The effect of preoperative magnesium supplementation on blood catecholamine concentrations in patients undergoing CABG

K. Pasternak¹, W. Dąbrowski², J. Dobija¹, J. Wrońska¹, Z. Rzecki², J. Biernacka²
¹ Department of General Chemistry; ² Department of Anaesthesiology and Intensive Therapy Feliks Skubiszewski Medical University of Lublin, Poland

Correspondence: Kazimierz Pasternak Prof. MD, PhD, Department of General Chemistry Feliks Skubiszewski Medical University of Lublin; Staszica 8, 20-081 Lublin, Poland; or Wojciech Dąbrowski MD; PhD; Department of Anaesthesiology Intensive Therapy Feliks Skubiszewski Medical University of Lublin; Jaczewskiego 8, 20-954 Lublin, Poland. <kazimierz.pasternak@am.lublin.pl>, <wojciechdabrowski@interia.pl>

Abstract. Background. It is well known that magnesium (Mg) plays an important role in many physiological processes such as regulation of blood catecholamine concentrations, particularly epinephrine (E) and norepinephrine (NE). The complex character of extracorporeal circulation (ECC) with intraoperative normovolemic haemodilution (NH) may alter blood Mg levels, which is likely to result in disorders of E and NE. The aim of this study was to analyze the influence of preoperative Mg supplementation on E and NE in patients undergoing CABG.

Patients and methods. Forty male patients undergoing CABG under general anaesthesia were included. Patients were randomly divided into two groups: A – the patients receiving pre-operative magnesium supplementation and B – patients without pre-operative magnesium supplementation. The Mg, E and NE blood concentrations were measured in five stages: 1) before anesthesia 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 Mg levels were determined by spectrophotometric methods, E and NE were measured by radioimmunoassay methods. Results. The CABG caused a decrease of Mg and an increase of E and NE in both groups, but the changes were significantly higher in group B. Conclusions. 1) CABG causes a decrease of Mg and an increase of E and NE; 2) Preoperative, oral supplementation of Mg substantially reduces intra- and postoperative disorders.

Keywords: magnesium supplementation, epinephrine, norepinephrine, CABG

Electrolyte disorders and their relationship with hormonal balance are one of the main subjects of clinical investigations [1, 2]. In some cases this problem is important, e.g. particularly in haemodynamically unstable patients undergoing surgical myocardial revascularization. The complex character of extracorporeal circulation (ECC) as well as the intraoperative therapy used may affect electrolyte and hormonal balance and lead to its disorders. Among them are disorders of blood magnesium concentration. It is well known that magnesium (Mg) plays a significant role in cell physiology and its deficiency may cause many disorders which often require intensive treatment. 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. It is worth stressing that even the smallest changes in Mg concentration in blood serum are reflected in its intracellular level, which, in turn, affects cellular function [3]. Moreover, even temporary or secondary deficiency of this element is likely to lead to significant clinical dysfunction of various organs and aggravate or alter the clinical picture of any underlying disease. Therefore, many researchers underline the role of normomagnesemia, especially in patients with myocardial pathology [4, 5]. Dysfunction of the myocardium is mostly associated with abnormal irritability and conductivity of the stimulus-transmitting system, which initially manifests itself on ECG as longer P-R and Q-T intervals, and, at higher degrees of deficiency, as tachycardia, atrial fibrillation, premature ventricular contractions and as ventricular fibrillation in extreme cases. On the other hand Mg plays an important role in the regulation of blood concentration of catecholamines, particularly epinephrine (E) and norepinephrine (NE). Any deficiency of blood Mg concentration results in hypercatecholaminemia followed by hypersensitization of the myocardial cells. This problem is particularly relevant in patients subjected to cardiosurgical procedures with ECC [6]. The complex nature of such procedures, especially intraoperative normovolemic haemodilution, may alter blood Mg levels, which is likely to result in the dysfunction of various organs, particularly postoperatively stunned myocardium.

The aim of this study was to analyze the influence of pre-operative magnesium supplementation on blood epinephrine and norepinephrine concentrations in patients undergoing surgical myocardial revascularization.

