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Myocardial Protection Related to Magnesium Content of Cold Blood Hyperkalemic Cardioplegic Solutions in CABG

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Abstract: The objective of this study was to investigate whether the addition of magnesium to a hyperkalemic cardioplegic solution containing 1.2~1.5 mmol/L ionized calcium improves myocardial protection. Twenty-seven coronary artery disease (CAD) patients underwent coronary artery bypass grafting (CABG) received hyperkalemic (20~22 mmol/L potassium) cardioplegic solutions containing 1.2~1.5 mmol/L ionized calcium and were randomized to one of the following groups: Group A (n = 9) received 3~4 mmol/L magnesium cool blood cardioplegia (4°C), Group B (n = 9) received 8~10 mmol/L magnesium cold blood cardioplegia (4°C). Group C (n = 9) received 16~18 mmol/L magnesium cold blood cardioplegia (4°C). The effect of myocardium protection of the three kinds of cardioplegic solutions were evaluated by clinical outcome, cTnI and CK-MB mass. Serial venous blood samples were obtained before induction, after cardiopulmonary bypass (CPB), postoperative 6 h, 24 h, 72 h, and 6th day, respectively. The percentage of myocardial autoresusciation in group B (100%) was significantly higher than that in groups A (77.8%) and C (66.7%). One patient in group A and two patients in group C needed an interim pacemaker, but none in group B. The period of postoperative mechanical ventilation and ICU stay in group B was shorter than in the other two groups. The level of cTnI and CK-Mb mass increased from postoperative 6 h ($p < .05$), reached peak in 24 h~72 h, and recovered postoperative 6th day. As compared with groups A and C, the plasma concentrations of cTnI and CK-MB mass in group B were significantly lower at 6 h, 24 h, and 72 h ($p < .01$). 8~10 mmol/L magnesium cold blood cardioplegia provides better myocardium protection than higher or lower concentrations.
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Magnesium in cardioplegic solutions can enhance myocardial preservation and may act by antagonizing calcium or by maintaining transcellular magnesium levels during ischemia. Inclusion of magnesium in cardioplegic solutions has been shown to increase ventricular performance after varying intervals of ischemia and reperfusion. The specific interaction between magnesium and calcium has not yet delineated. However, some studies proposed that magnesium acts as a physiological calcium channel blocker. The present study investigates whether there is an optimal magnesium concentration in cold blood cardioplegic solution during coronary artery bypass graft surgery (CABG). In this study, the cardioplegic solutions we applied is modified St. Thomas's hospital solutions, the concentration of magnesium is from 4~16 mmol/L calcium to 1.2~1.5 mmol/L.

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MATERIALS AND METHODS

Patients

The study was approved by the Fuwai Heart Hospital, Beijing, The People's Republic of China. Twenty-seven patients with coronary artery disease who received CABG were included in the prospective study. All patients had three vessel coronary artery disease without valve disease, and were first time sternotomies. Patients were divided to three groups according to the different concentrations of magnesium in the cardioplegia solution.

Blood Cardioplegia

Hyperkalemic (20~22 mmol/L potassium) (4°C) cold blood (4:1) cardioplegic solutions containing 1.2~1.5 mmol/L ionized calcium, were used in all cases. Group A (n = 9) received 3~4 mmol/L magnesium, Group B (n = 9) received 8~10 mmol/L (4°C), and Group C (n = 9) received 16~18 mmol/L magnesium (Table 1).

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Table 1. Clinical outcomes.

