Original Research Article

Correlation of magnesium deficiency with C-reactive protein in elective cardiac surgery with cardiopulmonary bypass for ischemic heart disease

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ABSTRACT

Background and objective: Cardiac surgery is associated with systemic inflammatory response, which is triggered by cardiopulmonary bypass (CPB) and possibly with underlying magnesium deficiency. Animal studies have shown that magnesium deficiency intensifies oxidative stress and inflammatory processes. We aimed to find a link between serum, erythrocyte, cardiac tissue magnesium concentration and C-reactive protein (CRP) as an inflammatory marker in patients undergoing elective cardiac surgery with CPB.

Materials and methods: The data of 27 patients undergoing elective cardiac surgery with CPB for ischemic heart disease were analyzed. Measurements were taken at the baseline, i.e., 24 h before surgery (serum magnesium, CRP); time point 1, before CPB (serum, erythrocyte and cardiac tissue magnesium); time point 2, after CPB (serum, erythrocyte and cardiac tissue magnesium), and time point 3, 15–17 h after surgery (serum, erythrocyte magnesium, CRP).

Results: There was a negative correlation between baseline serum magnesium and baseline CRP ($P = 0.009$; $r = -0.492$), negative correlation between cardiac tissue magnesium at the time point 1 and baseline CRP ($P = 0.021$; $r = -0.443$), and positive correlation between CRP at time point 3 and erythrocyte magnesium at time point 2 ($P < 0.001$; $r = 0.637$).

Conclusions: The data of our study verify that inflammatory marker CRP and magnesium concentration in serum and cardiac tissue before the surgery are inversely related in patients undergoing elective cardiac surgery with CPB. Well-planned further studies

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are needed to evaluate the importance of underlying magnesium deficiency on the severity of systemic inflammatory response and postoperative complications after surgery with CPB.

1. Introduction

The role of magnesium deficiency has been noted in the pathogenesis of many chronic diseases including cardiovascular diseases, metabolic syndrome, insulin resistant diabetes mellitus, etc. [1,2]. Animal testing has shown that magnesium deficiency intensifies oxidative stress and inflammatory processes. It was also observed that patients with lower dietary magnesium had higher serum levels of C-reactive protein (CRP), proinflammatory cytokines and neuropeptide (substance P) [1,3,4]. This may play an important role in the pathogenesis of cardiovascular diseases and cause reduced tolerance of heart muscle to ischemia [5,6]. Guerrero-Romero et al. sought a link between serum magnesium concentration and oxidative stress/inflammatory processes. The authors established that hypomagnesaemia is related to an increased number of inflammatory cytokines [7].

It is important to understand that serum magnesium level is not a good indicator of magnesium deficiency. Since blood serum contain less than 1% of the total body magnesium, serum magnesium concentration may appear normal even if there is an underlying magnesium deficiency because the major portion of it is present in bone, muscle, and other tissues. So the measurement of tissue magnesium level would let more accurate assessment of total body magnesium. Erythrocyte magnesium concentration is characterized by inertia and reflects longer lasting magnesium deficiency [8,9]. Some authors recommend to measure magnesium content in platelets or lymphocytes [8,10,11]. The others appeal to animal hypomagnesaemia models and state that tissue magnesium level reflects the body magnesium status more accurately [12].

Though the incidence of hypomagnesaemia in cardiac surgery was investigated in several studies, we failed to find publications on magnesium deficiency relation with inflammatory response in cardiac surgery patients. During cardiac surgery a systemic inflammatory response is also induced by the extracorporeal circulation. Having assessed the role of magnesium deficiency in the inflammatory process, it can be supposed that the inflammatory response in patients with magnesium deficiency will be more intensive. The present research is aimed to assess the relation of magnesium concentrations in serum, erythrocytes, and cardiac tissue with CRP as inflammatory marker in patients undergoing elective cardiac surgery with CPB for ischemic heart disease.

2. Materials and methods

The study took place in the Department of Cardiovascular and Thoracic Surgery, Hospital of Lithuanian University of Health Sciences (LUHS) Kauno Klinikos during 2009–2011. After approval of Kaunas Regional Biomedical Research Ethics Committee (protocol No. 89/2003) and having received the written consent of the patients, 27 patients undergoing elective coronary artery bypass grafting (CABG) under CPB were included in the prospective pilot study. The inclusion criteria were as follows:

(1) Elective cardiac surgery with CPB for ischemic heart disease;
(2) Men and women of 50–80 years old;
(3) No concomitant diseases causing active inflammatory process;
(4) Patients who have signed informed consent to participate in the study;

Demographic and surgical data of the patients are presented in Table 1.

