Effect of Magnesium on Modulating the Activity of Na⁺K⁺-ATPase, Ca²⁺-ATPase, Mg²⁺-ATPase and 5´-Nucleotidase in South Indian Patients Undergoing Coronary Artery Bypass Graft Surgery

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Effect of Magnesium on Modulating the Activity of Na\(^+\)K\(^+\)-ATPase, Ca\(^2+\)-ATPase, Mg\(^2+\)-ATPase and 5’-Nucleotidase in South Indian Patients Undergoing Coronary Artery Bypass Graft Surgery

G. A. Kurian\(^1\), M. Murugan\(^1\), J. Paddikkala\(^2\)

**Objectives:** Cardiac surgery performed with cardiopulmonary bypass is associated with extensive overproduction of reactive oxygen species which is characterized by cell membrane damage that leads to impairments of membrane-bound ionic pumps. Changes in myocardial enzyme activity correlated with the progression of myocardial morphological changes and increased permeability of myocyte micro vessels.

**Aim of the Study:** The present study was designed to assess the status of plasma lipid peroxides and erythrocyte membrane activities of Na\(^+\)K\(^+\)-ATPase, Ca\(^2+\)-ATPase, Mg\(^2+\)-ATPase and 5’-nucleotidase of South Indian patients undergoing coronary artery bypass graft (CABG) surgery. This study also focused on the role of intra-operative magnesium supplementation to preserve membrane permeability.

**Patients and Methods:** 51 South Indian patients who had undergone CABG surgery (with intra-operative magnesium supplementation) and 35 controls (without magnesium supplementation) were selected and matched. The activities of the above-mentioned enzymes and cardiac enzymes were measured in the erythrocyte membrane and plasma, respectively.

**Results:** The activities of erythrocyte ATPase were found to be significantly \((p < 0.05)\) decreased in patients who were not administered Mg\(^2+\) during revascularization procedure and were improved by magnesium supplementation. However, the plasma TBARS concentration in magnesium-treated and -untreated patients did not show any significant \((p < 0.05)\) change even though the level of TBARS was lower in the first group. The cardiac marker enzymes were found to be improved in their activities by Mg\(^2+\) supplementation.

**Conclusion:** These results predict increased oxidative stress and ionic imbalance during CABG procedure, both in plasma and erythrocyte membrane. The extensive administration of magnesium before release of the aortic cross clamp can protect cardiomyoctes by preserving the ionic status of the cell. J Clin Basic Cardiol 2006; 9 (online): 10–16.

**Key words:** Na\(^+\)K\(^+\)-ATPase, Ca\(^2+\)-ATPase, Mg\(^2+\)-ATPase, CABG, reperfusion injury, magnesium

Coronary artery bypass grafting (CABG) is one of the effective methods to improve the life expectancy and quality of life of patients with ischemic heart disease. However, coronary revascularization during CABG can elicit a number of adverse reactions that may limit its beneficial effects [1]. The pathogenesis of reperfusion injury is probably multifactorial and includes intracellular calcium overload and generation of oxygen-derived free radicals. Elevated cytosolic-free calcium levels can activate proteases that compromise plasma-membrane integrity, allowing calcium overload and irreversible damage to mitochondria. Previous studies reported the impairments of membrane-bound ionic pumps during heart surgeries as a result of membrane damage and changes in myocardial enzyme activity [2]. ATPase enzymes in the membrane are responsible for ionic pump regulation. Erythrocyte ATPases like Na\(^+\)K\(^+\)-ATPase, Mg\(^2+\)-ATPase and Ca\(^2+\)-ATPase are critical for normal erythrocyte functions such as exchanges of intra- and extra-cellular electrolyte homeostasis and membrane integrity. It has been reported that anesthesia and surgical trauma can lead to a significant decrease in the activities of these ATPases [3].

Several investigations have shown that peri-operative serum magnesium levels may be reduced in 70 % of patients undergoing conventional CABG [4] which can lead to coronary artery spasm [5]. Magnesium is a principal cofactor in more than 300 intracellular and extracellular processes, many of them are integrally involved in mitochondrial function, energy production, and maintenance of trans-sarcolemmal ionic gradients, cell-volume control, and resting membrane potential. Magnesium (Mg\(^2+\)), given early in the reperfusion period, has shown promising results in both clinical [6] and experimental studies [7]. There is, however, no consensus regarding the beneficial effects of Mg\(^2+\) on infarct size and mortality or how such actions should be explained. Two factors assumed to be of importance in ischemia-reperfusion-induced cardiomyocyte damage and death are cellular calcium (Ca\(^2+\)) overload and oxidative stress, both can alter the activities of erythrocyte ATPase. Both factors may be possible targets for the protective effect of Mg\(^2+\).

