The relation between blood and tissue magnesium levels and development of atrial fibrillation after coronary artery bypass surgery

Koroner arter baypas cerrahisi sonrası atriyal fibrilasyon gelişimi ile doku ve kan magnezyum düzeyleri arasındaki ilişki

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ABSTRACT

Objective: Atrial fibrillation (AF) is a common complication of cardiovascular surgery and its mechanisms are not well understood. The aim of our study was a prospective investigation of the relationship between AF development and tissue or blood magnesium levels.
Methods: This prospective observational study evaluated 20 patients undergoing elective initial coronary artery bypass graft (CABG) surgery. Right atrial appendage and skeletal muscle samples were obtained for tissue magnesium level analysis before, during (at 60th minute) and 30 minutes after cardiopulmonary bypass (CPB) with simultaneous blood samples. Daily measurements of blood Mg levels and continuous monitoring for AF were performed for 7 postoperative days. Statistical analyses were performed using ANOVA, independent samples t and Chi-square tests.
Results: AF developed in 5 out of 20 patients during postoperative period (25%). Patients with or without AF did not differ in terms of tissue and blood magnesium levels during and early after CPB and during 7 days after the operation. Blood magnesium levels were significantly higher in the whole study population on postoperative days 3 through 7 (day 3 - 1.13±0.11 mmol/L; day 4-, 1.18±0.07 mmol/L; day 5-1.15±0.10 mmol/L; day 6-1.17±0.08 mmol/L; and day 7, 1.22±0.08 mmol/L) compared to day 1 and day 2 (day 1-0.96±0.13 mmol/L and day 2-1.02±0.12 mmol/L; p<0.002 for all comparisons).
Conclusion: Although patients with and without AF did not significantly differ with regard to blood and tissue magnesium levels, the coincidence of an early postoperative reduction in magnesium levels in all patients and occurrence of all AF incidences at this time period suggests a potential association deserving further investigation. *(Anadolu Kardiyol Derg 2010; 10: 446-51)*
Key words: Coronary artery bypass grafting, atrial fibrillation, tissue magnesium level, blood magnesium level

ÖZET

Amaç: Atriyal fibrilasyon (AF), mekanizması halen tam olarak anlaşılmamakla birlikte kardiyovasküler cerrahi sonrası en sık karşılaşılan komplikasyonlardan biridir. Çalışmamızda, prospektif olarak doku ve kan magnezyum seviyelerine ile AF arasındaki ilişkinin araştırılması planlanmıştır.
Yöntemler: Bu prospektif gözlemsel çalışmada, elektif koroner arter baypas greft cerrahisi uygulanacak 20 hastanın kardiyopulmoner baypas öncesi, pompanın 60. dakikası, pompadan sonraki 30. dakikada eş zamanlı olarak atriyum dokusu, rektus abdominis kas dokusu ve kan örnekleri, ayrıca postoperatif 7 gün boyunca günlük kan örnekleri alındı ve magnezyum seviyelerine bakıldı. AF postoperatif 7.güne kadar sürekli monitorize edildi. İstatistiksel analizlerde ANOVA, bağımsız örneklem t ve Ki-kare testleri kullanıldı.
Bulgular: Postoperatif dönemde 20 hastadan 5'inde AF gelişti (%25). AF gelişen ve gelişmeyen hastalar arasında kardiyopulmoner baypas öncesi, sırası ve sonrasındaki kan ve doku magnezyum düzeyleri ve postoperatif 7 gün boyunca kan magnezyum düzeyleri açısından fark yoktu. Tüm hastalarda ise kan magnezyum düzeyleri 3 ile 7. günler arasında (3. gün -1.13±0.11 mmol/L; 4. gün -1.18±0.07 mmol/L; 5. gün - 1.15±0.10 mmol/L; 6. gün -1.17±0.08 mmol/L; ve 7. gün - 1.22±0.08 mmol/L), 1 ve 2. günlerle karşılaştırıldığında daha yüksekti (1. gün - 0.96±0.13 mmol/L ve 2. gün - 1.02±0.12 mmol/L; tüm karşılaştırmalar için p<0.002).
Sonuç: Bu çalışmada AF gelişen ve gelişmeyen hastalar arasındaki kan ve doku düzeyleri açısından fark istatistiksel anlamlılığa ulaşmamıştır. Ancak, tüm hastalarda erken postoperatif dönemde magnezyum düzeylerindeki anlamlı azalma ve tüm AF olgularının bu dönemde görülmüş olması, daha ileri araştırmayı gerektiren olası bir ilişki olduğunu düşündürmektedir. *(Anadolu Kardiyol Derg 2010; 10: 446-51)*
Anahtar kelimeler: Koroner arter baypas greft, atriyal fibrilasyon, doku magnezyum seviyesi, kan magnezyum seviyesi