### Patients and methods

The study was approved by the Bioethical Committee of Medical University of Lublin (No KE-0254/244/2000) and included the patients who underwent operations due to I° and II° coronary disease (according to CCS). Exclusion criteria were: any endocrinological, neurological or metabolic disease, myocardial infarction in last 6 months before surgery and lack of patient’s consent.

The patients underwent general anaesthesia with fentanyl, midazolam and etomidate. Muscle relaxation was obtained by injecting a single dose of pancuronium. The anaesthesia was maintained throughout the procedure using midazolam-fentanyl infusion and inhalatory fractionated doses of foran. During the implantation of aorto-coronary bypasses the circulation and ventilation were maintained by the heart-lung machine S III (Stockert). The following substances were used for priming: Ringer’s solution, 6% solution of hydroxyethylated starch (HAES), 20% mannitol, sodium hydroxycarbonate, and heparin. The same priming was used for all patients (without Mg). Cardioplegia was prepared using 0.9% salt solution supplemented with 3g of potassium chloride (Kalium chloratum, Polfa, PL) and 20 mL of sodium hydroxycarbonate.

The patients were randomly divided into 2 groups: A – the patients receiving pre-operative Mg supplementation and B – patients without pre-operative Mg supplementation. During the surgery and in the early postoperative period (zero postoperative day) all patients received potassium chloride 250 mg/h and Mg sulfate 200 mg/h.

Immediately after surgery all patients were transferred to the Postoperative Intensive Care Unit (PICU) where they received a short-term infusion of 5% glucose solution with insulin.

The blood specimens were obtained in 5 stages: 1) before anesthesia after the radial artery cannulation, 2) during normowolemic haemodilution 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 r/min., temp. 0°C); the obtained serum was frozen at -20°C. The Mg were determined by spectrophotometric methods. The E and NE were measured by radioimmunoassay methods.

The results were statistically analysed using Kruskall – Wallis and Friedman test for initial detection of differences, and Wilcoxon signed rank test, Mann-Whitney U and Spearman rank correlation tests for interstage and intergroup comparisons. Since data histograms showed skewed distributions nonparametric methods of analysis were chosen.

### Results

Forty men aged 50-72 (66.2 ± 7.5) were studied. Twenty-eight patients had myocardial infarction during the past 3 years and thirty five 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 disease nor was resuscitated because of circulatory arrest. The mean duration of the procedure was 189.2 min ± 32 and of anaesthesia 205 min. ± 40.
In all the patients the aorta was typically clamped and the mean closure time was 37.2 min. ± 12.5. The aorto-coronary anastomosis was performed in mild hypothermia of 35.2 °C ± 0.4. In all the cases weaning from the heart-lung machine was uneventful and there was no need of intra-aortic contrapulsation.

The mean blood Mg concentration in group A before surgery was 1.03 mmol/L. The initiation of cardiopulmonary bypass caused a decrease in blood Mg concentration that persisted throughout the examination period (figure 1, table 1). The same changes were observed in group B, however Mg blood concentration in stage 1 was 0.75 mmol/L (table 1). There were significant differences between these two groups in stages 1, 2 and 3 (table 1).

In group A, E increased from the stage 2 to 5 (figure 3) and similar changes were noted in group B (figure 4). There were significant differences between group A and B in stage 3 (table 1).

The NE level increased in both groups (figures 5 and 6), but higher blood concentrations were observed in group B (table 1). There were significant differences between group A and B in stage 2.

The Spearman correlation showed a significant relationship between Mg in stage 1 and E in stage 2, Mg and NE in stages 4 and 5 in group A. In group B significant relationship between Mg in stage 3 and E in stage 4, Mg and NE in stages 2 and 3 were observed (table 2).

**Discussion**

The effects of preoperative supplementation of Mg on its intra- and postoperative blood levels during ECC have not been explicitly documented in the literature. The lack of data on the advantages of such management in patients undergoing ECC procedures seems to point out the significance of observations undertaken. The complex character of ECC procedures as well as intra- and postoperative treatment used may significantly disturb the hormonal and electrolyte balance, although the relation between the E and NE concentration in blood and the Mg level...
Figure 1. Changes in magnesium blood concentrations in patients receiving pre-operative magnesium supplementation (Wilcoxon test, comparison with first stage).

