Ionised magnesium and calcium in plasma from healthy volunteers and patients undergoing cardiopulmonary bypass

C I O Brookes, C H Fry

Abstract

Objectives—To measure the concentration of ionised magnesium, $[Mg^{2+}]$, and ionised calcium $[Ca^{2+}]$, in plasma from healthy volunteers and patients undergoing cardiopulmonary bypass (CPB). These measurements were carried out because there have been few reliable measurements of these values in healthy volunteers and no direct measurements in this patient group.

Patients and methods—Dip cast ion selective electrodes were used to measure Mg^{2+} , Ca^{2+} , and H^+ in plasma at 37°C. These values were correlated with total metal concentrations, $[Mg]$ and $[Ca]$, plasma sodium $[Na]$, and albumin concentrations found by standard techniques. Blood samples were taken from the patient group immediately before and after CPB and a further sample 24 hours later.

Results—In healthy volunteers the $[Mg]$ was 0.86 (0.12) mM and $[Mg^{2+}]$, was 0.48 (0.06) mM, and the corresponding value for $[Ca]$ was 2.34 (0.06) and for $[Ca^{2+}]$ 1.01 (0.13) mM. Values for $[Mg]$, $[Ca]$, and $[Ca^{2+}]$ have been reported by others and those quoted here are similar. In the CPB group the preoperative $[Mg]$ was lower than the normal group but did not alter one hour after CPB and was slightly raised after 24 hours. The $[Mg^{2+}]$, however, was significantly reduced after 24 hours. Both $[Ca]$ and $[Ca^{2+}]$ were slightly reduced after 24 hours but when adjusted for plasma albumin concentrations they were unchanged over this period.

Conclusions—The most important finding is that around 24 hours after CPB the plasma $[Mg^{2+}]$ is significantly reduced, with no change to the total $[Mg]$. Corresponding changes to $[Ca]$ and $[Ca^{2+}]$ were much smaller. This supposes the presence of an Mg^{2+} binding ligand of unknown origin in the plasma that may contribute to the cardiac arrhythmias that occur in some patients at this time after CPB.

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The importance of plasma magnesium concentrations $[Mg]$ in determining cardiovascular function is increasingly becoming recognised.¹ Hypomagnesaemia is associated with myocardial injury, dysrhythmias, hypercoagulability,² arterial hypertension,³ and

coronary vasospasm.⁴ Patients with acute myocardial infarction or congestive heart failure are more likely to experience ventricular arrhythmias and fibrillation if hypomagnesaemic,⁵ and the deficiency has been implicated in several other arrhythmias, including torsades de pointes,⁶ multifocal atrial tachycardia,⁷ and those induced by digoxin.⁸ Several studies have suggested that Mg infusion after acute myocardial infarction will reverse many arrhythmias^{9,10} and limit infarct size and mortality¹¹⁻¹³; follow up studies showed that Mg treatment reduced mortality after one year, which was related to the reduction of arrhythmias and infarct size during the first week after infarction.¹⁴

Plasma Mg exists in two states: bound to covalent ligands such as plasma proteins, or freely ionised (Mg^{2+}). It is only Mg^{2+} that exerts biological activity so that any alteration to the concentration of Mg^{2+} binding ligands would alter the freely ionised concentration $[Mg^{2+}]$ without any change of values of total plasma Mg $[Mg]$. The studies listed have all relied on measurement of $[Mg]$ so that more significant relations between hypomagnesaemia and cardiovascular function may have been obscured. Direct measurement of Mg^{2+} with ion selective electrodes in extracellular fluids has until recently been hampered by the poor selectivity of Mg^{2+} selective ligands over interfering ions such as Na^+ and Ca^{2+} . Also, negatively charged plasma proteins have caused electrode drift, precluding accurate calibration. These problems have been largely overcome by the development of more selective Mg^{2+} sensitive neutral ligands¹⁵ and improvements in the design of the ion selective electrodes.¹⁶ A value of 0.71 mM is quoted for $[Mg^{2+}]$ and 0.92 mM is quoted for $[Mg]$ at room temperature.¹⁵

We have measured total and freely ionised Mg and Ca in plasma samples from healthy volunteers and patients undergoing cardiopulmonary bypass (CPB) surgery. We find that there are no large changes to $[Ca]$ and $[Mg]$ after such surgery but that $[Mg^{2+}]$ falls after several hours. This is not associated with a corresponding reduction in $[Ca^{2+}]$.

