Blood magnesium concentration and dopamine or dobutamine infusion demand in patients during CABG (Coronary artery bypass grafting) with normovolemic haemodilution

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Abstract. It is well known that magnesium (Mg) plays an essential role in cardiac protection. Mg has many beneficial effects on the myocardium and cardiac function, e.g., it improves contractility and reduces the number of cardiac arrhythmia episodes. The inotropically positive effects of Mg are interesting and worth stressing. High blood Mg concentration may result in an increase in cardiac contraction strength, which may be important for haemodynamic stabilization, and thus it is likely to decrease the demand for dopamine and dobutamine infusions. However, the exact determination of correlation between blood Mg concentrations and dopamine or dobutamine infusion demand is still unknown. The aim of the study was to assess the demand for dopamine or dobutamine infusion in relation to changes in blood magnesium concentrations in patients undergoing CABG (Coronary artery bypass graft) with extracorporeal circulation and normovolemic haemodilution. The study included 20 male patients, aged 53-70 (61.1 ± 6.9) who underwent general anaesthesia and coronary artery bypass grafting (CABG) with extracorporeal circulation (ECC) and normovolemic haemodilution (NH) due to stable angina pectoris. The patients were retrospectively divided into three groups: A – patients who did not receive dopamine or dobutamine infusion, B – those receiving only D infusion in the doses dependent on their clinical state and C – those receiving DB infusion in the doses dependent on their clinical state. Mg was measured in 7 stages: 1) just before anaesthesia after the radial artery cannulation, 2) during normovolemic haemodilution and ECC, 3) immediately after surgery, 4) in the evening of the surgery day, 5) in the morning of the 1st postoperative day, 6) in the evening of the 1st postoperative day, 7) in the morning of the 2nd postoperative day. The spectrophotometric methods were used to determine Mg. The CABG procedure resulted in a decrease in Mg. Its level returned to normal in the evening of surgery day. The NH caused a similar Mg decrease in groups A, B and C, but these significantly low values of Mg were observed only in stage 2. There was no correlation between blood Mg concentrations and dopamine or dobutamine infusion demand. In conclusion: 1) The CABG procedure resulted in decreased blood magnesium concentrations. 2) The Mg changes do not correlate with dopamine or dobutamine infusion demand.

Key words: magnesium, dopamine, dobutamine, CABG, extracorporeal circulation
It is well known that magnesium (Mg) is one of the intracellular cations essential for many vital functions. Its disorders may cause many life-threatening dysfunctions, particularly of the heart cells. Hypomagnesemia leads to supraventricular cardiac arrhythmias, atrial fibrillation, lengthened P-R and Q-T segments, or even ventricular fibrillation. Therefore, many authors emphasize a significant role of normomagnesemia in patients with cardiovascular diseases [1–3]. On the other hand, Mg has “inotropically positive” effects on the myocardium. The left ventricle work index elevated during Mg supplementation [4] in patients with the stunned myocardium after extracorporeal circulation (ECC – ExtraCorporal Circulation) seems to be interesting and worth stressing.

The beneficial effects of Mg on the extent of myocardial infarct in patients after ECC should be underlined. It is well known that Mg is a vasodilator of coronary vessels; it improves myocardial metabolism and inhibits cell calcium accumulation. Ravn et al. [5] who investigated the effect of Mg on the infarct extent in pigs showed that Mg infusion reduced the myocardial ischaemic area by more than 50% and stabilized heart mechanical function. Likewise, Christensen et al. [6] underlined that Mg reduced the extent of infarct but only when administrated before reperfusion. The positive effect of Mg may also result from its significant role in the patomechanism of reperfusion injury. Thus, it may be suggested that intraoperative Mg intravenous infusion is important and required in patients undergoing CABG (Coronary artery bypass grafting). On the other hand, many studies have underlined that ECC results in decreased blood Mg concentration [7, 8]. The complexity of ECC and the intra- and postoperative treatment administered may disturb hormonal balance, which results in increased blood hormone levels, mainly catecholamines [7]. It should be stressed that those changes result not only from surgical stress but also from intraoperative normovolemic haemodilution (NH) [7–9].

