The relationship between magnesium, epinephrine and norepinephrine blood concentrations during CABG with normovolemic hemodilution

K. Pasternak¹, W. Dąbrowski², T. Wyciszczok¹, A. Korycińska³, J. Dobija¹, J. Biernacka², Z. Rzecki²

¹ Department of General Chemistry; ² Department of Anaesthesiology and Intensive Care; ³ Department of Clinical Immunology; ⁴ Feliks Skubiszewski Medical University of Lublin, Poland

Correspondence: K. Pasternak, PhD, MD Chair and Department of General Chemistry, Feliks Skubiszewski Medical University of Lublin, Staszica 4, 20-081 Lublin, Poland or W. Dąbrowski, PhD, MD Chair and First Department of Anaesthesiology Intensive Care, Feliks Skubiszewski Medical University of Lublin, Jacewskiego 8, 20-954 Lublin, Poland. <wojciechdabrowski@interia.pl>

Abstract. The effects of procedures with extracorporeal circulation on the disturbance of relationships between blood magnesium (Mg), epinephrine, and norepinephrine levels have not been explicitly explained. It is assumed that both hypomagnesemia and increased concentration of the above mentioned hormones exert adverse effects on the myocardium often causing life threatening disorders. This problem is particularly important in cases of stunned myocardium, observed after extracorporeal circulation procedures. The complex nature of the procedures and the intraoperative normovolemic hemodilution (NH) employed are likely to alter Mg, epinephrine, and norepinephrine concentrations, as well as the above mentioned relations. The aim of the study was to evaluate the changes in blood Mg, epinephrine and norepinephrine concentrations in patients undergoing extracorporeal circulation and normovolemic hemodilution. The study encompassed 16 men operated on for stable coronary disease (I or II° according to the Canadian Scale). The patients were divided into two groups according to body weight: A) patients weighing less than 75 kg and B) patients weighing more than 75 kg. The degree of NH caused by constant volume of priming (1800 mL) was determined on the basis of hematocrit measurements and in relation to body weight. The examinations were conducted in 5 stages: 1) after radial artery cannulation before anaesthesia and surgery, 2) during hemodilution and deepest hypothermia, 3) after surgery before sending the patient to Intensive Postoperative care Unit, 4) in the first postoperative day, 5) in the second postoperative day. The observations showed an increase in epinephrine levels in group A in the second stage and of norepinephrine levels in stage 4. Decreased blood Mg levels were noted in all the patients in the second stage, however in group A significantly lower values were also observed in stage 3. Moreover, the correlation between Mg level changes and blood epinephrine and norepinephrine levels were observed. The study revealed significant effects of extracorporeal circulation procedures on adrenergic reactions as well as blood magnesium concentrations. It seems that the degree of NH is the main factor determining blood levels of Mg, epinephrine and norepinephrine during the use of a heart-lung apparatus, which may be particularly relevant in patients with impaired heart function and low body weight.

Keywords: magnesium, epinephrine, norepinephrine, CABG
It is well known that magnesium (Mg) is the fourth most common mineral salt in humans and that it plays a vital role in the physiology, particularly during stress situations. Hypomagnesemia is frequent perioperatively and causes considerable morbidity. The physiological level of Mg in blood serum ranges from 0.8 to 1.2 mmol/L, 24% combined with proteins, 10% in complexes and 65% in the ionized form; deficiency of Mg in blood may cause many disorders which often require intensive treatment. Therefore, many researchers underline the role of normomagnesemia in blood, especially in patients with myocardial pathology [1, 2]. Myocardium dysfunctions are mostly associated with abnormal irritability and conductivity of the stimulus-transmitting system, which on ECG initially manifests itself as longer P-R and Q-T waves, while at higher levels of deficiency – as tachycardia, atrial fibrillation, preterm ventricular beats and in extreme cases – ventricular fibrillation. Lower serum Mg concentrations have been found to be associated with an increased incidence of atrial fibrillation after cardiac surgery [3]. England et al. [4] underline a beneficial role of Mg supplementation in reducing ventricular dysrhythmias. Therefore, this problem is particularly important in patients subjected to cardiomedical procedures with extracorporeal circulation (ECC) [5]. The complex nature of such procedures, especially intraoperative normovolemic hemodilution (NH) may alter blood Mg levels, which is likely to result in some degree of stress adrenergic reaction and dysfunctions of many organs, particularly postoperatively stunned myocardium. The aim of the study was to analyze the changes in blood magnesium levels compared to blood epinephrine and norepinephrine concentrations in patients undergoing coronary artery bypass procedures with ECC and normovolemic hemodilution.