Patients and methods

ION SELECTIVE ELECTRODE MANUFACTURE AND CALIBRATION

Manufacture

Electrodes were manufactured from PVC tube with a ceramic plug over which was cast a thin layer of ion sensitive material. The ion sensitive materials used were: Mg^{2+} , ETH

Department of
Physiology, UMDS,
St Thomas's Campus,
London
C H Fry

Department of
Clinical
Pharmacology,
Hammersmith
Hospital, London
C I O Brookes

Correspondence to:
C H Fry, Department of
Physiology, UMDS,
St Thomas's Campus,
Lambeth Palace Road,
London SE1 7EH.

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5282 or ETH 7025 (3.3% w/w); Ca^{2+} , ETH 1001 (3.3% w/w); and H^+ , tri n-dodecylamine (1.0% w/w). These materials were incorporated in a PVC matrix (31.6%w/w Mg^{2+} and Ca^{2+} , or 32.8%w/w H^+) containing also bis (2-ethylhexyl) sebacate (63.0%w/w, Mg^{2+} and Ca^{2+} , or 65.7% w/w, H^+) and K tetrakis-[4-chlorophenyl borate] (2.2%w/w, Mg^{2+} and Ca^{2+} , or 0.5%w/w H^+). Full details of the manufacturing processes have been described.^{16,17} Selective electrodes for Mg^{2+} were filled with 1 mM MgCl_2 and 150 mM NaCl, Ca^{2+} sensitive electrodes with 1 mM CaCl_2 and 150 mM NaCl, H^+ sensitive electrodes with 58 mM Na citrate, 29 mM citric acid, and 63 mM NaCl. All filling solutions were saturated with AgCl. All materials were from Fluka Chemicals, Derbyshire, except ETH 5282 and ETH 7025, which were gifts from Professor W Simon, ETH, Zürich. A single streaming 3 M KCl liquid junction was used as a reference electrode. The potential difference between the reference and each ion selective electrode was measured with a high input impedance operational amplifier ($<10^{12}\Omega$) and the values were displayed on a digital read out.

Calibration

Electrodes sensitive to Mg^{2+} were calibrated in a solution in which the $[\text{MgCl}_2]$ varied between 0.3 and 10 mM and also contained 140 mM NaCl, 0–2 mM CaCl_2 and 10 mM N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulphonic acid] (HEPES), pH 7.4. Electrodes sensitive to Ca^{2+} were calibrated in a solution in which the $[\text{CaCl}_2]$ varied between 0.5 and 10 mM and also contained 140 mM NaCl, 0–1 mM MgCl_2 and 10 mM HEPES, pH 7.4. Electrodes sensitive to H^+ were calibrated with phosphate buffers made to pH 7.38 and 6.84. Figure 1 shows calibration curves for

either Mg^{2+} (A) or Ca^{2+} (B) selective electrodes. In (A) curves are shown in the absence or presence of 1 mM CaCl_2 . In (B) the Ca^{2+} electrode was calibrated in solutions containing zero and 1 mM MgCl_2 . The Mg^{2+} electrode showed a response to Ca^{2+} . This was evident as a reduced sensitivity at low $[\text{Mg}^{2+}]$ in the presence of 1 mM CaCl_2 . In theory an electrode selective only to the primary ion (Mg^{2+} or Ca^{2+}) should exhibit a linear response with the axes of fig 1. The continued deviation from linearity in zero Ca (A) and zero Mg solution (B) reflects interference from Na^+ . The range of $[\text{Na}^+]$ in the plasma samples was between 125 and 145 mM, and in separate experiments variation of the $[\text{Na}^+]$ in this range had no effect on the calibration curves of either electrode. Addition of 5 mM KCl or 20 mg/ml bovine serum albumin to the calibrating solutions were also without effect on the calibration curves. Thus it may be concluded that variation of plasma $[\text{Na}^+]$, $[\text{K}^+]$ or protein concentration would not influence the electrode readings.