It is well known that many patients with “stunned heart” just after ECC needed dopamine (D) or dobutamine (DB) infusion. Taking into account the inotropically positive action of Mg and significantly improved coronary flow, one can suppose that high blood Mg concentration may reduce this demand for D or DB. However, the exact correlation between the blood Mg concentration and demand for D or DB infusion is not clear.

The aim of the study was to assess the demand for dopamine or dobutamine infusion in relation to changes in blood magnesium concentrations in patients undergoing CABG with extracorporeal circulation and normovolemic haemodilution.

**Patients and methods**

The study was approved by the Bioethical Committee of the Medical University of Lublin (No KE-0254/244/2000) and included the patients who underwent surgery due to I° and II° coronary disease (according to CCS). The patient’s anaesthesia and ECC procedure were described in a previous publication [7].

All patients received the same premedication composed of lorazepam (Lorafen, Polfa, Poland) and morphine (Morphicum hydrochloricum, Polfa, Poland). The patients underwent general anaesthesia with fentanyl (Fentanyל, Polfa, Poland) in the dose of 0.01-0.02 mg/kg body wt., midazolam (Dormicium, Roche) - 0.05-0.1 mg/kg body wt. and etomidate (Hypnomidat, Janssen, Germany) - 0.1-0.5mg/kg. Muscle relaxation was obtained by injecting a single dose (0.08-0.1mg/kg body wt.) of pancuronium (Pavulon, Organon-Teknica, France). The anaesthesia was maintained throughout the procedure using midazolam-fentanyl infusion and inhalation of fractionated doses of foran (Isofluran, Abbot, USA). During the implantation of aorto-coronary by-passes the circulation and ventilation were maintained by the heart-lung machine S III (Stockert). The following substances were used for priming: Ringer’s solution (Ringer, Fresenius-Kabi, Germany) – 1000 mL, 6% solution of hydroxyethylated starch (HAES, Fresenius-Kabi, Germany) – 500 mL, 20% mannitol (Mannitol, Fresenius-Kabi, Germany) – 250 mL, sodium hydroxy carbonate (Natrium bicarbonatum, Polfarma, Poland) – 20 mL, and heparin – 75 mL. The same priming was used for all patients. Cardioplegia was prepared using 0.9% salt solution supplemented with 3g of potassium chloride (Kalium chloratum, Polfa, Poland) and 20 mL of sodium hydroxycarbonate. During surgery all patients received potassium infusions in the doses dependent on its blood concentrations. None of them received Mg supplementation before, during and after surgery.

The patients were retrospectively divided into three groups: A – patients who did not receive dopamine or dobutamine infusion, B – those receiving only D infusion in doses dependent on their clinical state and C – those receiving DB infusion in doses dependent on their clinical state.

The blood samples were collected from the radial artery in 7 stages: 1) just before anesthesia after the radial artery cannulation, 2) during normovolemic
haemodilution and ECC, 3) immediately after surgery, 4) in the evening of the surgery day, 5) in the evening of the 1st postoperative day, 6) in the morning of the 1st postoperative day, 7) in the evening of the 2nd postoperative day. Next the blood was immediately centrifuged (25000 r/min., temp. 0°C); the obtained serum was frozen at -20°C. The blood Mg concentrations were determined by spectrophotometric methods.

Transthoracic echocardiography was used for the ejection fraction (EF) and left ventricular isodiastolic diameter (LVIDd) measured (Teicholtz methods) for cardiac function control (before surgery and on the 1st and 2nd postoperative days).

The results were statistically analyzed using the Wilcoxon and Mann-Whitney U-tests to determine the interstage and intergroup relations.

Results

The study included 20 men aged 53-70 (61.1 ± 6.9). Sixteen patients had myocardial infarction during the 3 years preceding the operation and eighteen were treated for arterial hypertension (I° or II°). None of them was treated other than for cardiologic diseases or underwent resuscitation due to cardiac arrest (table 1).

In the group examined, six patients did not require pharmacological circulatory support (group A), seven received dopamine infusions in doses dependent on their clinical state (on average – 7.3 μg/kg body wt./min ± 3 in stages 3 and 4 - group B), and other seven (group C) received dobutamine infusions in stages 3 and 4 (on average - 5.7 μg/kg body wt./min ± 2.5). None of the patients needed catecholamine infusions in last stages.

