Minimally-Diluted Blood Cardioplegia Supplemented With Potassium and Magnesium for Combination of ‘Initial, Continuous and Intermittent Bolus’ Administration

Yoshitaka Hayashi, MD; Masakatsu Ohtani, MD; Yoshiki Sawa, MD*; Taizo Hiraishi, MD; Hiroshi Akedo, MD; Yasuhiro Kobayashi, MD; Hikaru Matsuda, MD*

Background The present study was designed to examine the hypothesis that minimally-diluted blood cardioplegia (BCP) supplemented with potassium and magnesium provides superior myocardial protection in comparison with the standard-diluted BCP for a combination of ‘initial, continuous, and intermittent bolus’ BCP administration.

Methods and Results Seventy patients undergoing elective coronary revascularization between 1997 and 2001 (M: F = 55:15, mean age 67.6 ± 7.5 years) were randomly divided into 2 groups: Group C (n = 35) was given the standard 4:1-diluted blood-crystalloid BCP, and Group M (n = 35) was given minimally-diluted BCP supplemented with potassium-chloride and magnesium-sulfate. The BCP temperature was maintained at 30°C. Cardioplegic arrest was induced with 2 min of initial antegrade BCP infusion, followed by continuous retrograde BCP infusion. Intermittent antegrade BCP was infused every 30 min for 2 min. The time required for achieving cardioplegic arrest was significantly shorter in Group M (47.5 ± 16.3 vs 62.5 ± 17.6 s, p < 0.0001). The number of patients showing spontaneous heart beat recovery after reperfusion was significantly larger in Group M (28 vs 15, p = 0.0029), and the number of patients suffering from atrial fibrillation during the postoperative period was significantly smaller in Group M (n = 3 vs 11, p = 0.034). Both the postoperative maximum dopamine dose (3.57 ± 2.46 vs 5.44 ± 2.23 μg/kg per min, p = 0.0014) and peak creatine kinase-MB (19.5 ± 8.5 vs 25.8 ± 11.9 IU/L, p = 0.0128) were significantly less in Group M. The number of patients showing paradoxical movement of the ventricular septum in the early postoperative echocardiography was significantly smaller in Group M (9 vs 24, p = 0.0007).

Conclusions These results suggest that ‘initial, continuous and intermittent bolus’ administration of minimally-diluted BCP supplemented with potassium and magnesium is a reliable and effective technique for intraoperative myocardial protection. ( Circ J 2004; 68: 467–472)

Key Words: Continuous and intermittent perfusion; Echocardiography; Intraoperative myocardial protection; Magnesium; Minimally-diluted blood cardioplegia

Blood cardioplegia (BCP) has been gaining clinical popularity for intraoperative myocardial protection because of its more physiological composition containing natural free-radical scavengers.1–3 However, the most effective way of BCP administration remains controversial, and current preferences to warm heart operation further require its establishment.4–6 Despite poor visualization of the operative field, continuous BCP administration has been suggested as preferable for meeting increased myocardial energy demand and avoiding warm ischemic injury under normothermic conditions.7–8 Intermittent or retrograde BCP administration appears insufficient for adequate myocardial protection in terms of possible normothermic ischemia or incomplete perfusion, although several advantages have been demonstrated under tepid-thermic cardioplegic arrest.9–11 Regarding the characteristics of each delivery technique, a combination of ‘initial, continuous, and intermittent bolus’ BCP administration seems to compensate for each demerit.

For clinical application of ‘initial, continuous, and intermittent bolus’ BCP administration, there remains a problem to be solved. Hemodilution caused by crystalloid volume in the cardioplegia solution enhances tissue water retention and myocardial damages after ischemia–reperfusion.12,13 ‘Initial, continuous, and intermittent bolus’ BCP administration can infuse a large amount of crystalloid solution into the myocardium, which may nullify the advantages of BCP.