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Introduction

Atrial fibrillation (AF) is a common complication of cardiovascular surgery occurring in approximately 25% to 40% of patients (1, 2). Despite improvements in surgical techniques and drug therapy, the incidence of this condition is increasing (1-3). It usually occurs 24 to 96 hours after surgery with a peak incidence on the second post-operative day (4, 5). Although post-operative AF usually does not result in long-term sequel, potential complications include thromboembolic events, hemodynamic compromise, and prolonged duration of hospitalization resulting in increased costs (2, 5, 6).

The mechanisms of AF are not well understood. Many causal factors have been proposed, but there is a lack of agreement on the fact that age is the single most important variable (2- 7). The other potential risk factors include male sex, hypertension, hypothyroidism, withdrawal of ß-blockers, impaired cardiac function, chronic renal failure, diabetes, cardiopulmonary bypass and cardioplegia, prolonged cross-clamp time, post-operative inotropic support, myocardial ischemia and reperfusion, right coronary artery disease, excessive catecholamine and electrolyte imbalance (2, 3, 7). Particularly hypomagnesemia has been identified as an independent predictor of post-operative AF (5, 6).

Hypomagnesemia is a common finding after open-heart surgery, which is usually the result of hemodilution, pre-operative and post-operative use of diuretics and catecholamine discharge (6). The association between magnesium deficiency and post-operative AF is still unknown; however, most postulated mechanisms to explain their relationship have consistently referred to the role of magnesium in stabilizing the cellular transmembrane potential. Magnesium is a cofactor for the activation of many enzymatic processes of cellular homeostasis, including the turnover of adenosine triphosphate (ATP), the energy source for contractility.

The aim of this study was to investigate blood and/or tissue magnesium levels during and after cardiac operation in an attempt to examine a potential relation with the development of AF.

Methods

Patient population

This prospective observational study evaluated 20 patients undergoing elective initial coronary artery bypass graft surgery (CABG). All patients were in sinus rhythm at the time of operation. Patients undergoing concurrent valvular surgery or repeat CABG were excluded from the study, as were the patients with an initial systolic blood pressure of less than 100 mmHg, a resting heart rate of less than 50 beats per minute, renal insufficiency (serum creatinine greater than 2.0 mg/dl), asthma, chronic obstructive pulmonary disease, or a prior history of AF. Clinical information was obtained from all patients by reviewing medical records. The study protocol was approved by local Ethics Committee and written informed consent was obtained from all patients prior to study entry.

Operative technique

The same cardiopulmonary bypass (CPB) protocol was performed in all patients. Antegrade cold blood cardioplegia free of magnesium was used in all patients. Cardioplegia was given after the completion of each distal anastomosis or every 20 minutes. Cold water was used for topical cooling. Body temperature was diminished to 28 to 32°C depending on the anticipated length of CPB time. Moderate hemodilution was aimed with a flow rate of 2.4 $L.min^{-1}.m^{-2}$, and mean systemic pressure was kept between 50 and 80 mmHg.

All patients underwent single atrial cannulation and all distal coronary anastomoses were performed during a single period of aortic cross clamping in a standard fashion. The left internal thoracic artery served as a bypass conduit in the majority of patients. Operative variables including cross-clamp time and CPB time were also recorded for comparison. All proximal anastomoses were done under partial clamping of the aorta.