CLINICAL AND EXPERIMENTAL METHODS

Blood samples and analysis

Venous blood (20 ml) was drawn through intravenous lines from 12 healthy volunteers and 20 patients undergoing cardiopulmonary bypass (CPB) for either coronary vein grafting or valve replacement. Blood was taken about one hour before CPB, about one hour after CPB, and then 24 hours after CPB. Samples were immediately centrifuged at 1000 g for 10 minutes and the plasma fraction was divided into two. One was frozen at -20°C for subsequent measurement of Mg^{2+} and Ca^{2+} , the second was retained for analysis of Na^+ , K^+ , albumin, total protein, $[\text{Ca}]$, and $[\text{Mg}]$. From the retained sample 1 ml was used to find the $[\text{Na}^+]$ and $[\text{K}^+]$ with a Synchron CX analyser, which incorporates a glass Na^+ sensitive electrode and a valinomycin based K^+ sensitive electrode. Albumin concentration was measured spectrophotometrically with bromocresol green ($A_{\text{max}} = 628 \text{ nm}$)¹⁸ and the rest of the retained sample was acidified with HCl ($<\text{pH } 1.5$) for measurement of $[\text{Mg}]$ and $[\text{Ca}]$ by atomic absorption spectrophotometry. Measurement of $[\text{Mg}]$ included a reaction with calmagite (COBOS BioAnalyser, Roche UK). Patients undergoing CPB formed two groups. One group received St. Thomas's cardioplegic solution (containing 16 mmol MgCl_2) and the other (whose hearts were made to fibrillate) received a single bolus of 16 mmol MgSO_4 . No differences in the results between these two groups were found. Rhythm disturbances were documented through continuous electrocardiographic monitoring and records were kept of plasma $[\text{Na}]$, K requirements, frusemide supplements, and antiarrhythmic drugs.

Experimental protocol and calculations

Measurements were carried out in a water jacketed chamber at 37°C into which protruded a reference, Mg^{2+} , Ca^{2+} , and H^+

Figure 1 Calibration curves of Mg^{2+} (A) and Ca^{2+} (B) sensitive electrodes. The ordinate in each curve is arbitrarily set at 0 mV in 10 mM of the primary ion, Mg^{2+} respectively. Values are mean (SD), $n = 2-6$.

sensitive electrodes. Electrodes were initially calibrated in the appropriate solutions after which the plasma sample was introduced into the chamber. The pH of the plasma sample was maintained between 7.37 and 7.45 and readings from the Ca^{2+} and Mg^{2+} selective electrodes taken. The influence of Mg^{2+} on the Ca^{2+} sensitive electrode is minimal (fig 1B) so that the plasma $[\text{Ca}^{2+}]$ could be determined directly from the Ca^{2+} electrode reading and the calibration curve. The effect of Ca^{2+} on the Mg^{2+} electrode was significant and it was necessary to calibrate the Mg^{2+} electrode again in a solution in which the $[\text{Ca}^{2+}]$ was that measured by the Ca^{2+} electrode. This calibration curve was then used to find the $[\text{Mg}^{2+}]$ of the plasma sample. To ascertain the accuracy with which the Mg^{2+} selective electrode could measure Mg^{2+} in the presence of Ca^{2+} , in some experiments 4 mM ethylene glycol tetra-acetic acid was added (at constant pH) to different fractions of the plasma sample to chelate Ca^{2+} , and the $[\text{Mg}^{2+}]$ was again measured. It was judged that Mg^{2+} ions were not bound by this procedure because of the lack of a pH change when MgCl_2 was added to the sample. In this situation the Mg^{2+} selective electrode was calibrated in solutions containing no added Ca^{2+} . Similar results were found with both procedures indicating that Ca^{2+} interference could be accurately estimated.

