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Changes in plasma total and ionized magnesium concentrations and factors affecting magnesium concentrations during cardiac surgery

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Abstract

The purpose of this study was to measure blood total and ionized magnesium concentrations ([TMg] and [Mg^{2+}], respectively) and to investigate factors that might be affecting their changes during cardiac surgery using hypothermic cardiopulmonary bypass. Eight patients were examined. All the patients received diuretics and predeposited autologous blood during surgery. No drugs containing Mg^{2+} were administered. Nine blood samples and eight urine samples were collected from the pre-induction period to the end of surgery. Hematocrit, [TMg], [Mg^{2+}], plasma concentrations of calcium ([Ca^{2+}]), creatinine, parathyroid hormone (PTH), urinary concentrations of TMg, and creatinine were measured, and the fractional excretion of Mg (FEMg) was calculated. Both [TMg] and [Mg^{2+}] decreased significantly in the prebypass period and remained significantly depressed thereafter. The ionized fraction of magnesium ([Mg^{2+}]/[TMg]) was decreased during the postbypass period. Hematocrit decreased significantly from the prebypass period, and FEMg increased significantly after aortic cross-clamping. In conclusion, hemodilution and renal loss were main causes of hypomagnesemia, and citrate in predeposited autologous blood may contribute to the decrease in [Mg^{2+}]/[TMg] in the postbypass period. These results suggest that magnesium supplementation under close monitoring of [Mg^{2+}] should be required during cardiac surgery.

Key words Cardiac surgery · Ionized magnesium · Hypomagnesemia · Hemodilution · Fractional excretion of magnesium

Introduction

Decrease in blood total magnesium (TMg) concentration ([TMg]) during cardiac surgery using cardiopulmonary bypass (CPB) has been demonstrated for over three decades [1–11]. In addition, it is shown that hypomagnesemia following cardiac surgery is associated with an increase in the incidence of dysrhythmia, and Mg administration could contribute to fewer postoperative dysrhythmias [5–7] or better myocardial recovery [7]. Ionized magnesium (Mg^{2+}) is approximately 70% of TMg in blood, and only this fraction is available for biological processes [12]. Therefore, the importance of the changes in blood Mg^{2+} concentration ([Mg^{2+}]) during cardiac surgery has been recognized. However, due to previous difficulties in the measurement of [Mg^{2+}] in the clinical setting, sufficient examination has not been carried out on changes in [Mg^{2+}] and their correlation with other factors [9–11]. In the past decade, a selective electrode for measuring [Mg^{2+}] was invented and has become clinically available [13]. Thus, we tested the hypothesis that both [TMg] and [Mg^{2+}] are decreased and that the ratio of [Mg^{2+}] to [TMg] changes during cardiac surgery using hypothermic CPB, and that several factors contribute to these changes.

Subjects and methods

After obtaining written informed consent and approval from the institution's ethics committee, we studied eight consecutive patients undergoing elective cardiac surgery using hypothermic CPB. Anesthesia consisted of a narcotic-based technique, using fentanyl (30–50 $\mu g \cdot kg^{-1}$), diazepam (0.6–0.8 $mg \cdot kg^{-1}$), and sevoflurane (0.5%–2%), and neuromuscular blockade with vecuronium. After tracheal intubation, ventilation was adjusted to maintain normocarbia. Acetated Ringer's solution was given during the pre- and postbypass period. No drugs containing Mg^{2+} were given throughout the surgery. Potassium chloride solution was given to adjust plasma potassium (K^+) concentration to between 3.5 and 4.5 Mm.

Hypothermic nonpulsatile CPB (28°C esophageal temperature) was performed and primed with 500 ml

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lactated Ringer's solution, 1000 ml hydroxyethyl starch, 50 ml 25% albumin, 150 ml mannitol, 50 ml 7% sodium bicarbonate, and heparin sulfate 10000 U. During CPB, the hematocrit (Ht) was maintained at above 20%. Cardioplegic solution consisted of 1000 ml lactated Ringer's solution and 50 mM of K^+. Diltiazem 30 mg was added to the initial 1000 ml of cardioplegic solution. Mg^{2+} was not added to the prime solution and cardioplegic solution. At the initiation of CPB, furosemide 30 mg was given intravenously. Dopamine, dobutamine (3–7 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively), and lidocaine (0.5 $mg \cdot kg^{-1} \cdot h^{-1}$) were given continuously after the weaning from CPB. Predeposited autologous blood was transfused in all patients during the postbypass period.