The CABG procedure (stages 2 and 3) resulted in a decrease in blood Mg concentration (figure 1). Mg returned to normal in the evening of surgery day.

The normovolemic haemodilution caused a similar decrease of blood Mg concentration in groups A, B and C (figures 2, 3, 4), but these significantly low values of Mg were observed only in stage 2. There were no intergroup changes between groups A, B and C.

There were no significant changes in EF and LVIDd measurements and these values did not correlate with blood Mg concentration before surgery and on the 1st and 2nd postoperative days. There were no correlations between blood Mg concentrations and dopamine or dobutamine infusion demand.

Discussion

Changes in blood Mg concentrations during cardio-surgical procedures are still being examined and are not yet explicitly described. Many reports underline the importance of normomagnesemia, particularly during surgery and in the early postoperative period [10, 11]. The antiarrhythmogenic effect of Mg is worth stressing. It is well known that intra- and postoperative arrhythmias may lead to low cardiac output and then to cardiogenic shock. Hypomagnesemia may also be a diagnostic factor allowing the prediction of many life-threatening arrhythmias [10, 12, 13]. The observations by Zaman et al. [13], which concerned the changes in the P wave and serum magnesium and potassium levels in patients after myocardial revascularization, seem to confirm this. According to them, hypomagnesemia observed on the first postoperative day is a relevant symptom preceding atrial fibrillation. Ceremuzynski et al. [14], who studied the blood Mg concentration in 588 consecutive patients with low left ventricular ejection fraction and heart insufficiency in II-IV NYHA class, underlined that intravenous Mg supplementation caused a significant decrease of ventricular arrhythmias. Many authors stressed the fact that early Mg supplementation prevented such complications [10,

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>59.4 ± 4.6</td>
<td>64.4 ± 8.1</td>
<td>60.5 ± 6.9</td>
</tr>
<tr>
<td>BMI</td>
<td>26.39</td>
<td>28.7</td>
<td>28.1</td>
</tr>
<tr>
<td>(median; min; max)</td>
<td>(23.11; 29.1)</td>
<td>(24.2; 29.92)</td>
<td>(23.5; 28.6)</td>
</tr>
<tr>
<td>EF</td>
<td>48.4%</td>
<td>52.9%</td>
<td>53.1%</td>
</tr>
<tr>
<td>(median; min; max)</td>
<td>(45%; 69%)</td>
<td>(42%; 59%)</td>
<td>(38%; 64%)</td>
</tr>
<tr>
<td>LVIDd</td>
<td>5.22 cm</td>
<td>5.59 cm</td>
<td>5.48 cm</td>
</tr>
<tr>
<td>(median; min; max)</td>
<td>(3.8 cm; 6.9 cm)</td>
<td>(3.1 cm; 7.9 cm)</td>
<td>(4.1 cm; 8.1 cm)</td>
</tr>
</tbody>
</table>

No significant differences between groups A, B and C.
Moreover, Parra et al. [11] pointed out a significant relation between hypomagnesemia and arrhythmia as well as low stroke volume. According to them, prolonged low Mg levels in serum exerted direct effects on perioperative mortality among patients subjected to CABG. Interestingly, clinically significant hypomagnesemia was mainly observed in patients treated with β-blockers, which may be important in patients with stunned myocardium just after ECC. Most of them needed inotropic drugs, such as dopamine or dobutamine infusion. Sommers et al. [17], who studied intracellular Mg concentrations and high-energy phosphate levels in pre- and postischaemic rat hearts, showed that stunned hearts had elevated Mg concentrations. According to them, dobutamine infusion improved the contractile

**Figure 1.** The changes in blood magnesium concentration in all 20 patients. Comparison with stage 1.

**Figure 2.** The changes of blood magnesium concentration in patients who did not receive dopamine or dobutamine infusion. Comparison with stage 1.
cardiac function but decreased Mg to preischaemic levels despite beneficial effects on intracellular energetic. Likewise, Howarth et al. [18] in their study on the effects of β-adrenergic heart cell stimulation by isoprenaline demonstrated efflux of Mg during its activation. Moreover, they underlined that perturbation of Mg had an important influence on myocardial contractility. Watanabe et al. [19] stated that intracellular Mg concentrations were controlled by sympathetic and parasympathetic activities (through β-adrenergic receptor stimulation). Furthermore, the prolonged stimulation of β-adrenoreceptors may be harmful to the cardiac function. In vitro β1-adrenoreceptor activation increased heart cell

**Figure 3.** The changes of blood magnesium concentrations in patients who received dopamine infusion. Comparison with stage 1.