Tissue and blood sample analyses

Right atrial appendage muscle and skeletal muscle samples from the rectus abdominis muscle were taken for tissue Mg^{++} level analysis before CPB, at the 60th minute of CPB and 30 minutes after the termination of CPB. Simultaneous blood samples were drawn for biochemical evaluation during each muscle sampling, and every day after the operation for 7 days. Blood samples were centrifuged for 5 minutes at 5000 revolutions per minute to obtain plasma. Tissue and plasma samples were frozen at -20°C until analysis and dry weight was calculated for each sample. Determination of Mg^{++} level was carried out by using a Shimadzu AA-6800 Atomic Absorption Spectrophotometer (Japan) with a Mg^{++} Hollow Cathode Lamp (Hollow Kathode Lamp L 233-12 NU). Compressed air/acetylene mixture was used. Muscle samples placed on beakers were weighed in an analytical balance and 1 ml of HNO3 is added to each 25 ml of sample. Then the beakers were heated on a hot-plate. The progress of this reaction could be followed visually and heating was usually terminated when nitric acid fumes appear. Solutions were then filtered through a blue band filter paper and put into a 25 ml volumetric flask. Then LaCl3 is added to each sample with 0.1 ml of concentrated HNO3 and the total amount made up to 25 ml with Milli-Q water. This solution was then ready to be read in the spectrophotometer. Blank solutions and samples prepared by standard methods were evaluated for magnesium levels by atomic absorption spectrophotometry. The normal values for plasma magnesium levels were 0.7 to 1.2 mmol/L.

Definition of arrhythmias

Patients were continuously monitored in the intensive care unit with bedside monitors and after discharge from intensive care unit with telemetry for AF. Twelve-lead electrocardiograms were obtained immediately after the operation and also recorded daily until the seventh post-operative day. AF was documented when an irregular supraventricular rhythm was present in the absence of P waves. Episodes of AF that recurred or continued into the following 24-hour period were recorded as an additional episode. Arrhythmia data were collected and recorded during the first 7 post-operative days.

Anesthesia technique

All patients received pre-medication with oral diazepam and an intramuscular injection of atropine before entering the operation room. Anesthesia was induced with intravenous fentanyl, diazepam and a muscle relaxant (pancuronium or vecuronium). After tracheal intubation, mechanical ventilation was initiated with oxygen and nitrogen, and anesthesia was maintained with midazolam and vecuronium infusion and sevoflurane inhalation.

Statistical analysis

SPSS version 15.0 for Windows software (SPSS Inc., Chicago, IL, USA) was used for the analysis of data. Normality was tested using Kolmogrov-Smirnov and Shapiro-Wilk tests. For the comparison of groups with regard to patient characteristics, independent samples t and Chi-square tests were used. A two-way analysis of variance (ANOVA) for repeated measurements with time (within-subject variable) and AF development (between-subject variable) as factors was used to compare groups with or without AF with regard to tissue and blood magnesium levels throughout the study period. Post hoc comparisons for magnesium levels of the whole patient group at different time points were done by Bonferroni corrected t-test for paired samples. A p value <0.05 was considered significant in all other comparisons.

Results

Patient characteristics

Baseline, clinical and operative characteristics of patients are given in Table 1. Overall, 5 (25%) patients developed AF: 3 patients on the day of the operation, 1 patient on the 1st postoperative day and 1 patient on the 2nd postoperative day. Patients with or without AF had similar characteristics except for a significantly higher (p<0.05) age among patients with AF (Table 1).

Tissue and blood magnesium levels during CPB and development of AF

The two groups did not differ in terms of change in blood (p=0.799), right atrial appendage (0.460) and skeletal muscle (p=0.905) magnesium levels before, during and after CPB (Fig. 1). However, when all patients were considered, CPB was associated with a high mean blood magnesium level compared to baseline (p=0.002), which was also maintained until 30 minutes of termination (p=0.008). On the other hand, right atrial appendage and skeletal muscle tissue magnesium levels were not affected by CPB (p=0.544 and 0.417, respectively) (Table 2) .