Patients and methods

The study was approved by the Bioethical Committee of the Medical University of Lublin (n° KE-0254/244/2000) and included patients who underwent operations due to I° and II° coronary disease (according to CCS - Canadian Cardiovascular Society).

In the evening preceding the operation the patients were administered premedication – oral lorazepam (Lorafen, Polfa, PL) – 2 mg and i.m. Promethazine (Dophergan, Polfa, PL) – 50 mg. One hour before anaesthesia all the patients received oral lorazepam – 3 mg and i.m. morphine (Morphicum hydrochloricum, Polfa, PL) – 0.1 mg/kg body weight. The patients underwent general anaesthesia with fentanyl (Fentanyl, Polfa, PL) at the dose of 0.01-0.02 mg/kg body weight., midazolam (Dormicum, Roche),- 0.05-0.1 mg/kg body weight. and etomidat (Hypnomidat, Janssen, G)-0.14-0.5mg/kg. Muscle relaxation was obtained by injecting a single dose (0.08-0.1 mg/kg body weight) of pancuronium (Pavulon, Organon-Teknika, F). The anaesthesia was maintained throughout the procedure using midazolam-fentanyl infusion and inhalatory fractionated doses of foran (Isofluran, Abbot, USA). During the implantation of aorto-coronary grafts circulation and ventilation were maintained by a heart-lung machine S III (Stockert). The following substances were used for priming: Ringer’s solution (Ringer, Fresenius-Kabi, G) – 1000 mL, 6% solution of hydroxyethylated starch (HAES, Fresenius-Kabi, G) – 500 mL, 20% mannitol (Mannitol, Fresenius-Kabi, G) – 250 mL, sodium hydroxycarbonate (Natrium bicarbonatum, Polfarma PL) – 20 mL and heparin – 75 mg. The same composition of priming solution was used for all patients. Cardioplegia was prepared using 0.9% salt solution supplemented with 3 g of potassium chloride (Kalium chloratum, Polfa, PL) and 20 mL of sodium hydroxy carbonate (Natrium bicarbonatum, Polfarma PL) – 20 mL and heparin – 75 mg. The same composition of priming solution was used for all patients. Cardioplegia was prepared using 0.9% salt solution supplemented with 3 g of potassium chloride (Kalium chloratum, Polfa, PL) and 20 mL of sodium hydroxy carbonate (Natrium bicarbonatum, Polfarma PL) – 20 mL and heparin – 75 mg. The same composition of priming solution was used for all patients. Cardioplegia was prepared using 0.9% salt solution supplemented with 3 g of potassium chloride (Kalium chloratum, Polfa, PL) and 20 mL of sodium hydroxy carbonate (Natrium bicarbonatum, Polfarma PL) – 20 mL and heparin – 75 mg. The same composition of priming solution was used for all patients. Cardioplegia was prepared using 0.9% salt solution supplemented with 3 g of potassium chloride (Kalium chloratum, Polfa, PL) and 20 mL of sodium hydroxy carbonate (Natrium bicarbonatum, Polfarma PL) – 20 mL and heparin – 75 mg. The same composition of priming solution was used for all patients. Cardioplegia was prepared using 0.9% salt solution supplemented with 3 g of potassium chloride (Kalium chloratum, Polfa, PL) and 20 mL of sodium hydroxy carbonate (Natrium bicarbonatum, Polfarma PL) – 20 mL and heparin – 75 mg. The same composition of priming solution was used for all patients. Cardioplegia was prepared using 0.9% salt solution supplemented with 3 g of potassium chloride (Kalium chloratum, Polfa, PL) and 20 mL of sodium hydroxy carbonate (Natrium bicarbonatum, Polfarma PL) – 20 mL and heparin – 75 mg. 