In recent reports, minimally-diluted oxygenated blood with a concentrated arresting agent such as potassium has been proposed as an alternative cardioplegic vehicle to the...
standard BCP.14,15 The minimal dilution technique is thought to increase the oxygen-carrying capacity during cardioplegia administration and reduce hemodilution-induced deleterious effects on myocardial protection.12–15 Furthermore, Hayashida et al demonstrated that minimally-diluted BCP protects the myocardium in association with preservation of myocardial metabolic activity after ischemia–reperfusion.16 In fact, minimally-diluted BCP has been used for intraoperative myocardial protection.16,17 There had been a focus on minimal additive agents that improve the myocardial protective effect of minimally-diluted BCP. As for the mechanism of myocardial ischemia–reperfusion, calcium overloading is considered a crucial factor that enhances myocardial injury after reperfusion.18 In addition, hyperkalemic cardioplegia solution partially depolarizes the cardiac myocyte membrane and may facilitate opening of the L-type calcium-channels.19 Magnesium is known to block the L-type calcium-channels and preserves myocardial intracellular metabolites after ischemia–reperfusion.19,20 Therefore, there is strong interest in effects of adding magnesium to minimally-diluted BCP.21,22

In the present study, we used a combination of ‘initial, continuous, and intermittent bolus’ BCP administration using 2 types of BCP, and examined the hypothesis that minimally-diluted BCP supplemented with potassium and magnesium provides superior myocardial protection in comparison with the standard-diluted BCP.

Methods

Study Population

Seventy consecutive patients who underwent elective coronary artery bypass grafting under cardiopulmonary bypass (CPB) in Osaka Minami National Hospital between 1997 and 2001 were enrolled in the present study. Fifty-five were men and 15 were women, and their ages at operation ranged from 47 to 83 years with a mean of 67.6±7.5 years. All patients gave their informed consent for the present study, and we followed the guidelines of the internal review board. The investigation conforms to principles outlined in the Declaration of Helsinki (Cardiovasc Res 1997; 35: 2–3).

The patients were prospectively randomized into one of 2 groups according to the cardioplegic solution used for intraoperative myocardial protection. Group M (n=35) was given minimally-diluted BCP supplemented with potassium-chloride and magnesium-sulfate, whereas Group C (n=35) was given the standard 4:1-diluted blood-crystalloid BCP and served as controls.

<table>
<thead>
<tr>
<th>Group C (n=35)</th>
<th>Group M (n=35)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at operation (years) 69.1±6.9</td>
<td>66.2±7.9</td>
<td>0.1165</td>
</tr>
<tr>
<td>M/F 23/12</td>
<td>26/9</td>
<td>0.5613</td>
</tr>
<tr>
<td>Bodyweight (kg) 58.5±9.4</td>
<td>59.7±9.2</td>
<td>0.5758</td>
</tr>
<tr>
<td>Preoperative ejection fraction (%) 52.0±15.3</td>
<td>49.6±15.1</td>
<td>0.4615</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min) 170.5±47.9</td>
<td>185.4±52.9</td>
<td>0.3216</td>
</tr>
<tr>
<td>Aortic cross-clamping time (min) 105.5±36.0</td>
<td>116.1±40.2</td>
<td>0.2490</td>
</tr>
<tr>
<td>No. of grafts 2.62±0.95</td>
<td>2.74±0.92</td>
<td>0.5804</td>
</tr>
</tbody>
</table>

The patients were prospectively randomized into one of 2 groups according to the cardioplegic solution used for intraoperative myocardial protection. Group M (n=35) was given minimally-diluted BCP supplemented with potassium-chloride and magnesium-sulfate, whereas Group C (n=35) was given the standard 4:1-diluted blood-crystalloid BCP and served as controls. The preoperative demographic and operative data of the patients are shown in Table 1. No patients had a history of preoperative arrhythmias. Preoperative echocardiography revealed no incidence of paradoxical movement of the ventricular septum in the study patients.