Postoperative blood magnesium levels and development of AF

Postoperative changes in blood magnesium levels in patients with or without AF are shown in Figure 2. The two groups did not differ in terms of blood magnesium levels throughout this early postoperative follow-up period. However, when all patients are considered, significantly lower levels were detected during the first few days of the postoperative period, after which a gradual increase was evident. Mean values on days 3 through 7 (day

Table 1. Baseline characteristics

Variables	Patients with AF (n=5)	Patients without AF (n=15)	*p
Age, years	65.6±5.3	57.0±8.3	0.044
Male sex, n (%)	5 (100)	14 (93.3)	0.750
Hypertension, n (%)	4 (80)	6 (40)	0.152
Pre-op β-blocker use, n (%)	3 (60)	8 (53.3)	0.604
Pre-op blood Mg level, mmol/L	0.9±0.3	0.8±0.2	0.634
Pre-op Htc, %	39.4±2.4	39.1±4.6	0.904
Cross-clamp time, min	54.4±23.1	53.7±15.4	0.936
CPB time, min	87.4±31.0	98.8±23.4	0.395
Duration of ICU stay, hours	21.8±1.8	22.1±6.6	0.914
Duration of mechanical ventilation, hours	8.0±2.3	9.5±3.2	0.335

Data are presented as mean±SD and proportions/percentages
*independent samples t-test and Chi-square test
CPB - cardiopulmonary bypass, Htc - hematocrit, ICU - intensive care unit, Mg - magnesium, pre-op - preoperative

Table 2. Tissue and plasma magnesium levels before and after CPB in study patients

Variables	Before CPB	During CPB	After CPB	F	p
Mean blood magnesium level, mmol/L	0.85±0.21	1.01±0.27*	1.01±0.27#	5.504	0.008
Mean tissue magnesium level (atrial appendage), mEq/L	374.9±212.0	365.7±217.2	335.0±233.7	0.631	0.544
Mean tissue magnesium level (skeletal muscle), mEq/L	322.2±204.2	408.8±261.0	292.8±199.3	0.420	0.417

Data are presented as mean±SD
ANOVA for repeated measurements analysis
Posthoc t-test for paired samples with Bonferroni correction for pairwise comparisons with a significance value < 0.017:
* - p=0.002, during versus before CPB
# - p=0.008, after versus before CPB
CPB - cardiopulmonary bypass