Most of the patients were men (89.47%). Physical status of the patients was evaluated by ASA classes (American Society of Anaesthesiologists physical status classification system for assessing the fitness of patients): 84.21% of the patients were evaluated as ASA III class and 15.79% were evaluated as ASA IV class. All patients had stable angina pectoris and their status was evaluated according to Canadian Cardiovascular Society (CCS) angina grading scale for classification of stable angina pectoris: 21.05% of the patients had CCS class II and 78.95% had CCS class III. All patients had arterial hypertension, most of them were overweight (Table 1). Before the surgery all patients were on chronic β-blocking agents and angiotensin converting enzyme (ACE) inhibitors therapy. The ACE inhibitors therapy was discontinued the day before the surgery. On the eve of the surgery all patients received premedication with 2 mg of lorazepam (benzodiazepine) and on the morning of the surgery patients received premedication with half of the

Table 1 – Patient demographic and surgery data.			
Parameter	Min value	Max value	Mean ± SD
Age, year	46	75	62.22 ± 7.77
BMI, kg/m^2	22.23	38.77	29.72 ± 3.98
LVEF, %	30	60	49.96 ± 8.99
CPB duration, min	61	156	95.15 ± 25.84
Aortic cross-clamping time, min	27	86	49.19 ± 15.04
Volume of cardioplegic solution, mL	1000	2000	1505.56 ± 302.66

BMI, body mass index; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass.

usual dose of β-blocking agent, 7.5 mg of midazolam (benzodiazepine) orally and 10 mg of morphine intramuscular injection.

During surgery, standard endotracheal anesthesia was applied (3 µg kg^{-1} h^{-1} fentanyl, 1–4 mg/h midazolam, and 1.5%–2% minimal alveolar concentration sevoflurane depending on the hemodynamics). The CPB system was filled with 1500-mL Ringer's acetate solution (composition: Na$^+$, 130 mEq/l; K$^+$, 5.4 mEq/l; Cl$^-$, 112 mEq/l; Ca^{2+}, 0.9 mEq/l; Mg^{2+}, 1.0 mEq/l; acetate, 27 mEq/l) and 1000 units heparin. A roller pump, a membrane oxygenator (Dideco D703, Mirandola), and a venous reservoir were used for CPB. Surgery was performed using a median sternotomy incision and standard CABG technique. The myocardium was protected using cold (2–4 °C) crystalloid antegrade cardioplegia (St. Thomas solution: NaCl, 110.0 mM; NaHCO$_3$, 10.0 mM; KCl, 16.0 mM; MgCl$_2$, 16.0 mM; CaCl$_2$, 1.2 mM; pH 7.8). During the surgery and after the surgery patients received standardized infusion therapy with Ringer's lactate solution (composition: Na$^+$, 131 mEq/l; K$^+$, 5.0 mEq/l; Cl$^-$, 111 mEq/l; Ca^{2+}, 2.7 mEq/l; lactate, 29 mEq/l) containing no magnesium.

The parameters were measured at the baseline and three next time points. The baseline measurements included CRP and magnesium concentrations in the blood serum 24 h before the surgery. Time point 1 was before CPB and time point 2 was after CPB. At time points 1 and 2, the magnesium concentration was measured in blood serum, erythrocytes, and cardiac tissue (left atrium cannulation site). Time point 3 was 15–17 h after surgery, and CRP, serum and erythrocyte magnesium concentrations in blood serum were measured at that time. Also the average time of artificial lung ventilation and the need for vasopressing agents after surgery were evaluated.

The tests of CRP and magnesium concentrations in the blood serum were performed at the Laboratory of Biochemistry, Hospital of LUHS Kauno Klinikos. Reference ranges for the magnesium and CRP concentrations in blood serum are 0.75–1.05 mM/l and 1–7.5 mg/l, respectively.

Magnesium concentrations in erythrocytes and cardiac tissue were measured at the Laboratory of Environmental and Health Research, Biomedical Research Institute, LUHS. The samples of cardiac tissue were put to weighted plastic tubes, once more weighted to find out a weight of the tissue sample and stored at −18 °C until the analysis. The sample of erythrocytes (0.5 mL) diluted with some drops of double-distilled water (ddH$_2$O), homogenized in 0.5 mL 0.125 M NaOH, and diluted to 5 mL with ddH$_2$O, mixed and stored at 5 °C until