Depending on NH, the patients were divided into 2 groups: A) those weighing < 75 kg and B) those weighing > 75 kg.

All the patients consumed their last meal 12 hours before surgery; immediately after the procedure they were transported to the Postoperative Intensive Care Unit (PICU) where they received a short-term infusion of 5% glucose solution with insulin and 3 or 6 g of potassium chloride. None of the patients received Mg infusion or any β blocker drug during surgery and the postoperative period.

The blood specimens were obtained in 5 stages: 1) just before anaesthesia after the radial artery cannulation, 2) during NH and ECC, 3) immediately after surgery, 4) in the morning of the 1st postoperative day, 5) in the morning of the 2nd postoperative day.

The blood samples were collected from the radial artery and immediately centrifuged (25000 rpm., temp. 0°C); the obtained serum was frozen at -20°C. The blood Mg concentrations were determined by spectrophotometric methods. The blood epinephrine and norepinephrine concentrations were measured by radioimmunoassay methods.
The results were statistically analyzed using the Wilcoxon, Mann-Whitney U and Spearman rank correlation tests in interstage and intergroup comparisons.

**Results**

The assessments were carried out in 16 men aged 53-70 (61 ± 6.9). 13 patients had myocardial infarction during the past 3 years and 14 were treated due to concomitant arterial hypertension (I° or II° according to WHO classification). None of the patients was treated for endocrinological, neurological and other systemic diseases or was resuscitated because of circulatory arrest. The mean duration of the procedure was 205 min ± 35 and of anaesthesia 235 min ± 30. In all the patients the aorta was typically clamped and the mean closure time was 45.1 min ± 15.5. The aorto - coronary by pass grafts were implanted in mild hypothermia 34.5°C ± 0.4. In all the cases weaning from the heart-lung machine was uneventful and there was no need of intra-aortic contrapulsion. Two patients from group A (7 patients) required dopamine infusions, 3- dobutamine infusions and 2 did not need catecholamine infusions. In group B (9 patients) two patients required dopamine infusion, 5 required dobutamine infusion and 2 required no inotropic drugs. In all the cases the postoperative course was without complications and the patients were extubated in the morning of the first postoperative day. During the examination period there were no important dysrhythmias or significant ST changes observed.

The hemodilution at initiation of cardiopulmonary bypass caused a decrease in hematocrit in both groups, however lower values were observed in group A. There were significant differences between group A and B in the 2nd (p < 0.001) and 3rd (p < 0.05) stages (table 1).

The observation of blood epinephrine concentrations showed an increase in the 2nd stage (in comparison with the 1st stage) only in patients with a body weight lower than 75 kg (p < 0.05). At the same stage there were significant differences between groups A and B (p < 0.05), and threefold blood epinephrine concentrations were noted in patients with a body weight lower than 75 kg (table 1, figure 1).

The blood norepinephrine concentrations analysis showed the highest increase in the morning of first postoperative day in group A (p < 0.05). These values were significantly higher than those in group B (table 1, figure 2).

The blood Mg concentrations decreased in the 2nd stage (p < 0.01) in group A (table 1, figures 3,4) and increased in the 4th stage in group B (p < 0.05).

The statistical analysis showed a significant relationship between blood Mg concentrations in the 1st stage and norepinephrine in the 2nd stage, Mg in the 2nd stage and norepinephrine in the 3rd stage (p < 0.05; R = -0.7907 and p < 0.01; R = -0.85714, respectively) in group A. A significant correlation was detected in the 1st stage between blood Mg and epinephrine concentrations (p < 0.05; R = 0.8), and between Mg and epinephrine in the 2nd and 4th stages (p < 0.01; R = -0.89286).

There were correlations between the blood levels of hematocrit and epinephrine in the 2nd stage (p < 0.01, R = 0.8829) in group A.