Figure 2. Changes in magnesium blood concentrations in patients without pre-operative magnesium supplementation (Wilcoxon test, comparison with first stage).
Figure 3. Changes in epinephrine blood concentrations in patients receiving pre-operative magnesium supplementation (Wilcoxon test, comparison with first stage).

Figure 4. Changes in epinephrine blood concentrations in patients without pre-operative magnesium supplementation (Wilcoxon test, comparison with first stage).
Figure 5. Changes in norepinephrine blood concentrations in patients receiving pre-operative magnesium supplementation (Wilcoxon test, comparison with first stage).

Figure 6. Changes in norepinephrine blood concentrations in patients without pre-operative magnesium supplementation (Wilcoxon test, comparison with first stage).
is known and well documented in the literature [6-11]. Many researchers stress the strict correlation between the blood Mg and NE concentrations and myocardial insufficiency [10, 12]. This correlation was confirmed by Samejim et al. [10], who in their study on interrelations between concentrations of Mg and NE in the blood and myocardial insufficiency demonstrated the reverse relationship between the above-mentioned factors. According to Banfi et al. [13], the development of myocardial insufficiency is strictly connected to the activation of the neurohormonal system, and 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. Therefore many researchers believe that the blood NE concentration is a relevant diagnostic factor of myocardial insufficiency [9, 14, 15]. However, it is difficult to determine explicitly whether high levels of the hormone in question observed in our study caused myocardial insufficiency. Nevertheless, it is worth stressing that high NE levels were accompanied by a significant drop in blood Mg concentrations, which may confirm their relations as mentioned above.

Moreover, the “inotropically positive” action of Mg on the myocardium seems interesting and worth discussing. The Mg substitution-induced increased index of the left ventricle work [16] may result from the inhibitory effects of the element analyzed on the intracardiac secretion of NE [9] as well as from the inhibition of N type calcium receptors [17]. Significantly higher Mg levels were observed in our study in the group of patients receiving preoperative Mg supplementation and less frequent use of inotropically positive agents in this group seem to confirm the favourable effects of Mg on the myocardium, however, further observations are required to determine these relations explicitly. It should be also emphasized that preoperative supplementation of Mg deficiency may produce beneficial effects already before the initiation of the procedure discussed, since it is well known that high blood levels of this element reduce the reactivity of adrenals and nerve endings, which leads to easier stabilization of the circulatory system. Studying the blood E and NE concentrations in pigs receiving Mg preparations and standard diet before slaughter, D’Souza et al. [18] noted significantly lower NE values in animals with high blood Mg levels. A significantly higher content of muscle glycogen observed by the above authors in this group of animals and lower levels of muscle lactates at higher pH of the muscle cells should also be stressed. This fact seems to be extremely important in cardiosurgical patients, although precise cellular changes in such patients are unknown and their determination requires additional studies.

Preoperative supplementation of magnesium also has favourable effects on the adrenergic response of the organism during the procedure of endotracheal intubation. The increased blood concentrations of

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**Tableau 2. The Spearman correlation test.**
catecholamines observed during intubation [19-23] are dangerous, particularly in cardiac patients. This is confirmed by Puri et al. [24] who in their studies on haemodynamic disorders during intubation of patients undergoing surgical revascularization of the myocardium observed an increase in the stroke volume index without ST changes in patients receiving Mg infusions compared to the group without such infusions, in whom increased work of the myocardium was associated with significant EKG changes. Moreover, a smaller increase in mean arterial pressure and systemic vascular resistance in response to intubation is worth noticing. For these reasons the researchers conclude that Mg infusions have more beneficial effects stabilizing the cardiovascular system than lidocaine. Dube and Granry [2] also emphasize that preoperative Mg supplementation before induction of anaesthesia stabilizes the cardiovascular system and facilitates the control of the adrenergic response to intubation. The lower blood NE levels observed in our study in patients receiving Mg are in agreement with the data quoted, however the effects of high concentrations of this element on the haemodynamic changes during intubation require further observation. Nevertheless, it is worth stressing that in the group of patients receiving Mg, the initial (stage 1) concentration of NE was already lower, although the difference was not statistically significant. Therefore it may be assumed that preoperative Mg supplementation favourably affects the adrenergic response to intubation in patients undergoing surgical revascularization of the myocardium and should be the treatment of choice in such cases.