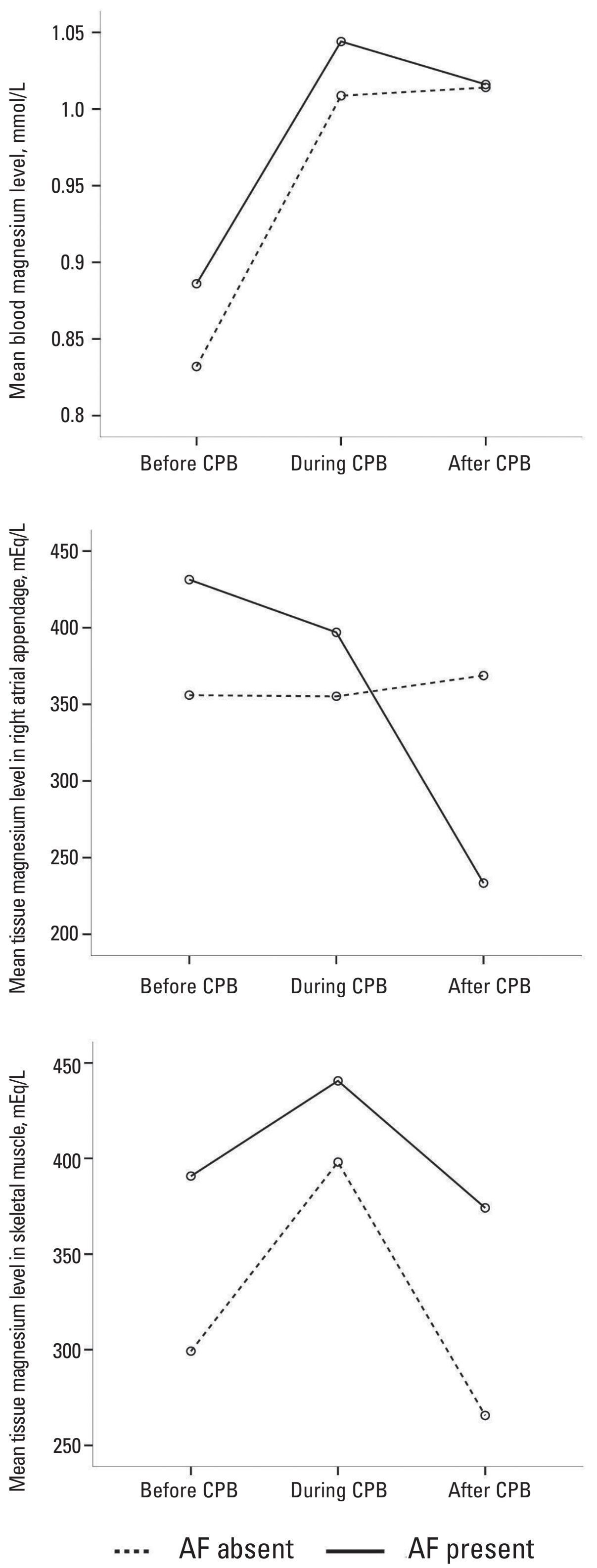

Figure 1. Changes in blood and tissue magnesium level before, during and after CPB

Two-way ANOVA analysis, p>0.05

AF - atrial fibrillation, CPB - cardiopulmonary bypass

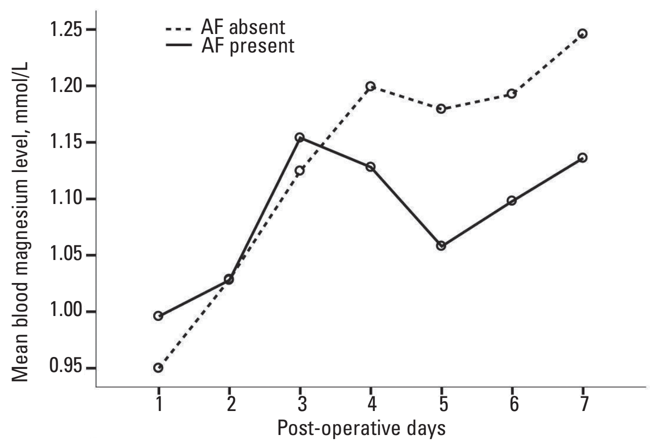

Figure 2. Changes in blood magnesium level during the 7 postoperative days

Two-way ANOVA analysis, p>0.05

AF - atrial fibrillation, CPB - cardiopulmonary bypass

3-1.13±0.11 mmol/L; day 4-1.18±0.07 mmol/L; day 5-1.15±0.10 mmol/L; day 6-1.17±0.08 mmol/L; and day 7-, 1.22±0.08 mmol/L) were significantly higher compared to day 1 and day 2 (day 1-0.96±0.13 mmol/L and day 2-1.02±0.12 mmol/L; p<0.002 for all comparisons).

Discussion

In this study, no significant difference was detected between patients with or without AF with regard to blood magnesium levels during early postoperative period. However, the number of patients with AF is very limited as were the total study population. It is of note that, all episodes of AF developed during the first two postoperative days, during which blood magnesium levels were significantly lowest among the whole study population. Thus, this potential relation between AF development and blood magnesium levels merits further investigation with larger sample sizes.

The reported incidences of AF after CABG range from 25 to 40% (2). Despite recent improvements in pre-operative management, AF occurrence has not decreased during the years and is associated with significant morbidity. Magnesium, β-blockers, Ca++-channel antagonists, digoxin, oral and intravenous amiodarone, cardioversion, radiofrequency ablation are among the medications and interventions used for AF treatment.

Magnesium not only changes cellular transmembrane potentials to decrease signal transduction, but also acts as a cofactor for Na-K ATP'ase to regulate cellular K+ levels and stabilize intracellular calcium. Low magnesium levels after CPB is a frequent finding. Hemodilution, hormonal changes, stress-related epinephrine release, diabetes mellitus, postoperative use of digoxin, ß-blockers and diuretics are thought to be contributing factors for the development of postoperative hypomagnesemia (8-10). In the study by Spasov et al. (11) , magnesium deficiency was shown to provoke cardiac rhythm disturbance.

