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Biochemical changes in liver and kidney functions of patients subjected to revascularization in CABG procedure: Role of magnesium supplementation

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Abstract

Introduction: Some of the previous studies reported distant organ injury like liver injury and renal failure after cardiac surgery, whereas in other studies no injury was identified. Magnesium (Mg) deficiency commonly occurs in critical illness and correlates with a higher mortality and worse clinical outcome in the intensive care unit (ICU). Accordingly, this study was designed to assess the effect of magnesium on liver and kidney function abnormalities during CABG procedure in an Indian population.

Methods: A clinical trial (n= 52) was conducted to determine the effects of magnesium (16mEq) on distant organs, administered just before the release of aortic cross clamp in patients undergoing coronary bypass operations. We took five blood samples at different times during cardiac surgery and analyzed the levels of ALT, AST, ALP, uric acid, total protein and creatinine. Cardiac marker enzymes like CPK MB, Troponin I and LDH were analyzed. Moreover, the antioxidant enzymes in erythrocytes like catalase, glutathione peroxidase, superoxide dismutase and glutathione reductase activity were determined along with the level of TBARS.

Results: Patients undergoing surgical myocardial revascularization revealed a decrease of antioxidant enzyme activities of erythrocytes in patients with and without magnesium administration during ischemic reperfusion. The product of lipid peroxidation (thiobarbituric acid reactive substances) in erythrocytes increased but the extent of release was more in patients treated without magnesium. Similarly, a significant improvement in the cardiac marker enzymes was observed in Mg treated patients. The altered biochemical changes in liver and kidney associated with ischemic reperfusion suggested the impact of revascularization injury and improved significantly in Mg treated patients.

Conclusion: These results reveal an increase in oxidative stress after CPB in erythrocytes; thereby it can adversely affect distant organs like liver and kidney. The extensive treatment of patients with magnesium influences the cellular response to ischemia and thus induces protection to heart and other organs.

Key words: anti oxidant, liver function, kidney function, myocardial ischemia, reperfusion, magnesium

Introduction

Over the past 30 years, the CAD rates have doubled in India whereas CAD rates have declined by 50% in most developed countries during the same period. CABG that accounted for less then 10% of all cardiac surgeries in 1980, today accounts for more than 60% and every year 25000 coronary bypass operations are being carried out in India [1].

Coronary artery bypass grafting (CABG) is a very effective procedure for reducing angina and stabilizing ventricular function. It has been convincingly established that cardiopulmonary bypass routinely used in cardiac surgery induces an oxidative stress that has a deleterious effect on the endogenous antioxidant defense pool [2].

Although CABG may be successful in revascularizing the heart, the surgical procedure may have adverse effects on distant organs such as brain, liver and even kidney. CPB has patho-physiologic sequelae, including incidence of neurologic dysfunction, postoperative myocardial infarction, bleeding, renal failure and respiratory failure. However, early studies have shown that ethnicity may also contribute to the variability seen in clinical outcomes following CABG. Gray and his co-workers found a 2-fold increase in the risk of death between African-Americans and white patients at 5 years following CABG [3]. More recently, Verderber documented significant differences in the hospital course of post CABG patients of Japanese and Pacific islands [4]. However, there has not much study been done on Indian population that directly investigates the relation between biochemical changes and heart, liver and kidney function during revascularization injury.

In the present study, we aimed to study the effect of Mg^{2+} in ameliorating organ abnormalities during open heart surgery. Moreover this prospective study was also designed to correlate the impact of post-operative biochemical and metabolic changes on clinical outcomes in the Indian patients with severe left ventricular dysfunction undergoing coronary artery revascularization by on-pump techniques.

Patients and methods

Patient population

We studied patients undergoing CABG operation in whom full re-vascularization was expected. Ethical approval was provided by the ethics committee of the Institute of Cardiovascular Diseases, Madras Medical Mission. A written consent was obtained from each patient.

Ninety-two patients (72 male and 20 female, mean age of 62.6 ± 11.2yr) as a total undergoing elective CABG for stable angina pectoris during January 2003 to December 2004 were included in this study. Patients were randomly assigned to magnesium-treated group or magnesium-untreated group. Fifty-two patients (42 male and 10 female) have received magnesium. Forty patients (30 male and 10 female) were not given magnesium. The exclusion criteria for the study population include age > 80 or < 18, cardiogenic shock or prolonged cardiopulmonary resuscitation, kidney failure, obstructive pulmonary disease and coronary intervention within the last 30 days. Demographic data is given in table 1. The flow of patients through the study and reasons for exclusion are detailed in the figure A.