Parameter	Group A n = 9	Group B n = 9	Group C n = 9
Female:male	5:4	5:4	3:6
Age (years)	58 ± 8.2	58.6 ± 7.6	60 ± 6.0
Weight (kg)	80 ± 11	75 ± 15	73 ± 9
CTR (%)	0.49 ± 0.06	0.51 ± 0.04	0.50 ± 0.03
LVEF (%)	45 ± 6	45 ± 7	45 ± 5
Graft vessels (*N*)	3.2 ± 0.72	3.4 ± 0.63	3.1 ± 0.57
Autoresuscitation	77.8%	100%*	67.7%
Temperature (°C)	31.5 ± 0.9	30.2 ± 1.2	31.3 ± 1.4
Time of CPB (min)	110 ± 18	105 ± 21	97 ± 13
Cross clamp (min)	72 ± 9	67 ± 13	69 ± 9
Intubation (h)	12 ± 1.6	8.8 ± 1.9**	11.2 ± 2
ICU stay (h)	34 ± 20	22 ± 9**	36 ± 15

*$p < .05$ to group C, **$p < .01$ to groups A and B.

Anesthesia

Standard general anesthesia was achieved in all groups with fentanyl, isofurane, and enfurane.

Cardiopulmonary Bypass

Cardiopulmonary bypass (CPB) was conducted with a Stockert heart–lung machine (Stockert, Munich, Germany) with roller pump, Affinity membrane oxygenator (Medtronic, Inc., Minneapolis, MN) was used, tubing pack with cardioplegia delivery (blood:crystalloid = 4:1) system (Perfect, Beijing, China), and an arterial filter (Xi Jing, Xian, PRC). Nonpulsatile CPB was used at a flow rate of 2.6~3.0 L/min/kg. Mean arterial pressure was maintained (65~85 mmHg) by adjusting blood flow rate.

Evaluation Index

Preoperative clinical indexes of patients in three groups were recorded and included: age, weight, cardiac-thoracic ratio (CTR), left ventricular ejection fraction (LVEF).

Perioperative clinical indexes of patients in each group were recorded as follows: CPB time, coronary circulation arrest time, temperature, the number of grafted vessels, ratio of myocardial auto resuscitation, ratio of requirement for temporary pacemaker, postoperative ventilation support time, and ICU stay time.

Plasma level markers of myocardial damage (cardiac troponin I, cTNI and CK-MB mass) were obtained from serial venous blood samples before induction, after CPB, postoperative 6 h, 24 h, 72 h, and 6th day, respectively. Measurement of cTNI was performed with a recently developed enzyme immunoassay (ELISA) by our institution.

Statistical Analysis

Differences among groups were tested by one-way analysis of variance (ANOVA). When significant differences were found, Fisher's protected least-significant post hoc analysis was completed. Statistical significance accepted at $p < .05$. All data are expressed as mean ± standard deviation (SD).

RESULTS

Preoperative Clinical Indexes

No significant preoperative differences were found between three groups (Table 1).

Perioperative Clinical Indexes

There were no significant differences in nasopharyngeal temperature, CPB time, coronary circulation arrest time, and the number of grafting vessels. The percentage of myocardial autoresusciations in group B (100%) was significantly higher than that in groups A (77.8%) and C (66.7%). One case in group A and two cases in group C needed the interim pacemaker, but no cases in group B. The period of postoperative mechanical ventilation and ICU stay in group B was shorter than the other two groups.

Cardiac Troponin and CK-mb Mass

There were no significant differences in cTNI and CK-mb mass among the three groups before anesthesia induction. The plasma level of cTnI (Table 2) and CK-Mb mass (Table 3) increased from postoperative 6 h ($p < .05$), reached peak in 24 h~72 h, and recovered 6th day postoperative. Compared with groups A and C, the plasma concentration of cTnI and CK-Mb mass in group B were significantly lower at 6 h, 24 h, and 72 h ($p < .01$).

DISCUSSION

The purpose of this study was to determine the optimal magnesium concentration for myocardial preservation in cardioplegic solution containing 1.2~1.5 mmol/L ionized calcium when the solution was used to produce hypothermic arrest at 28°C. We found the clinical index of group B to be better than the other two groups, and the level of cTnI and CK-Mb mass increased from postoperative 6 h ($p < .05$), reached peak in 24 h~72 h, and recovered postoperative 6th day. As compared with groups A and C, the plasma concentrations of cTnI and CK-Mb mass in group B were significantly lower at 6 h, 24 h, and 72 h ($p < .01$).