Results

VALUES IN PLASMA FROM NORMAL VOLUNTEERS

The $[\text{Mg}]$, $[\text{Mg}^{2+}]$, $[\text{Ca}]$, and $[\text{Ca}^{2+}]$ were measured in the plasma of 12 healthy volunteers (table). The proportion of $[\text{Mg}^{2+}]$ and $[\text{Ca}^{2+}]$ compared with $[\text{Mg}]$ and $[\text{Ca}]$ was 56% for Mg and 43% for Ca. The variability of these values was investigated by measuring each of them over five successive days. Blood samples were taken from three subjects at mid morning each day and the plasma was separated immediately. There was no significant trend in any of the values over this period. For these three subjects the values obtained on the first day have been included in the table.

Total and freely ionised magnesium and calcium ($[\text{Mg}]$, $[\text{Ca}]$, $[\text{Mg}^{2+}]$ and $[\text{Ca}^{2+}]$), $[\text{Na}^+]$, and albumin concentrations in plasma from healthy volunteers and patients undergoing cardiopulmonary bypass

Variable	Controls	Before operation	After operation	
			1 h	24 h
$[\text{Mg}]$ (mM)	0.86 (0.12)	0.67 (0.07)*	0.70 (0.09)	0.73 (0.11)*
$[\text{Mg}^{2+}]$ (mM)	0.48 (0.06)	0.53 (0.16)	0.50 (0.17)	0.18 (0.05)***
$[\text{Ca}]$ (mM)	2.34 (0.06)	2.25 (0.15)		2.06 (0.10)***
$[\text{Ca}^{2+}]$ (mM)	1.01 (0.13)	1.07 (0.27)		0.95 (0.27)**
$[\text{Na}]$ (mM)	145 (1)	138 (5)		139 (3)
Albumin (mg/ml)		36.9 (5.0)		33.6 (4.6)*
$[\text{Mg}]/\text{albumin}$		0.018 (0.002)		0.022 (0.004)**
$[\text{Mg}^{2+}]/\text{albumin}$		0.014 (0.004)		0.005 (0.001)***
$[\text{Ca}]/\text{albumin}$		0.062 (0.008)		0.062 (0.007)
$[\text{Ca}^{2+}]/\text{albumin}$		0.029 (0.008)		0.029 (0.008)

*p < 0.05; **p < 0.01; ***p < 0.001 compared with values before operation period (t test).
†p < 0.001 between controls and patients before operation.
Values are mean (SD); n = 12 controls and 20 patients.

VALUES IN PLASMA FROM PATIENTS UNDERGOING CPB

The table shows values from 20 patients who underwent CPB during cardiac surgery. Samples were taken immediately before the operation in the premedication room, one hour after CPB, and a final one 24 hours after bypass. The table also shows values of plasma $[\text{Na}^+]$, and albumin. The albumin values were measured to correct the magnesium and calcium concentrations for any possible net dilution or concentration of the plasma over the period of examination. Figure 2 shows these values of $[\text{Mg}]$, $[\text{Mg}^{2+}]$, and $[\text{Ca}^{2+}]$ before and after CPB.