Operative Procedures Related to Cardiopulmonary Bypass

Anesthesia was introduced and maintained with diazepam, fentanyl, and inhaled isoflurane. The patients were placed in the supine position and a median full sternotomy was done. After systemic heparinization (3 mg/kg bodyweight of heparin-sulfate), CPB was instituted in a routine fashion. The CPB circuit comprised a roller pump, a membrane oxygenator with a venous reservoir (Quadrox; Japan Life-Line Co, Ltd, Tokyo, Japan), an arterial filter, and heparin-coated tubing lines (Hepaflex-II; Ube Jun-Ken, Tokyo, Japan), which were primed without blood components. CPB was controlled by l-stat management with blood-flow rates of 2.2–2.6L/min per m² to maintain a mean arterial pressure between 60 and 80mmHg, using vasoac-
tive agents such as chlorpromazine-hydrochloride and norepinephrine if necessary. Perfusate blood temperature was controlled and maintained at 32–34°C with a heat exchanger. Myocardial protection was achieved by a combination of ‘initial, continuous, and intermittent bolus’ infusion of tepid BCP (30°C). All the anastomoses, both proximal and distal, were completed during a single period of aortic cross-clamping. When poor visualization prevented a sufficient and comfortable anastomosis procedure, the coronary shunt-tube (JMS Bypass-Tube; JMS Co, Ltd, Hiroshima, Japan) was used. The patients were rewarmed after aortic unclamping, and CPB was terminated when intravesical temperatures reached 35°C. Dopamine was administered on the basis of each patient’s hemodynamic condition just after termination of CPB.

‘Initial, Continuous and Intermittent Bolus’ BCP Administration

Fig 1 is a schematic diagram of the protocol for ‘initial, continuous, and intermittent bolus’ BCP administration. In brief, initial BCP was infused antegrade from the aortic root just after aortic cross-clamping for 2 min at the rate of 200 ml/min, and continuous BCP was subsequently started retrogradely from the coronary sinus (CS). Intermittent bolus BCP was infused every 30 min for 2 min at the rate of 200 ml/min in an antegrade fashion. The flow rate of the initial continuous BCP was set at 100 ml/min and that of secondary continuous BCP was reduced to 80 ml/min. Afterwards, the continuous BCP flow rate was maintained at 60 ml/min. The BCP temperature was controlled at approximately 30°C with a heat exchanger. During retrograde BCP perfusion, the CS pressure was approximately 30 mmHg and epicardial veins remained engorged with the bright red blood.

Components of Standard-Diluted BCP (Modification of Buckberg-Suggested BCP)

Two kinds of crystalloid solution were prepared for the standard 4:1-diluted blood-crystalloid BCP using glucose-containing sodium-chloride (Denosalin-2; Terumo Co Ltd, Tokyo, Japan), potassium-chloride (2 mmol/ml), trishydroxymethylaminomethane (THAM-SET; Ohtsuka Pharmaceutical Co, Tokyo, Japan), and citrate-phosphate-dextrose (CPD) solution (Terumo Co, Ltd) (Table 2). Oxygenated blood was obtained from the oxygenator and mixed with one of these crystalloid solutions by means of 1/4-tubing lines and double-headed coupled roller pumps. The more hyperkalemic crystalloid solution was used for

### Table 2 Crystalloid Solution for the Standard 4:1-Diluted Blood-Crystalloid Cardioplegia

<table>
<thead>
<tr>
<th></th>
<th>High-potassium crystalloid (Initial)</th>
<th>Low-potassium crystalloid (Continuous and intermittent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosalin-2 (Terumo Co Ltd, Tokyo Japan)</td>
<td>200 ml</td>
<td>500 ml</td>
</tr>
<tr>
<td>Potassium chloride [2 mmol/ml]</td>
<td>12 ml</td>
<td>10 ml</td>
</tr>
<tr>
<td>THAM-SET (Ohtsuka Pharm, Tokyo, Japan)</td>
<td>70 ml</td>
<td>160 ml</td>
</tr>
<tr>
<td>CPD (Terumo Co Ltd)</td>
<td>20 ml</td>
<td>30 ml</td>
</tr>
<tr>
<td><strong>Total volume</strong></td>
<td><strong>302 ml</strong></td>
<td><strong>700 ml</strong></td>
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### Table 3 Infusion Protocol for Minimally-Diluted Blood Cardioplegia