Nine arterial blood samples were collected at following time points: 5 min before the induction of anesthesia (t_1), 5 min after the induction of anesthesia (t_2), 3 min after anticoagulation with heparin (t_3), 5 min after the start of CPB (t_4), 3 min after aortic cross-clamping (t_5), at the start of the rewarming (t_6), immediately after the weaning from CPB (t_7), 30 min after the weaning from CPB (t_8), and at the end of the surgery (t_9). Urine samples were collected at the eight intervals following the induction of anesthesia (t_2–t_9). Blood samples were analyzed for plasma [Mg^{2+}], Ht, pH, and ionized calcium concentration ([Ca^{2+}]), using the Nova Stat Profile 8 analyzer (Nova Biomedical, Waltham, MA, USA). Plasma parathyroid hormone (PTH) concentration ([PTH]; normal range, 160 to 520 $pg \cdot ml^{-1}$) was measured using a radio-immunoassay kit (YSI-7740; Yamasa, Chiba, Japan). [TMg] and urinary total Mg concentrations ([UMg]) were measured by an automatic chemical analyzer (7170; Hitachi, Tokyo, Japan), using xylidyl blue I (magnesium-HR II; Wako Junyaku, Osaka, Japan). The ratio of [Mg^{2+}] to [TMg] (i/T) was calculated. Plasma and urinary concentrations of creatinine ([Cr] and [UCr], respectively) were measured by the automatic chemical analyzer (7170; Hitachi) with the Jaffe method. The fractional excretion of Mg (FEMg) at each sampling point was calculated from the following formula [14]:

$$\mathrm{FEMg} = \frac{[\mathrm{UMg}] \times [\mathrm{Cr}]}{(0.7 \times [\mathrm{TMg}]) \times [\mathrm{UCr}]} \times 100\ (\%)$$

Urine samples were analyzed qualitatively with test papers (Hemastix; Bayer, Berkshire, UK) to detect hemolysis.

The values for results are presented as means ± SD. Statistical analysis was performed with two-way repeated-measures analysis of variance, followed by fisher's protected least significant difference (PLSD). $P < 0.05$ was considered statistically significant.

Results

Two male patients received aortic valve replacements, and five male patients and one female patient received coronary artery bypass grafting. Age, height, and body weight of the eight patients were 56.3 ± 12.7 years, 159.5 ± 11.5 cm, and 67.2 ± 12.4 kg, respectively. Durations of the surgery, CPB, and the aortic crossclamping were 365.0 ± 96.1 min, 161.0 ± 37.0 min, and 89.0 ± 39.3 min, respectively. Total amount of fluid infused during the pre- and postbypass period, total amount of predeposited autologous blood used, and the amount of pump solution were 4090 ± 1258 ml, 709 ± 479 ml, and 1941 ± 411 ml, respectively. Estimated blood loss and urinary output were 562 ± 242 ml and 3914 ± 1475 ml, respectively.

Measured and calculated values are shown in Table 1. Both [TMg] and [Mg^{2+}] decreased significantly at t_3, and remained significantly decreased thereafter. The

Table 1. Changes in plasma ionized and total magnesium concentrations ([Mg^{2+}] and [TMg], respectively), the ratio of [Mg^{2+}] to [TMg] (i/T), the fractional excretion of magnesium (FEMg), hematocrit (Ht), and plasma concentrations of ionized calcium ([Ca^{2+}]) and parathyroid hormone ([PTH])