it was analyzed. The samples of heart tissue were processed and mineralized in Multiwave 3000 (Anton Paar) by standard method. Magnesium in biological media was determined by graphite furnace atomic absorption spectrometry (Perkin-Elmer, Zeeman 3030). Low sorption plastic tubes and labware used were repeatedly washed with 2.4 M nitric acid followed by repeated double-distilled water rinse to ensure they were free of contamination. Taking care of eliminating the chronic marginal magnesium deficits normal erythrocyte magnesium concentration ranges are 1.65–2.65 mM/l of packed cells [13,14]. The published data on magnesium content in cardiac tissue are not very abundant. We failed to find data on cardiac magnesium concentration in healthy people. There are studies on magnesium concentration in rat ventricle as well as in patients with heart failure, undergoing cardiac surgery [15–18]. But it is difficult to compare data due to different methods used in these studies. Moller et al. measured magnesium concentration in right atrium and found it ranging from 3.55 to 7.66 µmol/g wet weight (after calculation adjustment 83.592–186.138 µg/g wet weight) [17].

The statistical analysis was performed using the SPSS 15.0 software. The data are presented as mean and standard deviation (M ± SD). The analyzed parameters were described using the general statistical status, distribution, and symmetry. A test of Kolmogorov–Smirnov was used to check the normal data distribution. Paired-sample t test was used to calculate statistically significant difference between mean values of CRP at baseline and time point 3, serum magnesium at baseline and time point 1, time point 2 and time point 3, erythrocyte magnesium at time point 1 and time point 2, time point 2 and time point 3 time point 1 and time point 3, cardiac tissue magnesium ant time point 1 and time point 2. The correlations between mean serum magnesium, erythrocyte magnesium, cardiac tissue magnesium and CRP at baseline and time point 3 parameters, as well as between serum magnesium and erythrocyte magnesium, serum magnesium and cardiac tissue magnesium, erythrocyte magnesium and cardiac tissue magnesium were evaluated by the Pearson correlation. When statistical hypothesis was verified, the significance was set at $P < 0.05$.

3. Results

Table 2 presents the changes of serum and erythrocyte magnesium levels during the study. The mean serum

Table 2 – Magnesium concentration in serum, erythrocytes, and cardiac tissue.				
Parameter	Baseline	Time point 1	Time point 2	Time point 3
Blood serum, mmol/l	0.86 ± 0.07[*]	1.10 ± 0.09	1.70 ± 0.26[*]	0.95 ± 0.08
Erythrocytes, mmol/l	NM	4.21 ± 0.64	3.99 ± 0.19	3.33 ± 0.21
Cardiac tissue, µg/g	NM	269.01 ± 147.32[**]	230.10 ± 41.17[**]	NM
C-reactive protein, mg/l	2.07 ± 2.18[*]	NM	NM	135.83 ± 31.12[*]

CPB, cardiopulmonary bypass; CRP, C-reactive protein; baseline, before surgery; time point 1, before CPB; time point 2, after CPB; time point 3, 15–17 h after surgery; NM, not measured.
[*] $P < 0.001$.
[**] $P = 0.034$.

magnesium concentration remained within the reference range being the highest at time point 2 (1.70 ± 0.26 mM/l). It was significantly higher comparing to the levels at the baseline (0.86 ± 0.07 mM/l, $P < 0.001$) and time point 3 (0.95 ± 0.08 mM/l, $P < 0.001$).

The erythrocyte magnesium concentration was evaluated at time point 1 (before CPB), time point 2 (after CPB), and time point 3 (15–17 h after surgery). Its concentration during the study period decreased. At time point 1, the mean erythrocyte magnesium concentration (4.21 ± 0.64 mM/l) was highest, at time point 2, it was lower (3.99 ± 0.19 mM/l), and the lowest erythrocyte magnesium concentration was detected at time point 3 (3.33 ± 0.21 mM/l). Thought the differences in the erythrocyte magnesium concentration between time points 1 and 2 as well as between time points 2 and 3 were not significant ($P = 0.176$ and $P = 0.097$, respectively), a statistically significant difference between time points 2 and 3 was observed ($P < 0.001$).

The magnesium concentration in the cardiac tissue was measured at the moment of left atrium cannulation and decannulation (time points 1 and 2, before and after CPB, respectively). At time point 2, the mean cardiac tissue magnesium concentration decreased significantly (from 269.01 ± 147.32 to 230.10 ± 41.17 μg/g, $P = 0.034$).

The mean baseline CRP level was 2.07 ± 2.18 mg/l, and at time point 3 (15–17 h after surgery), the mean CRP level (135.83 ± 31.12 mg/l) increased significantly ($P < 0.001$).