While analysing the effects of Mg supplementation, the antiarrhythmogenic action of this element should be stressed, particularly in the post-infusion period. Many researchers emphasize the dangers associated with hypomagnesemia in patients after ECC procedures [25-27]. This fact is likely to result from hypokalemia accompanying low Mg levels [28, 29]. According to Whang and Ryder [28], low levels of potassium are related to blood Mg deficiencies in 61 % of cases and therefore potassium supplementation should be connected with Mg supply. According to Treggiari et al. [30], on the other hand, postoperative Mg substitution is ineffective for reducing artial fibrillation episodes, although low levels of the element in question predispose this pathology.

Another factor, which may induce perioperative arrhythmias, is likely to be a decrease in the myocardial arrhythmogenic threshold for E mentioned earlier [31]. It should be stressed that the high levels of E observed in our study in the postoperative period may favour arrhythmias in cases of hypomagnesemia, however, precise determination of these relations requires additional observation.

Furthermore, the analgesic effects of Mg seem interesting and important. In the recent years controversy has arisen and numerous clinical studies have been devoted to it [32-34]. It is thought that Mg has inhibitory effects (through affecting the calcium channels) on the brain’s NMDA receptors. According to Tramer et al. [34] and Telci et al. [35], this antagonistic action may limit the induction of the central sensitization by reducing the sensitivity of the peripheral receptors nociceptive to pain. For these reasons the patients receiving Mg require less morphine, less frequently complain of postoperative discomfort and sleep disorders, occurring in the first 48 hours after the administration of first doses of morphine. Similar advantages of Mg administration were demonstrated by Koining et al. [36]. They found the preoperative supply of this element significantly reduces the need for analgesics both during the surgical procedure and in the immediate postoperative period. Kara et al. [32] observed lower intra- and postoperative use of fentanyl and morphine in patients who received Mg during hysterectomy. Therefore it may seem that this element has definite analgesic effects. However, such effects of Mg are inconsistent with the observations by Ko et al. [33] who studied the Mg changes in the cerebro-spinal fluid during hysterectomy and found no significant Mg changes, although a difference in concentrations of this element was demonstrated in blood serum. The negative relation between the need for analgesics and Mg concentration in the cerebro-spinal fluid is also worth stressing. It should be also added that hysterectomy procedures are not the most painful ones, which might have affected the findings.

It is also difficult to determine the Mg analgesic activity in our cases as the procedures of surgical revascularization using the transsternal approach belong to the most stressful operations. Therefore, all the patients are administered high doses of analgesics in the postoperative period; moreover, combined anaesthesia (epidural and general) is used more and more commonly.

Discussing the effects of preoperative Mg substitution on homeostasis in ECC its beneficial effects on the intensification of postoperative apoptotic processes should also be emphasized as hypomagnesemia favours intensified processes of cell self-destruction. The main damaging mechanisms are thought to be disorders of the energetic balance of the cell resulting from low levels of this element [37-39] and effects of high blood concentrations of catecholamines, NE in particular [7]. The observed
hypomagnesemia-induced dysfunction of the sodium-potassium pump and ATPase results in a decrease in intracellular potassium and elevation in calcium, which is likely to substantially limit the adaptive ability of the cell, particularly in stress situations. Such disorders also lead to reduced transmembranous potential in the mitochondria [37] causing the cell oedema. This is confirmed by the observations by Marcoccie et al. [37] who examined the causes of disorders of the transmembranous mitochondrial potential and observed low intracellular levels of Mg accompanied by the accumulation of calcium ions. It is difficult, however, to determine explicitly the direct effects of Mg substitution on the intensification of apoptosis of cells; nevertheless the recent reports increasingly stress the influence of extracorporeal circulation procedures on the process of their self-destruction [40]. Therefore, periparative Mg substitution may seem right although further studies are required to determine its precise effects on apoptotic processes.

Conclusion

1) CABG with normovolemic haemodilution causes a decrease in blood magnesium concentration and an increase in blood adrenaline and norepinephrine concentrations.

2) Preoperative, oral supplementation of magnesium substantially reduces intra- and postoperative disorders of blood magnesium concentrations and significantly attenuates adrenergic response to operative stress.

References