<table>
<thead>
<tr>
<th>Dose</th>
<th>Roller pump (ml/min)</th>
<th>Syringe pump (ml/h)</th>
<th>Actual flow-rate (ml/min)</th>
<th>Duration (min)</th>
<th>[K+] (mmol/L)</th>
<th>[Mg++] (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>200 (Push 4 ml then) 200</td>
<td>203.3</td>
<td>2</td>
<td>15.4</td>
<td>3.25</td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>100</td>
<td>50</td>
<td>100.8</td>
<td>30</td>
<td>9.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Second</td>
<td>200</td>
<td>100</td>
<td>201.7</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Continuous</td>
<td>80</td>
<td>40</td>
<td>80.7</td>
<td>30</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Third</td>
<td>200</td>
<td>100</td>
<td>201.7</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Continuous</td>
<td>60</td>
<td>30</td>
<td>60.5</td>
<td>30</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fourth</td>
<td>200</td>
<td>100</td>
<td>201.7</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Continuous</td>
<td>60</td>
<td>30</td>
<td>60.5</td>
<td>30</td>
<td>2</td>
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</tr>
<tr>
<td>Fifth</td>
<td>200</td>
<td>100</td>
<td>201.7</td>
<td>2</td>
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<tr>
<td>Continuous</td>
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<td>30</td>
<td>60.5</td>
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</tr>
<tr>
<td>Sixth</td>
<td>200</td>
<td>100</td>
<td>201.7</td>
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<tr>
<td>Continuous</td>
<td>60</td>
<td>30</td>
<td>60.5</td>
<td>30</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Seventh</td>
<td>200</td>
<td>100</td>
<td>201.7</td>
<td>2</td>
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</table>
initial BCP. Final potassium concentrations in the BCP were 19.3 mmol/L (initial) and 9.1 mmol/L (continuous and intermittent).

Components of Minimally-Diluted BCP
A syringe pump containing ‘35 ml of 1 mmol/ml potassium-chloride and 15 ml of 0.5 mmol/ml magnesium-sulfate’ was connected only to the 1/4-tubing line to be mixed with arterial blood obtained as mentioned before. The infusion protocol is shown in Table 3. The final concentrations of potassium in the minimally-diluted BCP solution were approximately 15.4 mmol/L (initial) and 9.8 mmol/L (continuous and intermittent). Those of magnesium were approximately 3.25 mmol/L (initial) and 2.0 mmol/L (continuous and intermittent).

Assessment Parameters
The time required to achieve cardioplegic arrest after starting initial cardioplegia administration was measured to assess the effect on rapid hyperpolarization. The incidence of spontaneous heart beat recovery immediately after aortic unclamping and that of atrial fibrillation during the postoperative period were used to evaluate the myocardial protective effects concerning the specialized conduction system. The total amount of crystalloid solution administered during aortic cross-clamping as cardioplegia was calculated. The maximum dose of dopamine required after the termination of CPB and the peak plasma creatine kinase-MB (CK-MB) concentration were measured as indexes of myocardial damage. On the 7th postoperative day, the incidence of paradoxical movement of the ventricular septum was evaluated using M-mode echocardiography.

Statistical Analysis
All data are expressed as mean ± standard deviation. Chi-square test for independence and unpaired Student’s t-test were used to compare values between the groups. Analyses were performed with the StatView ver-5.0 statistical package (Abacus Concepts Inc, Berkeley, CA, USA). A p-value <0.05 was considered statistically significant.
Results

All patients in the present study tolerated the surgical procedures and were discharged. No complications related to BCP administration were observed. Perioperative myocardial infarction was not identified in either group as evidenced by new Q-wave in 2 or more contiguous ECG leads, poor R-wave progression, new left bundle branch block or unstable ventricular rhythm. No circulatory assistance such as intraaortic balloon pumping or percutaneous cardiopulmonary support was required in either group.

The time required to achieve cardioplegic arrest after starting initial cardioplegia administration was significantly shorter in Group M (47.5±16.3 s) than in Group C (62.5±17.6 s, p<0.0001) (Fig 2). The number of patients showing spontaneous heart beat recovery after myocardial reperfusion was significantly greater in Group M (n=28, 80.0%) than in Group C (n=15, 42.9%, p=0.0029), and the number of patients suffering from atrial fibrillation during postoperative period was significantly smaller in Group M (n=3, 8.6%) than in Group C (n=11, 31.4%, p=0.034) (Fig 2). The total amount of crystalloid solution infused as cardioplegia during aortic cross-clamping was significantly less in Group M (62.8±22.3 vs 73.6±38.2 mL, p<0.0001).