**Figure 4.** The changes of blood magnesium concentrations in patients who received dobutamine infusion. Comparison with stage 1.
apoptosis, whereas β2-adrenergic activation reduced the process of cell self-destruction [20]. According to Dostanic et al. [21] this pathology resulted from mitochondria pathways. Examining the effect of β-adrenergic stimulation by isoproterenol, dobutamine and metaprolol in mice hearts they showed that catecholamine infusion resulted in decreased Bcl-1 and increased Bax and BNIP1 expression, which was characteristic of mitochondria-dependent apoptosis pathway activation. It is difficult to define precisely the role of Mg decrease in the initiation of myocyte apoptosis during β-adrenoceptor activation. However, it seems that intracellular Mg levels may depend on β-adrenoreceptor activity and generally have protective effects on heart cell function.

Analyzing the changes in blood Mg levels, the correlation between Mg and ischaemic heart area is worth stressing. This seems to be very important in patients with post-extracorporeal stunned hearts, who require inotropic drug infusion. In the study on the effects of Mg infusion on myocardial infarct extent in 21 3-month-old pigs Ravn et al. [5] demonstrated that intravenous Mg infusion was capable of reducing the infarct extent by more than 50%. Moreover, the Mg treatment had positive effects on EF and left ventricular function. Likewise, other authors described the myocardial infarct reducing effect of Mg [6, 22, 23], however, its mechanism is still not well known. Vigorito et al. [24] reported that Mg increased coronary blood flow in normal, unchanged heart arteries; Dickens et al. [25] showed that Mg blocked free radical formation in cell cultures, while du Toit et al. [26] demonstrated that Mg decreased cystolic calcium levels by inhibition of the inward flux of calcium ions through sarcolemmal calcium channels and possibly intracellular sites as well. Therefore, it may be assumed that Mg supplementation is particularly relevant in patients with impaired heart function after extracorporeal circulation, because the reduction of cardiac ischaemia have an impact on dopamine or dobutamine demand and thus for cardiac contractility.

Analysing the dopamine or dobutamine demand in relation to blood Mg concentrations in patients with post-extracorporeal stunned heart, the catecholamine dependence on this electrolyte is worth stressing. Mg is known to affect E and NE secretion to the circulatory system. Moreover, Mg reduces intramyocardial norepinephrine concentrations, which is important for diastolic heart function [27]. Examining the development of myocardial insufficiency Banfi et al. [28] showed that this pathology was strictly connected with the activation of the neurohormonal system, the production and release of NE, in particular. A drop in stroke volume and decrease in myocardial contraction cause an increase in the metalloprotein 2 level leading to the accumulation of the above - mentioned substances in fibroblasts. Increased concentrations of these substances significantly limit the diastole of the myocardium contributing to further impairment of its function. On the other hand, Mg has a beneficial effect on diastolic left ventricular function [2, 15, 29]. According to Moens et al. [30], Mg affected the potassium-potassium pump and ATPase leading to a decrease in intracellular potassium, elevation in calcium and myocyte swelling. Therefore, high blood Mg concentrations prevent the production of oxygen reactive species which initiate myocyte apoptosis; this in turn results in post - reperfusion myocardial cardiogenic insufficiency [31].

All these facts seem important for dopamine or dobutamine demand in patients with stunned myocardium; however, this relation is not fully explained and requires further detailed studies.

Conclusion

The study showed significant effects of coronary artery bypass grafting with extracorporeal circulation procedures on blood magnesium concentrations. However, changes in blood Mg concentrations did not correlate with dopamine or dobutamine infusión demand. Further studies are needed to determine accurate effects of this relation and dopamine and dobutamine influence on heart contractility function.

References