	[Mg^{2+}] (mM)	[TMg] (mM)	i/T	FEMg (%)	Ht (%)	[Ca^{2+}] (mM)	[PTH] ($pg \cdot ml^{-1}$)
t_1	0.52 ± 0.10	0.88 ± 0.13	0.60 ± 0.15	—	39.7 ± 2.0	1.11 ± 0.07	286.3 ± 116.9
t_2	0.49 ± 0.10	0.86 ± 0.11	0.58 ± 0.13	4.1 ± 1.9	37.6 ± 2.7*; **	1.09 ± 0.06	335.0 ± 141.4
t_3	0.44 ± 0.07*;**	0.76 ± 0.10*;**	0.59 ± 0.09	4.2 ± 3.2	33.7 ± 3.3*;**	1.02 ± 0.05*;**	326.3 ± 139.1
t_4	0.37 ± 0.09*;**	0.65 ± 0.10*;**	0.56 ± 0.09	5.8 ± 5.6	22.1 ± 3.4*;**	0.90 ± 0.08*;**	572.5 ± 273.9*;**
t_5	0.40 ± 0.05*	0.67 ± 0.08*	0.60 ± 0.09	17.1 ± 17.1*;**	21.7 ± 3.4*	0.97 ± 0.07*;**	423.8 ± 191.8*;**
t_6	0.42 ± 0.05*;**	0.74 ± 0.08*;**	0.58 ± 0.07	19.3 ± 12.3*	22.3 ± 4.5*	1.03 ± 0.08*;**	388.8 ± 165.1*
t_7	0.39 ± 0.05*	0.71 ± 0.08*	0.56 ± 0.08	25.2 ± 11.7*	23.8 ± 3.2*	1.05 ± 0.08	390.0 ± 165.4*
t_8	0.34 ± 0.06*;**	0.67 ± 0.07*;**	0.51 ± 0.10*	24.3 ± 9.9*	24.5 ± 2.3*	0.92 ± 0.10*;**	471.3 ± 159.6*
t_9	0.33 ± 0.06*	0.68 ± 0.08*	0.49 ± 0.08*	19.5 ± 8.5*	29.6 ± 2.1*;**	0.93 ± 0.09*	510.0 ± 221.3*

* $P < 0.05$ vs 5 min before the induction of anesthesia; ** $P < 0.05$ vs the preceding value

Data values are displayed as means ± SD. t_1, 5 min before the induction of anesthesia; t_2, 5 min after the induction of anesthesia; t_3, 3 min after anticoagulation with heparin; t_4, 5 min after the start of CPB; t_5, 3 min after aortic crossclamping; t_6, at the start of rewarming; t_7, immediately after the weaning from CPB; t_8, 30 min after the weaning from CPB; t_9, at the end of the surgery

CPB, cardiopulmonary bypass

i/T value decreased significantly at t_8 and t_9. FEMg increased significantly at t_5 and remained significantly higher thereafter. Ht decreased significantly from t_2 to t_9. The [Ca^{2+}] value decreased significantly at t_3 and demonstrated its minimum value at t_4. The [PTH] value increased significantly in response to the decrease in [Ca^{2+}] at t_4, and remained significantly higher than the pre-induction value. The [Ca^{2+}] value increased significantly compared with preceding values in response to the increase in [PTH] during CPB and returned to near the pre-induction value immediately after the weaning from CPB. During the postbypass period, [Ca^{2+}] was significantly decreased again, and [PTH] was still significantly increased compared with the pre-induction value.

The mean values for pH at each point remained almost in the physiological range (7.41–7.49). Urinary qualitative analysis revealed the occurrence of hemolysis in all patients during CPB.

Discussion

One of the major findings of this study was that both [TMg] and [Mg^{2+}] decreased significantly in the prebypass period and remained significantly depressed thereafter. Studies measuring [TMg] during cardiac surgery using CPB have suggested the following possible mechanisms for hypomagnesemia: (1) hemodilution by an intraoperative solution which does not include Mg [1–4,6,8,10,11], (2) renal loss of Mg [2,8], and (3) Mg influx into the intracellular space [4]. However, sufficient examinations have not been carried out on changes in [Mg^{2+}] and other factors during cardiac surgery. Moreover, changes in FEMg during cardiac surgery have never been reported, though several studies have measured the urinary concentration of Mg [1–4,8].

In the present study, the significant decrease in Ht reflects hemodilution by intravenous fluid administered during the pre- and postbypass period and the solution used for CPB. On the other hand, the values of FEMg remained at less than 6% until t_4. Therefore, the main cause of the significant decreases in [TMg] and [Mg^{2+}] until the early phase of CPB would have been hemodilution rather than renal loss. The significant increase in FEMg from t_5 to t_9 indicates that not only the hemodilution but also the increase in renal excretion of Mg contributed to the hypomagnesemia observed following the aortic crossclamping.