Surgical technique

A standard cardiopulmonary bypass technique was used throughout the study. The extracorporeal circuit was primed with Ringer's lactate solution 1.5 liter and mannitol 100ml. In 52 patients, myocyte preservation was effected with magnesium (16 mEq.) administration just before the release of aortic cross clamp. Perfusion pressure was maintained between 50 and 70 mmHg during bypass.

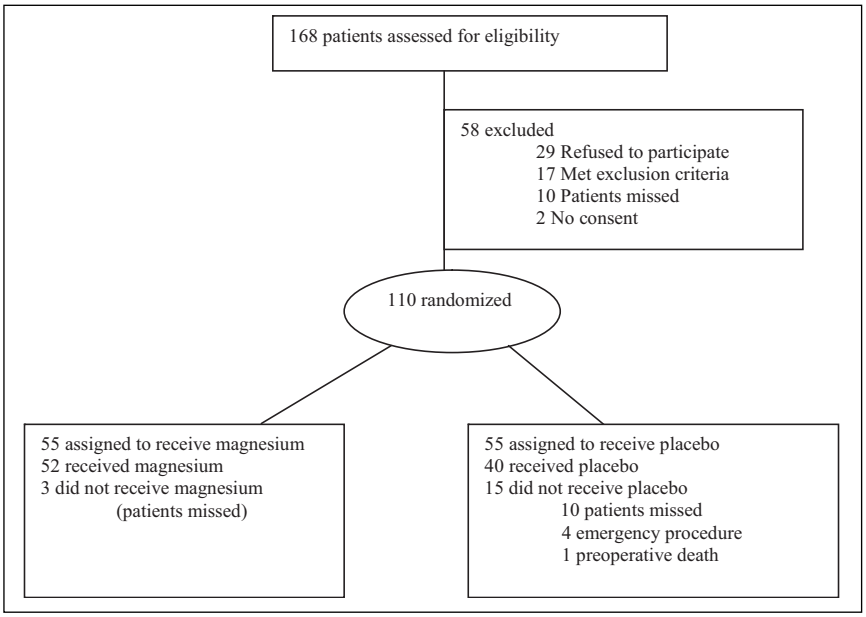

Figure A

Anesthesia technique: On the day of surgery the patient was premedicated with morphine (0.2 mg/kg) and promethazine (0.5 mg/kg) intramuscularly 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 appropriately sized tube (generally 9.0mm for males and 7.5mm for females). Anesthesia was maintained with 50% nitrous oxide (N_2O) along with halothane 0.5% to 1%. Morphine (0.05 mg/kg) was given before incision and 0.15 mg/kg was added to the pump prime. Additional morphine (0.1 mg/kg) and vecuronium (0.1 mg/kg) were administered during rewarming. Post CPB anesthesia was maintained with 50% O_2, 50% N_2O, halothane 0.5 to 1% and vecuronium (1/4 th of induction dose).

CPB technique: The bypass circuit was primed with a mixture of Ringer's lactate and HAES sterile to achieve a priming volume of 1500ml. CPB management was standardized throughout the study period. Cannulation was accomplished by use of ascending aorta and a separate caval cannula inserted through the right atrium, superior vena cava. CPB was instituted at a flow rate of 2.4 l/min/m^2 and the perfusate was cooled to 28° – 32° C. Albumin and packed RBCs were added to the pump prime to maintain the oncotic pressure and the hematocrit. Cold blood cardioplegic solution was injected at a total volume of 20 – 30 ml/kg over a period of 3 – 4 minutes. The infusion of cardioplegic solution was repeated at 20 – 25 minute intervals.

Mean arterial pressure was continuously monitored and maintained between 50 and 60 mmHg. The haematocrit was maintained above 22%. Urine output was monitored throughout the procedure. Blood sugar was monitored using a glucometer intraoperatively and sugar levels maintained between 180 and 240 mg%.

After surgery was completed, CPB was discontinued and heparin was neutralized with protamine. Patient received inotropic support by administration of dopamine and adrenaline was added if required to attain haemodynamic stability.