The maximum dopamine dose required after the termination of CPB was significantly less in Group M (3.57±2.46 μg/kg per min) than in Group C (5.44±2.23 μg/kg per min, p=0.0014), and the postoperative peak plasma CK-MB concentration was significantly less in Group M (19.5±8.5 vs 25.8±11.9 IU/L, p=0.0128) (Fig 3). The number of patients showing paradoxical movement of ventricular septum in the early postoperative echocardiography was significantly smaller in Group M (n=9, 25.7%) than in Group C (n=25, 78.6%, p=0.0007) (Fig 3).

Discussion

Current experimental studies have focused on preischemic treatments to enhance the tolerance to myocardial damage. As for cardioplegic myocardial protection, the composition and delivery method of the cardioplegic solution have been considered of most concern. Though only a combination of ordinary modifications, minimally-diluted BCP supplemented with potassium and magnesium seems to provide superior myocardial protection in comparison with the standard 4:1-diluted BCP for ‘initial, continuous and intermittent bolus’ BCP administration.

Previous studies indicated that approximately 15 min of myocardial ischemia is tolerable even under tepid intermittent cardioplegia although the duration of ischemia that can be tolerated under normothermic cardioplegic arrest remains to be established. As for the issue of adequate myocardial perfusion during cardioplegic arrest, the combination of ‘antegrade and retrograde’ and ‘continuous and intermittent’ BCP administration appears to be an ideal delivery technique. The use of minimally-diluted BCP certainly resolves the possible demerit that a large amount of crystalloid solution is infused into the myocardium during cardioplegic ischemia. Therefore, the series of cardioplegic procedures used in the present study are applicable to warm heart operations.

Magnesium has been widely used in the management of reperfusion-induced ventricular arrhythmias due to its likely role in myocardial protection. It has been reported that magnesium can prevent myocardial damage in patients with acute myocardial infarction. However, the optimal concentration in the cardioplegia solution remains controversial. Caputo-proposed intermittent antegrade warm BCP contains 1.25–2.5 mmol/L of magnesium. St. Thomas solution includes 16 mmol/L of magnesium-dichloride, and Tyers solution has 1.5 mmol/L of magnesium. Miyoshi et al have recently demonstrated that the optimal magnesium concentration is between 2.4 and 4.8 mmol/L for the prevention of reperfusion-arrhythmias in isolated rat hearts. In the present study, 2.0 mmol/L of magnesium in the minimally-diluted BCP provided more effective myocardial protection than the standard 4:1-diluted BCP for ‘initial, continuous and intermittent bolus’ BCP administration.

Paradoxical movement of the ventricular septum is considered a symptom of myocardial ischemia, right ventricular volume overload or left bundle branch block. It is frequently observed in the echocardiography after open heart operations. Allen et al indicated that postoperative paradoxical movement of ventricular septum may be attributed to inadequate perfusion of the right ventricle by retrograde cardioplegia. Although all patients in the present study received sufficient BCP perfusion by the combination of ‘antegrade and retrograde’ and ‘continuous and intermittent’ BCP administration, the incidence was lower in the minimally-diluted BCP-treated group. The relationship between intraoperative myocardial protection and ventricular septal paradoxical movement remains unclear.

The present study has 2 different factors such as the degree of dilution and the enrichment with magnesium, and thus it is difficult to find the crucial factor for the superior myocardial protection. The efficacy of minimal dilution remains to be established, and Velez et al have recently demonstrated the possible disadvantages in models of surgical revascularization. As for a series of cardioplegia administration, it has not yet been examined on the basis of experimental conditions. Further investigations are needed to elucidate the mechanism of myocardial protection by this method and improve its efficacy.

In conclusion, we used a combination of ‘initial, continuous and intermittent’ BCP administration for intraoperative myocardial protection using 2 types of BCP. Although the present study has methodical limitations and there remain several issues to be examined, ‘initial, continuous and intermittent bolus’ administration of minimally-diluted BCP supplemented with potassium and magnesium could be a reliable and effective technique for intraoperative myocardial protection.

References