Some authors have reported decreased AF frequency after administration of magnesium to cardiac surgery patients as well as acute myocardial infarction patients. Additionally, magnesium acts like an intracellular calcium antagonist, suggesting that magnesium treatment may decrease cardiac contractility. In contrast, studies have shown increased myocardial performance after magnesium prophylaxis. Magnesium decreases reperfusion injury, increases myocardial performance and protects myocardium, probably through its calcium channel antagonist effect and through its role as a cofactor in oxidative phosphorylation and in adenosine triphosphate restoration pathways. Kramer et al. (12) investigated the role of magnesium levels on cardiac pathophysiology and found that magnesium deficiency triggered inflammatory process and promoted cardiac dysfunction and cardiomyopathy. Also magnesium has a vital role in muscle relaxation by activating the intracellular magnesium troponin subunit and inhibiting actomyosin adenosine triphosphatase (13-15).

In a study with 200 patients, 6 mmol of $MgSO_4$ was administered to the study group in 100 ml 0.9% NaCl solution infused at a rate of 25 ml per hour for 5 days starting one day before the operation. The control group only received 100 ml 0.9% NaCl infusion. Post-operative AF frequency was 2% in study group compared to 21% in the control group, and the incidence was highest on the first two postoperative days (16). However, another 200-patient study in which study group received 3 gr $MgSO_4$ infusion in 100 ml 0.9% NaCl solution (50 cc/hour) for 5 days failed to reveal any significant difference between control and study groups with regard to AF rates.

In the studies on magnesium treatment, a major concern is the dosage and duration (10). Presence of a real hypomagnesemia should be first identified before the determination of magnesium treatment dose. Hypomagnesemia diagnosis is done by plasma level measurements but magnesium is an intracellular electrolyte and plasma level reflects less than 1% of the total body level (7, 8). It must be recognized that the correlation between serum magnesium levels and clinical signs and symptoms is poor, and that normal serum magnesium level may coexist with tissue magnesium deficiency. Thus, plasma magnesium level may be normal in the presence of magnesium depletion. By measuring the retention of administered magnesium, Manners and Nielsen (17) showed that 17% of patients undergoing cardiac surgery were magnesium depleted and that there was significant positive balance in every patient despite normal serum magnesium levels.

Tissue magnesium measurements can show hypomagnesemia more accurately and the treatment dose can then be determined accordingly. Studies about tissue magnesium levels are very limited in the literature. In one study, sublingual epithelial cellular, atrial and plasma magnesium levels of patients were compared with sublingual epithelial cellular and plasma levels of normal people. Sublingual epithelial cells and atrial tissues of patients had significantly lower magnesium concentrations than those of normal people, but this relation was not true for plasma magnesium levels (18).

Since tissue magnesium levels reflect better the real amount of magnesium present, we obtained tissue samples (atrial and skeletal) for magnesium determination before, during and after CPB, in addition to blood samples. In addition, all patients were continuously monitored for the development of AF along with daily blood magnesium level assessments for one week after the operation. Although a significant rise in blood magnesium levels was observed during and immediately after CPB in all patients, patients with or without AF did not differ with this regard. Since magnesium was not administered to any of the patients during the operations, this rise may be attributed to tissue breakdown due to CPB. On the other hand, CBP does not seem to affect tissue magnesium levels and we did not find a difference between patients with or without AF with regard to tissue magnesium levels. One may expect decreased tissue magnesium levels among patients with AF, since potential genesis of atrial fibrillation by electrolyte imbalance would occur at the cellular level. But, even if CBP has an effect on tissue levels, this may reach detectable levels after some time and the difference may be evident postoperatively, during which tissue sampling was not possible in our study design. The high incidence of AF within the first few postoperative days may be associated with a late onset decrease in tissue magnesium levels.

Study limitations

The major limitation of the present study is the relatively small sample size resulting in limited power, which may give rise to type II statistical error. Therefore, negative results should be evaluated cautiously and firm conclusions should be avoided.

Conclusion

In this study, the difference between patients with and without AF with regard to blood and tissue magnesium levels failed to reach statistical significance, thus our findings do not support a causal relationship between magnesium levels and AF development. On the other hand, the coincidence of an early postoperative reduction in magnesium levels in all patients and occurrence of all AF incidences at this time interval suggests a potential association deserving further investigation.

Conflict of interest: None declared.

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