All 20 patients received K supplements to maintain their serum concentrations at 4–5 mmol/l. These requirements varied between 20 and 150 mmol in the 24 hours after CPB (mean (SD) 76 (30) mmol). There was, however, no correlation between the K requirement and $[\text{Mg}]$, $[\text{Ca}]$, $[\text{Mg}^{2+}]$, or $[\text{Ca}^{2+}]$ 24 hours after CPB. Frusemide supplements were given to improve urine output in 13 patients, varying between 20 and 250 mg over the 24 hour period, and again no correlation was found between $[\text{Mg}]$, $[\text{Ca}]$, $[\text{Mg}^{2+}]$, or $[\text{Ca}^{2+}]$ and diuretic quantity given 24 hours after CPB. Antiarrhythmic treatment was necessary for five patients who had rhythm disturbances in this period. Four patients had paroxysmal atrial tachyarrhythmias and received digoxin or amidorone, and one patient had haemodynamically significant ventricular extrasystoles that were suppressed with lignocaine.

Figure 2 shows that one hour after CPB $[\text{Mg}]$ and $[\text{Mg}^{2+}]$ were unaltered compared with the preoperative values. After 24 hours, however, $[\text{Mg}^{2+}]$ was significantly reduced by a mean (SD) of 0.35 (0.15) mM, despite a small but significant rise in $[\text{Mg}]$. The $[\text{Ca}^{2+}]$ and $[\text{Ca}]$ both showed small but significant reductions. The plasma $[\text{Na}^+]$ was not signifi-

Figure 2 Values of $[\text{Mg}]$ and $[\text{Ca}]$ (whole box) and $[\text{Mg}^{2+}]$ and $[\text{Ca}^{2+}]$ (shaded box) in plasma samples from patients undergoing cardiopulmonary bypass surgery. Samples were taken before operation and one and 24 hours after surgery. Significance values are compared with the preoperative value, *p < 0.05; **p < 0.01; ***p < 0.001. Values are mean (SD), n = 20.

cantly changed throughout the experimental period, but plasma albumin concentrations were reduced 24 hours after CPB. Division of $[Mg]$, $[Ca]$, $[Mg^{2+}]$ and $[Ca^{2+}]$ by the $[Na^+]$ of each sample gave the same conclusions as those found from comparing the individual concentrations and have not been included in the table. Division by the albumin concentrations of each sample altered some of the conclusions compared with the unaltered values. The $[Mg^{2+}]$ remained significantly reduced and was still accompanied by a small rise in $[Mg]$. The $[Ca]$ and the $[Ca^{2+}]$ ratios, however, were now similar both before and 24 hours after CPB.

The $[Mg]$ and $[Mg^{2+}]$ were compared between the small group of patients ($n = 5$) showing dysrhythmias and those who remained in sinus rhythm ($n = 15$). No significant differences were found with either variable ($[Mg]$ 0.80 (0.14) *v* 0.71 (0.09); $[Mg^{2+}]$ 0.17 (0.04) *v* 0.19 (0.06)).

Discussion

The experiments have shown that $[Mg^{2+}]$ and $[Ca^{2+}]$ in plasma can be measured and changes detected under particular conditions. The Mg^{2+} selective electrodes showed significant and variable Ca^{2+} sensitivity which needed correction in the samples both to measure Mg^{2+} and to maintain constant pH. Figure 1(4) shows the calibration curves of the three electrodes used in our study, but many other electrodes exhibited a greater Ca^{2+} interference, which rendered them useless. Further work is required to be able to manufacture consistently usable electrodes.

About 60% of the total Mg in plasma from normal volunteers is ionised. This value is similar to that found by others at room temperature.¹⁵ The concentration and fraction of Ca^{2+} is also similar to that measured by others.¹⁹ It is of interest that with the small data sets reported here the preoperative $[Mg]$ was significantly less in patients about to undergo CPB than that in healthy volunteers (table 1: 0.67 (0.07) *v* 0.86 (0.12); $p < 0.001$, unpaired *t* test). The $[Mg^{2+}]$ was not dissimilar (table 1: 0.53 (0.16) *v* 0.48 (0.06); $p > 0.05$, unpaired *t* test) and shows that alterations to $[Mg]$ are not necessarily reflected in the ionised fraction. One possible reason for the low $[Mg]$ in the patient group is that all but six were taking frusemide as a diuretic, which is known to lead to both K^+ and Mg^{2+} loss in the urine.²⁰ No significant differences were measured in either $[Ca]$ or $[Ca^{2+}]$ in the two groups.