The correlations between measured magnesium concentrations and CRP at various measurement points were calculated. Figure shows statistically significant correlations that were identified in the study: there was a negative correlation between CRP at the baseline and serum magnesium at time point 1 ($r = -0.503$, $P = 0.028$) (Figure A), negative correlation between baseline CRP and cardiac tissue magnesium at time point 1 ($r = -0.304$, $P = 0.021$) (Figure B), and positive correlation between CRP at time point 3 and erythrocyte magnesium at time point 2 ($r = 0.731$, $P < 0.001$) (Figure C).

4. Discussion

Many studies have been conducted on the significance of magnesium in cardiac surgery. But most of the researches rely only on the serum magnesium concentration which does not reflect the magnesium content in the body accurately [19,20]. As a result, it is not clear whether the patients with the normal serum magnesium concentration had magnesium deficiency, which plays important role in the pathophysiology of inflammation and can influence the rate of postoperative complications. Malpuech-Brugere et al. in their study confirmed that inflammatory response was associated with magnesium deficiency [21]. It is known that magnesium deficiency initiates a systemic stress response by activation of neuroendocrinological pathways as shown by modifications in production or activity of neuromediators [22]. Rodriguez-Moran et al. also proved that a decreased serum magnesium concentration is related with low-grade chronic inflammatory syndrome [3]. The latter has a role in the impairment of endothelial function and is associated with ischemic heart disease. In our study, a negative correlation between

preoperative CRP and serum magnesium before CPB (time point 1) supports the results of these studies. In addition, a negative correlation between preoperative CRP and cardiac magnesium before CPB (time point 1) also shows that underlying magnesium deficiency activates oxidative stress and low-grade chronic inflammatory syndrome. Patients suffering from heart failure are especially exposed to the risk of undiagnosed chronic magnesium deficiency because usually they receive prolonged treatment with diuretics, ACE inhibitors, and digoxin. Although the patients in our study were given chronic ACE inhibitors therapy due to heart failure, they did not receive diuretic or digoxin therapy before surgery. It is know that the chronic use of loop diuretics and thiazides can lead to magnesium deficiency. But there are data showing that plasma magnesium status is stable in patients treated with various angiotensin II antagonists alone [23,24]. Our data show the changes of magnesium content throughout the study period, but the magnesium level in serum, erythrocytes, and cardiac tissue remain within reference ranges (or equivalent to that).

We failed to find any correlation between cardiac tissue magnesium and serum or erythrocyte magnesium at any time point of the measurements in our study. According to the published literature some authors found correlation between serum magnesium and tissue magnesium [25], while others did not find [15,26,27]. Those studies were conducted in different populations of patients and in normal adults. Different results found by different authors offer the idea that the main pathology itself plays important role in alteration of magnesium metabolism, because in normal adults magnesium content in mononuclear cells correlated well with the magnesium concentration in skeletal muscle [18]. It was suggested that in congestive heart failure, the mononuclear cell membrane is more fragile and there may be alterations in magnesium transport across the cellular membrane.

The published data confirm the relation of hypomagnesemia and oxidative stress, increased inflammatory markers [1,6,12,19,21]. The dynamics of inflammatory markers after the surgery in our study is typical: CRP concentration after the surgery increase in comparison to baseline concentration. It is mainly related to systemic inflammatory reaction caused by surgery itself (surgical trauma, CPB). Unfortunately, we failed to detect correlation (negative) between baseline serum magnesium and postoperative CRP (time point 3), which could have indicated that low serum magnesium before surgery enhances the expression of systemic inflammatory reaction after the surgery.

Excessive fat or fibrous tissue in the heart tissue samples could misrepresent the data of magnesium concentration in cardiac tissue and show inappropriate low magnesium concentration, which could have failed to correlate with serum or erythrocyte magnesium levels. Both cardiac tissue samples were taken from the right atrium cannulation site under eye control. Myocardial biopsies at that site have very low fat or fibrous tissue content, so it is unlikely that it could have influenced correlation results.

