phase of rewarming might require over-therapeutic concentrations to overcome active thermoregulatory vasoconstriction and depression of left ventricular contractility. In the present study, the administration method of low-dose amrinone with reloading was applied to obtain a temporary over-therapeutic amrinone concentration at the start of rewarming. The reloading method could temporarily produce the high concentration in the present study. In spite of temporary over-therapeutic concentrations, the reloading method was as effective for rewarming as the high-dose method (the AMR 15 group), which maintained the over-therapeutic concentrations during the rewarming period. These findings suggest that the optimal therapeutic range of amrinone concentration is enough for the cooling induction but that over-therapeutic concentrations are required for the rewarming induction.

The higher therapeutic concentration of amrinone has a higher possibility of side effects, especially hypotension, with continuous high-dose infusion of amrinone.[25–27] This appeared to be the reason that heart rates and mean arterial pressure in the AMR 15 group at some defined points during the rewarming period were faster and lower, respectively, than the control group. However, those hypotension and tachycardia values were not unacceptable for anesthetic management and did not necessitate any treatment; in fact, the observed tachycardia in the amrinone groups seemed desirable rather than unacceptable as prevention against bradycardia due to hypothermia.[28] However, we should pay attention to accidental hypotension due to amrinone, especially in patients who demonstrate cardiovascular instability prior to anesthesia. Also, tachycardia could increase myocardial oxygen consumption; thus, we should also pay attention to accidental myocardial ischemia, especially in patients who have coronary arterial disease. With more suitable methods that have fewer side effects, low-dose amrinone with reloading may be practical for the management of intraoperative hypothermic therapy. Needless to say, we should pay attention to accidental hypotension and tachycardia in any case of amrinone use.

As another concern of the rewarming period, postoperative rebound hyperthermia has been reported.[1] However, postoperative rebound hyperthermia was not observed in the present study. The passive rewarming method employed in this study might contribute to preventing postoperative rebound hyperthermia. In this study, the tympanic temperature at extubation in the ReAMR group (far over 36.0°C) was significantly higher

than that of the control group in spite of stopping active rewarming. This might suggest that lack of most careful temperature management would have caused postoperative rebound hyperthermia, especially in the ReAMR group.

We cannot deny that our present study has some limitations. First, we failed to show significant differences in cardiac index throughout the study in both amrinone groups compared with the control group, although the amrinone groups showed a tendency for higher cardiac index. The results might have been ascribed to the limitation that this present study population was made up by a relatively small number of patients. However, we do not think that it was a serious problem because in this study population we could successfully demonstrate the main end point of this study, which was to show that both amrinone groups accelerated the rewarming rate. Otherwise, the results might suggest that the acceleration of rewarming rate was mainly attributed to the vasodilatory effect of amrinone rather than inotropic effect of it. Second, we did not use any methods other than temperature gradients to assess peripheral circulation. Plethysmography or laser Doppler flowmetry would have assessed peripheral circulation more appropriately in this study. However, a previous study demonstrated that skin surface temperature gradients correlate well with laser Doppler flowmetry.[29] Therefore, it is not unreasonable to think that application of temperature gradients was appropriate to assess peripheral circulation. Third, in regard to the validity of cardiac output measurement by dye dilution technique using ICG under mild hypothermia, the concern has not been investigated as far as we know. However, we think that the method is also valid under mild hypothermia because the pulse spectrophotometer could detect pulse wave well and continuously, although it changed to some extent. In addition, we do not think that mild hypothermia of 34.5°C is low enough to disturb pulse wave detection completely. Finally, one may suppose that the effect of amrinone on rewarming rate is small and may offer little clinically significant advantage because amrinone was applied to rewarm the patients under deliberate mild hypothermia of 34.5°C in this study. However, we believe that amrinone would be also effective to rewarm from deliberate moderate hypothermia, *e.g.*, 32–33°C, or accidental hypothermia if amrinone were to be applied to such a situation.

In summary, we investigated the effects of amrinone on the cooling and rewarming rates during deliberate mild intraoperative hypothermia for neurosurgery. The administration of 5 and 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ amrinone with a 1.0-mg/kg loading dose of amrinone similarly accelerated the cooling rate of core temperature. In contrast with the previous study, to accelerate the rewarming rate of core temperature, intravenous amrinone at an infusion rate of 15 or 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with a supplemental 1.0-mg/kg reloading dose of amrinone was required. These results suggest that a high dose of amrinone is required to accelerate the rewarming rate of core temperature during mild hypothermic conditions. The optimal method of amrinone administration is unknown. However, considering the efficacy of low-dose amrinone on the cooling rate and hypotensive effect of high-dose amrinone during the hypothermic conditions, the reloading method combined with a low-dose infusion of amrinone may be practical for this purpose.

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