Table 2. Result of cTNI in three groups.

Parameter	Group A	Group B	Group C
cTNI1	0.39 ± 0.3	0.40 ± 0.23	0.44 ± 0.11
cTNI2	1.96 ± 1.0†	1.30 ± 0.38*‡	2.02 ± 0.70†
cTNI3	6.80 ± 0.9†	5.2 ± 0.60*†	6.50 ± 1.1†
cTNI4	8.0 ± 1.8†	4.6 ± 0.60**†	7.5 ± 2.2†
cTNI5	6.2 ± 2.0†	1.0 ± 0.36**‡	5.9 ± 1.8†
cTNI6	0.38 ± 0.17	0.42 ± 0.18	0.33 ± 0.2

†$p < .01$; to baseline values.
‡$p < .05$; to baseline values.
*$p < .05$ to group C.
**$p < .01$ to groups A and B.

Table 3. Result of CK-Mb mass in three groups.

Parameter	Group A	Group B	Group C
CK-Mb mass1	0.38 ± 0.12	0.4 ± 0.1	0.4 ± 0.15
CK-Mb mass2	4.6 ± 0.9†	2.5 ± 0.4**†	4.4 ± 1.6†
CK-Mb mass3	9.2 ± 1.5†	7.9 ± 1.1*†	10 ± 1.2†
CK-Mb mass4	10 ± 0.8†	7.5 ± 0.9*†	9.4 ± 0.9†
CK-Mb mass5	4.6 ± 2.0†	3.1 ± 0.6*†	4.5 ± 1.8†
CK-Mb mass6	0.9 ± 0.1‡	0.6 ± 0.08‡	0.86 ± 0.2‡

*$p < .05$, **$p < .01$; compare with three groups.
‡$p < .05$, †$p < .01$; compare with baseline values.

The indexes of cTnI and CK-Mb mass are sensitive to the damage to myocardial (1). Magnesium and calcium ions are the most abundant intracellular cations, excluding potassium, and are critical to almost all intracellular reactions. Calcium ion is the main regulatory factor of the myocardial contraction apparatus, and magnesium is a co-factor of the magnesium-dependent ATPase enzyme, which provides energy for myocardial contraction and allows the sodium–potassium membrane pumps to maintain intercellular hemostasis.

Hearse and associates (2) have shown that a cardioplegic solution with 16 mmol/L of Mg^{2+} and 1.2 mmol/L Ca^{2+} provided significant postischemic ventricular protection at 37°C and 28°C. The current results confirm these but go further by showing that magnesium provides increased protection down to at least 24°C. Reynolds and co-workers (3) evaluated the effects of multidose magnesium-containing cardioplegic solution with 0.1 mmol/L Ca^{2+} and 16 mmol/L Mg^{2+} at 8°C. Hypothermia is an important adjunct to cardioplegia and can provide significant protection to the ischemic myocardium.

Ischemic injury may be characterized in part by the loss of ATP stores, intracellular acidosis, free radical formation, and intracellular edema. All of these disrupt the normal internal milieu of the cell during ischemia and are exacerbated upon reperfusion. The damage that occurs during the calcium paradox is probably only a more severe form of the damage that occurs with ischemic arrest in the presence of calcium.

The exact mechanism of magnesium's action is not known at this time, but probably acts through two mechanisms. The first action is that of a co-factor in all energy-requiring reactions. Loss of intracellular cellular magnesium is one of the earliest signs of myocardial injury with a twofold increase in magnesium efflux occurring during hypoxia (4). During cardioplegic arrest, mechanical contraction of the sarcomere is not needed; however, continued operation of the sodium–potassium exchange membrane pumps dose requires the presence of ATP and magnesium. Because ATP is utilized and production is slowed during ischemia, we would expect to observe a loss of free magnesium from the cell. Tani and colleagues (5) have shown that intracellular sodium concentration increases during ischemia and that the higher the calcium concentration in the reperfusing solution, the higher the exchange of intracellular sodium for calcium and the more the resulting cellular injury. Excessive calcium entry through the Na^+/Ca^{2+} exchange pump is one major factor that determines the recovery of function during reperfusion.