**Discussion**

It is well known that stress situations result in the catecholamines release. The stress of intubation is associated with higher blood epinephrine concentration, tachycardia and increased blood pressure. The catecholamine release from the adrenal medulla and adrenergic nerve endings is reduced by Mg. Patients treated with Mg showed a lower increase in heart rate and systolic blood pressure after intubation [6], and plasma epinephrine and norepinephrine concentrations are markedly lower in such patients [7]. It seems that this problem is very important in critically ill and hemodynamically unstable patients, as increased blood catecholamine concentrations are undesirable in such cases. Their increased levels are likely to lead to myocardial ischaemia manifesting itself in the changes in ST waves on ECG and to hemodynamic insufficiency [8]. However, it may be thought that blood concentrations of epinephrine and norepinephrine are also affected by the depth and kind of anaesthesia used. It is worth stressing that the high doses of analgesics applied in our study seem to minimize the effects of operative stress on the adrenergic reaction [9]. Thus it may be assumed that the increased epinephrine and norepinephrine levels observed in our study resulted mainly from the extracorporeal circulation procedure itself. However, it should be emphasized that high blood concentrations of catecholamines unfavorably affect the myocardium [10], which is undoubtedly an undesirable condition in patients operated on for myocardial organic injury [11]. The above-mentioned disorders may also be influenced by decreased blood concentrations of Mg, which are likely to intensify them to a great extent [1, 3, 4, 6]. The increase in catechola-
mine concentration and decrease in blood Mg concentration observed in our study may be thought to have adverse effects on the myocardium, however an explicit explanation of such disorders requires further studies.

The increased blood levels of epinephrine and norepinephrine found in our study seem to confirm the literature findings concerning extracorporeal circulation procedures [9, 12]. Significant differences in epinephrine concentrations in patients of both groups in the 3rd stage are worth pointing out. These changes may result from the dopamine or dobutamine infusions used [13], yet the relations between the blood epinephrine concentration and treatment used were not dealt with in this study. Furthermore, intraoperative NH applied in the study is likely to cause fluctuations of the above mentioned hormones. According to Estafanois et al. [17], who studied the effects of normovolemic hemodilution on blood norepinephrine concentrations in dogs, the higher the blood dilution, the higher the norepinephrine concentration. Therefore it may be supposed that higher norepinephrine concentrations during the deepest hypothermia and hemodilution in patients with lower body weight may result from higher hemodilution. It is not easy, however, to explain an increase in this parameter during the first postoperative day. This increase is likely to result from the late reaction to higher hemodilution, which is inconsistent with the findings of others [14, 15].

### Table 1. Changes of hematocrite, epinephrine, norepinephrine and magnesium blood concentrations.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Stages</th>
<th>GROUP A</th>
<th></th>
<th>GROUP B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>median</td>
<td>40.3 **</td>
<td>28.9 **</td>
<td>33.1 **</td>
</tr>
<tr>
<td></td>
<td>quartile 1</td>
<td>37.3</td>
<td>20.15</td>
<td>25.85</td>
</tr>
<tr>
<td></td>
<td>quartile 3</td>
<td>41.9</td>
<td>21.5</td>
<td>29.85</td>
</tr>
<tr>
<td>Epinephrine (ng/mL)</td>
<td>median</td>
<td>0.063</td>
<td>0.167 *</td>
<td>0.098</td>
</tr>
<tr>
<td></td>
<td>quartile 1</td>
<td>0.0605</td>
<td>0.15</td>
<td>0.0545</td>
</tr>
<tr>
<td></td>
<td>quartile 3</td>
<td>0.066</td>
<td>0.332</td>
<td>0.103</td>
</tr>
<tr>
<td>Norepinephrine (ng/mL)</td>
<td>median</td>
<td>0.205</td>
<td>0.208</td>
<td>0.143</td>
</tr>
<tr>
<td></td>
<td>quartile 1</td>
<td>0.205</td>
<td>0.208</td>
<td>0.143</td>
</tr>
<tr>
<td></td>
<td>quartile 3</td>
<td>0.111</td>
<td>0.1305</td>
<td>0.1305</td>
</tr>
<tr>
<td>Magnesium (mmol/L)</td>
<td>median</td>
<td>0.0798</td>
<td>0.687 *</td>
<td>0.978</td>
</tr>
<tr>
<td></td>
<td>quartile 1</td>
<td>0.0786</td>
<td>0.6733</td>
<td>0.81775</td>
</tr>
<tr>
<td></td>
<td>quartile 3</td>
<td>1.09935</td>
<td>0.9665</td>
<td>0.993</td>
</tr>
</tbody>
</table>