It is difficult to compare our data to other studies because of different investigation methods used. In our study we measured cardiac magnesium content as μg/g wet weight. After calculation adjustments of the data in our study we
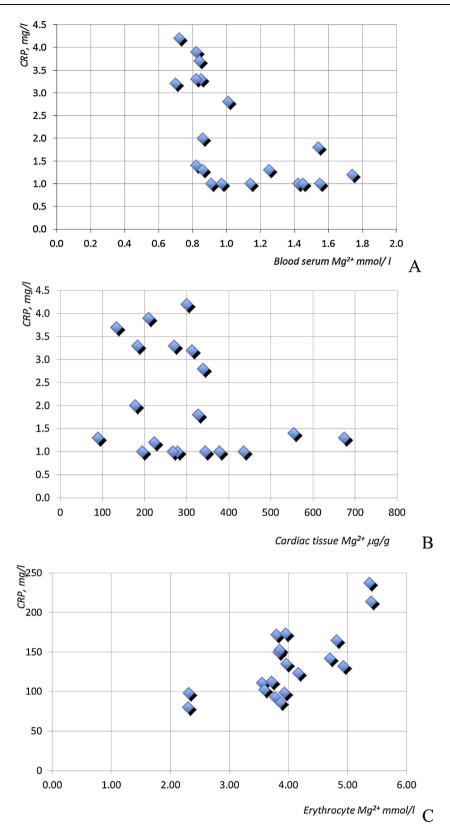
Figure – Significant correlations between CRP at baseline and serum Mg at time point 1 (*r* = −0.503, *P* = 0.028) (A), CRP at baseline and cardiac tissue magnesium at time point 1 (*r* = −0.304, *P* = 0.021) (B), CRP at time point 3 and erythrocyte magnesium at time point 2 (*r* = 0.731, *P* < 0.001) (C).

found relatively high cardiac tissue concentration in comparison to the study by Moller et al., who studied patients with congestive heart failure [17].

In our study, the CRP concentration 15–17 h after surgery (time point 3) increased significantly indicating highly expressed systemic inflammatory response. The pathophysiology of this process depends on many factors. CPB can activate the immune system via leukocyte interactions with the foreign surfaces of the CPB circuits. Different mechanisms seem to be involved such as surgical trauma, transfusion, blood loss, and hypothermia. We suppose that the background of magnesium status can heavily influence the inflammatory response to CPB.

Serum magnesium remained within the reference range showing no severe hypomagnesemia. During surgery, serum magnesium increased and it was significantly higher after CPB (time point 2) in comparison to the baseline levels. It may be explained by infusion of crystalloid cardioplegic solution (St. Thomas), which contains 13.54 mM/l of magnesium, and these results correspond to the results of our previous study as well as the study by Amaya et al. [28–30].

We measured the magnesium concentration not only in blood serum, but in erythrocytes and cardiac tissue as well. Animal and human studies have shown that erythrocyte magnesium concentration changes are inert; they are only detected after several weeks of changes in dietary magnesium intake [5,8]. In our study, the erythrocyte magnesium level remained within the reference range throughout the study. The study population did not receive chronic diuretic therapy. We suppose that such preoperative treatment kept erythrocyte magnesium content stable. On the other hand, patients included in the study had no serious concomitant diseases and had normal or higher than normal BMI, which indicates no nutrition disorders.

Anyway during the study period, the erythrocyte magnesium concentration showed a tendency to decrease. Magnesium content in cardiac tissue decreased significantly after CPB (time point 2) as well. These decreases together with an increase in serum magnesium imply that an increase in the serum magnesium concentration is caused not only by crystalloid solution (St. Thomas) but by magnesium redistribution from the intracellular fluid compartment to blood serum after CPB. So it is obvious that stingy magnesium supplementation by crystalloid cardioplegia does not prevent a decline in tissue magnesium. According to our results, the concentration of serum magnesium before surgery matches the cardiac magnesium level before CPB. Anyway, changes in the serum magnesium concentration do not reflect changes in the tissue magnesium level during elective cardiac surgery with CPB for ischemic heart disease.

The result which puzzled was a strong correlation between the erythrocyte magnesium level after CPB (time point 2) and CRP 15–17 h after surgery (time point 3). It may be associated with intracellular/extracellular magnesium shifts during CPB and requires further investigations to prove or deny the correlation.

No significant correlation was found between serum magnesium, erythrocyte magnesium and cardiac tissue magnesium concentration at different time points and the duration of artificial lung ventilation in ICU or the need of vasopressing agents after the surgery.

However, the analysis of relations between magnesium status and inflammatory processes require further comprehensive research involving a larger sample size.

The limitations of this study included a small number of patients, and the fact that other inflammatory biomarkers, such as procalcitonine, interleukin-6, and tumor necrosis factor-alpha were not measured for comparison. Well-planned further studies are needed to confirm the results of our study.

5. Conclusions

The data of our study verify that C-reactive protein, an inflammatory marker, and the magnesium concentration in serum and cardiac tissue before surgery are inversely related in patients undergoing elective cardiac surgery with cardiopulmonary bypass. Well-planned further studies are needed to evaluate the importance of underlying magnesium deficiency on the severity of expression of systemic inflammatory response and postoperative complications after surgery with cardiopulmonary bypass.

Conflict of interest

The authors state no conflict of interest.

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