The aim of the present study was to investigate the effect of extra-cellular Mg\(^2+\) on erythrocyte ATPase activity which may be altered under the pathological condition mediated by ROS and Ca\(^2+\) accumulation during CABG procedure. For this purpose, we chose South Indian patients assigned to undergo CABG procedure. They were randomly administered Mg\(^2+\) during revascularization.

**Patients and Methods**

**Population**

We studied patients undergoing CABG in which full revascularization was expected. Ethical approval was provided by the ethical committee of the Institute of Cardiovascular Diseases, Madras Medical Mission. Written consent was obtained from each patient.

92 south Indian patients (72 male, 20 female; mean age: 62.6 ± 11.2 yrs) as a total were included in this study. Patients were randomly assigned to magnesium-treated and magnesium-untreated groups. 52 patients (42 male, 10 female) re-
received magnesium, 40 patients (30 male, 10 female) did not. Patients who used antioxidants such as captropil and allopurinol were excluded from the study. Patients who received blood transfusion or blood products during operation were also excluded since the antioxidant properties of such products are not as yet established. None of the patients were taking vitamins or dietary supplements with established antioxidant properties before the study. None of the controls had a history of cerebrovascular disease.

Anesthesia Technique
On the day of surgery, patients were pre-medicated with morphine (0.2 mg/kg) and promethazine (0.5 mg/kg) i. m. about 30–45 minutes prior to induction of anesthesia. Anesthesia was induced with thiopentone (5 mg/kg), and vecuronium was used to accomplish endotracheal intubation with an appropriately sized tube (generally 9.0 mm for males; 7.5 mm for females). Anesthesia was maintained with 50 % nitrous oxide (N2O) along with halothane 0.5–1 %, morphine (0.05 mg/kg) i. m. about 30 minutes after intubation. The endotracheal tube was appropriately sized tube (generally 9.0 mm for males; 7.5 mm for females). Anesthesia was maintained with 50 % nitrous oxide (N2O) along with halothane 0.5–1 %, morphine (0.05 mg/kg) i. m. about 30 minutes after intubation. The endotracheal tube was

Surgical Technique
A standard cardiopulmonary bypass technique with normothermia (> 32 °C) was used throughout the study. The extracorporeal circuit was primed with Ringer’s lactate solution 1.5 l and mannitol 100 ml. In 52 patients, myocyte preservation was effected with magnesium (2 g/kg) administration just before release of the aortic cross clamp. Perfusion pressure was maintained between 50 mm Hg and 70 mm Hg during bypass. Cardiopulmonary bypass operation was instituted using ascending aortic cannulation and two-stage venous cannulation in the right atrium. The extracorporeal circuit consisted of a membrane oxygenator and a roller pump primed with crystalloid solution. Cardioplegia was given retrogradely except for the first two-thirds of crystalloid cold cardioplegia, which was given anterogradely. All distal and proximal anastomoses were completed before the aortic crossclamp was removed. At the end of CABG, heparin was neutralized by protamine chloride until the activated clotting time was less than 180 s. In the CABG group, hematocrit was kept more than 20 % during CPB.

Sampling and Analysis
Paired coronary sinus and arterial blood samples were taken according to the following time scheme: just before the induction of anesthesia – group 1; 10 minutes after aortic cross clamp on – group 2; 30 minutes after aortic cross clamp on – group 3; 10 minutes after aortic cross clamp off – group 4; during re-warming – group 5. Groups 2 and 3 referred to the ischemic state of the heart while group 4 referred to the ischemic reperfusion (revascularization) state.

Erythrocyte Membrane Preparation
Erythrocyte membranes or ghosts were prepared as described [8]. Briefly, the washed erythrocytes were lysed with 15 vol of 5 mmol/l of phosphate buffer (pH 8.0) and subsequently washed five additional times with the same lysing buffer. Membranes were collected after each wash by centrifugation at 4 °C for 10 min. at 10,000 g. This procedure yielded approximately 1 mg of protein/ml blood, as measured by the Lowry method [9], using bovine serum albumin as standard.

Biochemical Parameter
Na+K+-ATPase activity was estimated by the method of Nakao [10] in which 0.2 ml of the erythrocyte membrane or enzyme preparation was incubated with 1.0 ml of the reac-

Statistics
Data are presented as mean ± standard deviation. Data analyses were performed using SPSS software version 12.0. Comparisons within groups were made using repeated measures using one-way ANOVA. Comparisons between groups (pre-operative and surgical data) were carried out using chi-square-test. Continuous, normally distributed data was analyzed by t-test (single comparisons). Continuous non-normal data was analyzed with the Mann-Whitney-U-test.