Although no single homeostatic control has been demonstrated for Mg^{2+}, its cellular availability is closely regulated by the gastrointestinal tract, kidney, and bone [15]. The filtration-reabsorption process in the kidney, in particular, plays an essential role in the Mg balance [16]. About 80% of total plasma Mg is ultrafilterable across the glomerular membrane, and approximately 95% of filtered Mg is reabsorbed [15,16]. Because there is no evidence for the tubular secretion of Mg, only 3% to 5% of filtered Mg is excreted in the urine [15,16]. The principal factors that alter Mg reabsorption in the loop include diuretics; hormones such as PTH, glucagon, and calcitonin; and changes in [Mg^{2+}] and [Ca^{2+}] [15,16]. Inhibition of sodium chloride transport by furosemide or osmotic change of tubular fluid by mannitol produces urinary Mg excretion [15]. Therefore, the administration of furosemide and mannitol partly explain the significant increase in FEMg after the start of CPB in the present study.

The influence of Ca^{2+} and PTH on Mg metabolism remains uncertain. It is reported that hypocalcemia of any etiology increases Mg excretion in urine, and PTH reduces urinary Mg excretion by enhancing renal reabsorption [16,17]. On the other hand, it has been demonstrated that a significant increase in [PTH] in response to a small but significant decrease in [Ca^{2+}] (0.065 mM) did not affect serum ultrafiltrable Mg concentration, and that a small acute decrease in serum ultrafiltrable Mg concentration (0.03 mM) did not affect PTH secretion, although whether a larger acute decrease of Mg affects PTH secretion remains uncertain [18]. In our study, the changes in the Ca-PTH relation until the end of CPB were consistent with the results of Robertie and colleagues [19], where hypocalcemia induced by hemodilution was observed at the start of CPB, and the Ca-PTH relation was preserved during hypothermic nonpulsatile CPB. However, we could not find a close relationship between the fluctuation in Mg and the Ca-PTH relation. In addition, we could not prove whether the Ca-PTH relation was involved in the regulation of [TMg] and [Mg^{2+}] during cardiac surgery, because the measured [TMg] and [Mg^{2+}] values in our study were determined by the net of the influx and efflux of Mg in the kidney and other organs. In our study, PTH-induced potential increases in [TMg] and [Mg^{2+}] may have been masked by the excessive renal loss of Mg during CPB.

Clinical and experimental studies have demonstrated that increased circulating catecholamine causes hypomagnesemia, as the influx of magnesium into the intracellular compartment is under the influence of β-adrenergic activity [4,20–22]. Therefore, both endogenous catecholamines released by surgical nociception and exogenous catecholamines given after the end of CPB may have partly contributed to the hypomagnesemia in our study.

Another important finding in our study was that the i/T was significantly reduced during the postbypass period. The formation of citrate-magnesium salt from citrate included in the predeposited autologous blood administered during the postbypass period is thought to be the main reason for the decrease in the ionized frac-

tion of Mg. The binding of citrate with a divalent cation is a possible reason for the significant decrease in Ca^{2+} despite the significant increase in [PTH] during the postbypass period. It is thought, theoretically, that an increase in hydrogen ion concentration should increase Mg^{2+}, because the hydrogen ion competes with Mg^{2+} for binding sites on proteins. However, Mg^{2+} is little affected by pH change from 7.4 to 7.8 [12], and pH was maintained at almost the physiological range in our patients. In addition, changes in the serum concentration of albumin in our patients were small (3.1 to 4.3 $g \cdot dl^{-1}$). Therefore, changes in the pH and the serum concentration of albumin could not explain the decrease in the i/T during the postbypass period.

Urinary qualitative analysis demonstrated hemolysis during CPB in our study. Because Mg concentrations in erythrocytes are three times higher than the serum level [15], mechanical hemolysis induced by the CPB apparatus may partly explain the significant increase in [Mg^{2+}] and the small degree of increase in [TMg] that we observed during CPB.

In conclusion, significant decreases in both [TMg] and [Mg^{2+}] were observed during cardiac surgery using nonpulsatile hypothermic CPB. The hypomagnesemia until the start of CPB was mainly due to hemodilution. In contrast, enhanced renal loss of Mg was found to play a major role in the hypomagnesemia during CPB and the postbypass period. Moreover, the ionized fraction of Mg decreased during the postbypass period in patients receiving predeposited autologous blood. The results of our study imply that Mg supplementation, with close monitoring of [Mg^{2+}], should be given during cardiac surgery using hypothermic CPB.

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