**INTERGROUP RELATIONSHIPS IN EACH STAGE**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>GROUP A</th>
<th>GROUP B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit A:B</td>
<td>–</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Epinephrine A:B</td>
<td>–</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Norepinephrine A:B</td>
<td>–</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Magnesium A:B</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* p < 0.05. ** p < 0.01.
Changes of epinephrine blood concentrations in group A

Figure 1. Changes of epinephrine blood concentrations in patients with body weight less than 75 kg – comparison with first stage.

Changes of norepinephrine blood concentrations in group A

Figure 2. Changes of norepinephrine blood concentrations in patients with body weight less than 75 kg – comparison with first stage.
Figure 3. Changes of magnesium blood concentrations in patients with body weight less than 75 kg – comparison with first stage.

Figure 4. Changes of magnesium blood concentrations in patients with body weight more than 75 kg – comparison with first stage.
infusions administered to some patients in the 3rd stage may also be of some importance [13], which also seems to explain the discrepancies in concentrations of this parameter in both groups examined. Nevertheless, further comprehensive studies are needed to explain precisely the causes of norepinephrine increases in the first postoperative day.

NH also alters the serum Mg levels [16-18]. According to Inoue et al. [16], intraoperative hemodilution is a major factor contributing to decreased Mg blood levels. Ichikawa [17] reported that decreased blood levels of this element was not only the result of hemodilution but might also be observed in the direct postoperative period. Polderman and Girbes [5] suggest that the mechanism responsible for this may be a combination of increased urinary excretion and intracellular shift, induced by a multi-stage character of ECC procedures, not only by NH. A decrease in body temperature during surgery and high urinary magnesium excretion play the main role in this pathology. Probably tubular dysfunction of the kidney results in urinary Mg excretion [5] but the effects of ECC on the kidney function are difficult to assess. Furthermore, hypomagnesemia during CABG is attributed to NH [19]. Examining the changes in blood Mg concentrations in cardiosurgical patients, Satur et al. [19] observed that initiation of NH caused a 17.3% decrease in serum Mg levels, which persisted until the first postoperative day. They concluded that the main reasons of Mg depletion are: the most important – NH and the second one – intraoperative and postoperative cellular depletions. Likewise, similar changes of blood Mg concentrations were observed in our examinations, particularly in patients with body weight lower than 75 kg.

The use of mild hypothermia (34.5°C) suggests that the degree of NH significantly alters Mg blood levels; however further observations are needed to determine the above relations in detail.

Analysing the changes in blood Mg levels, the correlations between Mg decreases and epinephrine and norepinephrine changes are worth stressing. Studying the effects of Mg infusion on blood norepinephrine concentration Shimosawa et al. [20] demonstrated, that Mg ions block N-type Ca<sup>2+</sup> channels at nerve endings inhibiting norepinephrine release and its blood concentration. Furthermore, the effects on intramyocardial norepinephrine concentrations are worth stressing. Ohtsuka et al. [21] analyzed the effects of Mg substitution on levels of the hormone in question and observed its significantly lower levels in patients with Mg infusions, which in their opinion, indicates inhibitory effects of Mg on intracardiac norepinephrine release. In our study, high blood Mg concentrations correlated with low norepinephrine levels and decreased blood Mg levels during NH significantly correlated with increased concentrations of both catecholamines. Therefore our findings are consistent with the data from the literature [20, 21].

Conclusions

1. Procedures with extracorporeal circulation result in increased epinephrine and norepinephrine concentrations and decreased Mg concentrations.
2. Higher hemodilution intensifies adrenergic reactions.
3. Procedures with extracorporeal circulation do not affect relationships between changes of blood Mg, epinephrine, and norepinephrine levels.

References