Results
There were no hospital mortalities or peri-operative myocardial infarctions in either group. The initial post-operative serum magnesium level was higher in patients receiving magnesium (Tab. 1). In patients who did not receive intra-operative magnesium, the incidence of post-operative hypomagnesemia (< 1.8 mg/dl) was 35 %, compared with 9 % in patients who received intra-operative magnesium.

Table 2 shows the activities of Na+K+-ATPase, Ca2+-ATPase, Mg2+-ATPase, and 5’-nucleotidase in the erythrocyte membranes of patients who received and did not receive intra-operative magnesium during CABG. Comparing the values of the above enzymes in patient samples who did not receive Mg2+, a significant improvement was observed in the erythrocyte ATPase activity during revascularization in Mg2+-supplemented patients. However, there was no great difference in the activity of 5’-nucleotidase in both groups during ischemic reperfusion.
The changes in the activities of cardiac enzymes are shown in Table 3. The enzymes showed a similar pattern of changes in patients who received and did not receive magnesium. Even though cardiac enzyme activities were elevated in Mg²⁺-treated patients, their increase was not as prominent as in patients who received Mg²⁺-ATPase during early and later time intervals of the surgery procedure. However, there was a significant change between the groups as the TBARS level did not vary significantly in its concentration in different time intervals of the surgery procedure. However, there was a significant change between the groups as the TBARS level did not vary significantly in its concentration in different time intervals of the surgery procedure. However, there was a significant change between the groups as the TBARS level did not vary significantly in its concentration in different time intervals of the surgery procedure. 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Magnesium – Coronary Artery Bypass Graft Surgery

The experiments reported in the present study were designed to determine the effect of magnesium administration on the plasma lipid peroxidation and erythrocyte membrane ATPase changes during the revascularization procedure in CABG patients. Our results indicate that the activity of erythrocyte membrane Na⁺K⁺-ATPase decreased significantly during revascularization procedure and recovered in the late phase. A similar pattern of changes was shown by other ATPases in the erythrocyte membrane like Ca²⁺-ATPase and Mg²⁺-ATPase. An increased concentration of TBARS in the plasma was observed during revascularization procedure, although it was not statistically significant when compared to group 1. However, patients pre-treated with magnesium showed improved activities of both enzymes during revascularization. The inhibition of red-cell membrane ATPase activity in the revascularization procedure reflects the probability of noxious factors released into the blood that may directly or indirectly destroy or inhibit cell-membrane function or ATPase activity.

Since Ca²⁺-ATPase is an extrusion pump, diminished activity would lead to an intracellular calcium accumulation in vascular smooth muscle cells [18] and this may be of primary importance in the origin of increased peripheral vascular resistance, a characteristic feature of the ischemic reperfusion injury [19]. Magnesium inhibits calcium overload during initial phases of reperfusion through inhibition of calcium transport across most calcium channels [20]. Mg²⁺ increases calcium ATPase, which moves calcium back into the SR and into the extracellular space [21]. Numerous studies suggested that magnesium possesses class-IV (calcium channel-blocking activity) and class-I (sodium channel-blocking activity) antiarrhythmic properties, which result in an increase in conduction time through the atrioventricular node and accessory pathways as well as an increase in the refractoriness of the conducting system [22].

The decreased activity of Na⁺K⁺-ATPase might be correlated with direct destructive effects of some fluid factors such as complements, oxygen radicals and/or LPO on enzymatic molecular conformations and functions [23]. The suppressed activity of Na⁺K⁺-ATPase has also been reported by other workers in the early post-operative period [24]. Our data showed that decreased activities of Na⁺K⁺-ATPase, Mg²⁺- and Ca²⁺-ATPase were improved in the patient samples who received Mg²⁺ during revascularization procedure.

The improved 5'-nucleotidase activity in the erythrocyte membranes of Mg²⁺-treated CABG patients (Tab. 2) indicates the possible early recovery of coronary blood flow that will increase the supply of oxygen to the myocardium [25]. This is made possible by the release of adenosine (the product of 5'-nucleotidase) that causes the arteriolar dilation. This reduces coronary flow, which provides more substrate and oxygen and enables increased phosphorylation and replenishment of ATP.

Increased plasma concentration of TBARS (Tab. 4) during revascularization predicts the release of free radicals from the myocardium. This may oxidize the sulphydryl group of...
enzymes suggested the cardio-protective nature of Mg²⁺ significantly lower troponin I level along with other cardiac marker effects of magnesium during ischemic reperfusion. The significance of magnesium in the presence of extra-labile phosphate compounds: application to the ATPase in the presence of phospho-creatine. Anal Biochem 1975; 69: 261–7.


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