Cardiac standstill in this patient group at St Thomas's Hospital was induced with either hypothermic cardioplegic solution, containing 16 mM $MgCl_2$ ²¹ or the patients were made to fibrillate and given a single bolus of 16 mmol $MgCl_2$. It is anaesthetic policy at this hospital to give Mg before CPB as significant hypomagnesaemia has been shown to follow cardiac surgery without this supplement.²² Therefore it was not possible to compare these data with those from patients

not receiving $MgCl_2$ during CPB. An original objective was to find whether $[Mg]$ and $[Mg^{2+}]$ were raised in such patients who had undergone CPB. No differences, however, in $[Mg]$ or $[Mg^{2+}]$ were recorded immediately after bypass, but 24 hours later $[Mg^{2+}]$ was significantly lowered, despite a small but significant rise in $[Mg]$. The $[Mg]$ data should be compared with those of others who also noted a transient hypermagnesaemia.^{22, 23} The fact that $[Mg^{2+}]$ fell some hours after CPB may be implicated in the high incidence of arrhythmias at about this time²⁴ and suggests that such problems may be reversed by Mg infusion. We noted a 25% incidence of arrhythmias in our small sample but we were unable to correlate $[Mg^{2+}]$ with the presence of such disturbances. Such arrhythmias cannot be explained by hypokalaemia as supplementation with K maintained normal physiological values throughout this period. Clearly a larger sample needs to be studied to clarify the relation between $[Mg^{2+}]$ and arrhythmogenesis.

Such measurements imply that there is an increase in some Mg^{2+} binding ligand during the first 24 hours after operation and may be related to the solutions used after CPB or some factor released into the blood stream perioperatively. This ligand would seem to have a preference to bind Mg^{2+} over Ca^{2+} . Despite the higher initial $[Ca^{2+}]$ compared with $[Mg^{2+}]$ either preoperatively or immediately after operation, the $[Mg^{2+}]$ fell by 0.35 (0.15) mM but the $[Ca^{2+}]$ was reduced by only 0.12 (0.16) mM. The difference between the two reductions is significant ($p < 0.001$). The fall of $[Mg^{2+}]$ was highly correlated to the preoperative $[Mg^{2+}]$ ($r = 0.96$, $p < 0.001$) so that a constant proportion was removed from the plasma at this time whereas such a correlation was lacking with the $[Ca^{2+}]$ data. Moreover the reduction of both $[Ca]$ and $[Ca^{2+}]$ was mirrored by a reduction of the plasma albumin concentration, so that when the $[Ca]$ and the $[Ca^{2+}]$ were corrected for a unit albumin concentration (table) there was no significant fall of either variable. The reduction of ionised $[Mg^{2+}]$ and the increase of total $[Mg]$ were both accentuated when adjusted for the albumin concentration, which suggests that a ligand with a specificity for Mg^{2+} over Ca^{2+} must be present during this period. One possibility is that components of plasma substitutes used during and after surgery persist for a considerable time. All patients received hetastarch, which may show divalent cation binding ability. In vitro experiments will find if this is a likely possibility. Another possibility is that acute phase proteins released in response to operative stress may show such selective binding. Such a hypothesis may be tested by making measurements on plasma samples taken from patients undergoing laparotomy or those who have had extensive trauma.

In conclusion, these experiments show that measurement of $[Mg^{2+}]$ is possible in plasma samples if care is taken to also measure the

[Ca²⁺] to allow for correction of effects of interference. Moreover, significant changes to the [Mg²⁺] can take place independently of [Mg]. If the ionised fraction is that which exerts biological actions on cardiac and vascular smooth muscle some caution must be exercised when interpreting data from measurements of total Mg in plasma.

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