The second proposed method of action is that of a calcium antagonist. White and Hartzell, using voltage clamp experiments, have shown that magnesium inhibits the opening of the voltage-dependent calcium channel and does so more during periods of channel phosphorylation or at relatively high energy states within the cell. When energy is less available, as during ischemia, calcium entry into the cell is increased. Whether this occurs by actual blockade of these channels or merely modulation of conductivity is not known. Magnesium has also been shown to block the release of calcium from the sarcoplasmic reticulum (6); thereby, leading to lower cytosolic levels and also to an increased uptake of calcium into the sarcoplasmic reticulum. Favaron and Bernardi (7) have demonstrated in vitro that magnesium ion will increase the mitochondrial uptake of calcium at a lower concentration gradient than without magnesium, which may also be a protective mechanism against higher intracellular concentrations of calcium.

High concentration of magnesium inhibits calcium ion influx. Therefore, increasing the concentration of Mg^{2+} can attenuate Ca^{2+} intracellular accumulation response to ischemia reperfusion, keep the cell's ultrastructure intact, and inhibit myocardial stunning, and as a result, promote cardiac function recovery, and decrease arrthythmia. However, overload of (>15 mmol/L) magnesium may be harmful to the myocardium. Extracellular magnesium competitively occupies the bonding location in the cell membrane of calcium. However, in the period of ischemia, magnesium inhibits the exchange of Na^+/Ca^{2+} (8), the magnesium flushed away leads to Ca^{2+} bonding location exposure, and induces a number of Ca^{2+} influx intracellular mediate cell injury. Simultaneously, extracellular higher Mg^{2+} cause an increase in intracellular Mg^{2+}, inhibit combining with Ca^{2+}, resulting in effect, in negative myocardium contraction. In summary; 8~10 mmol/L magnesium cold blood cardioplegia provides more myocardium protection than lower or higher concentrations in CABG patients.

REFERENCES

1. Chocron S, Alwan K, Yan Y, et al. Warm reperfusion and myocardial protection. Ann Thorac Surg. 1998;66:2003–7.
2. Hearse DJ, Stewart DA, Braimbridge MV. Myocardial protection during ischemic cardiac arrest: The importance of magnesium in cardioplegic infusates. J Thorac Cardiovasc Surg. 1978;75:877–85.
3. Reynolds TR, Geffin GA, Titus JS, et al. Myocardial preservation

related to magnesium content of hyperkalemic cardioplegic solutions at 8°C. Ann Thorac Surg. 1989;47:907–13.
4. Polimeni PI, Page E. Further observation of Mg transport in rat ventricular muscle. In: Recent Advances in Studies on Cardiac Structure and Metabolism, vol 4. Dhalla NS, ed. Baltimore: University Park Press, 1972:217–31.
5. Tani M, Teely JR. Mechanisms of reduced reperfusion injury by low Ca^{2+} and/or high K^{+}. Am J Physiol. 1990;258:1025–31.
6. Hasselbach W, Fassold E, Migala A, et al. Magnesium dependence of sarcoplasmic reticulum calcium transport. Fed Proc. 1981;40:2657–61.
7. Favaron M, Bernardi P. Tissue specific modulation of the mitochondrial calcium uniporter by magnesium ions. FEBS Lett. 1985;183:260–4.
8. Takashi I, Naruto M, Naoaki T, et al. Regulation of intracellular calcium concentrations by calcium and magnesium in cardioplegic solutions protects rat neonatal myocytes from simulated ischemia. J Mol Cell Cardiol. 1998;30:1105.