Sampling and analysis

Coronary sinus blood samples were taken at different time interval namely: T1) before aortic cross-clamp on; T2) 10 minutes after aortic cross-clamp on; T3) 30 minutes after aortic cross-clamp on; T4) 10 minutes after aortic cross-clamp off; T5) during rewarming. Blood samples taken at T2 and T3 are referred the ischemic state of the heart while the blood sample taken at T4 is referred the ischemic reperfused (revascularization) state. Thiobarbituric acid reactive substances (TBARS) were measured on plasma samples anticoagulated with EDTA with the technique described by Yagi [5]. The antioxidant enzymes like super oxide dismutase [6], catalase [7], glutathione peroxidase [8], glutathione reductase [9] were also measured. Serum troponin, CPK MB, lactate dehydrogenase, alanine transaminase, aspartate transaminase, alkaline phosphatase and calcium were analyzed by Sigma diagnostic kits. Protein concentrations were determined by the method of Bradford [10]. Urea, uric acid and creatinine were estimated by readymade kit using enzymatic methods.

Erythrocyte preparation

Approximately 5mL of blood was drawn and rinsed with heparin [10^6 U/L of phosphate buffered saline (PBS)] to serve as anticoagulant. Erythrocytes were separated from plasma by centrifugation at 4000 × g for 10 min at room temperature. After removal of the buffy coat, they were transferred to another tube and washed twice with 10vol of PBS (150 mmol/L NaCl in 5 mmol/L phosphate, pH 7.4) and collected by centrifugation at 10,000 × g for 10 min at 4°C. At this stage they were referred to as washed erythrocytes.

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 were analyzed by t-test (single comparisons). Continuous non normal data were analyzed with the Mann Whitney U test.

Results and discussion

Organ dysfunction and multiple organ failure that result in low cardiac output syndrome (LCOS) are among the main causes of prolonged hospital stay after cardiac surgery. The reasons may be multifactorial including myocardial ischemia during cross-clamping, reperfusion injury, cardioplegia-induced myocardial dysfunction, activation of inflammatory and coagulation cascades, and un-reversed pre-existing cardiac disease [11]. The perioperative (≤ 30-Day) morbidity data is given in table 2.

Previous experimental reports suggested that hepatic metabolic function does not differ by type of surgery to the end of the operation. However, there are reports emphasizing postoperative hepatocellular injury within CABG-CPB group [12]. In this study we evaluate the function of liver during CABG procedure through biochemical investigations. Wilkinson and his co-workers reported that changes in enzyme levels are good markers of soft tissue damage [13]. Thus, as evident from the result, marked elevations in the activity of ALP, ALT and AST (the indicator of hepatic function) during revascularization phase (fig 1) suggest a possible alteration in hepatic membrane permeability. In fact, ALP activity can be associated with inflammatory conditions of the liver [14]. As per early reports, extracorporeal circulation in CABG operation, by increasing contact of blood with foreign substances, can induce systemic inflammatory responses [15].

According to Bickel, the concentration of uric acid will increase during ischemia/reper-

Table 1: Preoperative clinical data

Variables	Received magnesium	Did not receive magnesium
N	52	40
Sex		
Male	42	30
Female	10	10
Mean age ± SD	63.7 ± 12.7	62.1 ± 11.4
Hypertension	25	18
Diabetes	20	12
Angina class		
I	12	10
II	33	30
III - IV	07	10
Coronary lesions (stenosis ≥ 70)		
Left anterior descending artery	49	38
Left circumflex artery	27	23
Right coronary artery	30	13
Posterior descending artery	20	15
Pre operative medicines		
B blockers	36	24
Calcium channel blockers	10	9
Diuretics	2	2
ACE inhibitors	4	5
Post operative magnesium level		
Initial magnesium	2.37 ± 0.54	1.86 ± 0.40
Initial potassium	4.17 ± 0.50	4.22 ± 0.40
CPB time	84.4 ± 25.5	83.8 ± 24.7
Aortic cross-clamp time	58.8 ±18.9	57.2 ± 19.5

Table 2: Perioperative (≤ 30-Day) Morbidity

Complications	Received magnesium (n=52)	Did not receive magnesium (n= 40)
Acute renal failure	1 (1.92%)	1 (2.5%)
Atrial fibrillation	5 (9.61%)	6 (15%)
Atrial flutter	2 (3.84%)	2 (5%)
Cardiac arrest	0	1 (2.5%)
Low cardiac output	0	1 (2.5%)
Myocardial infarction	1 (1.92%)	1 (2.5%)
Ventricular arrhythmias	0	1 (2.5%)

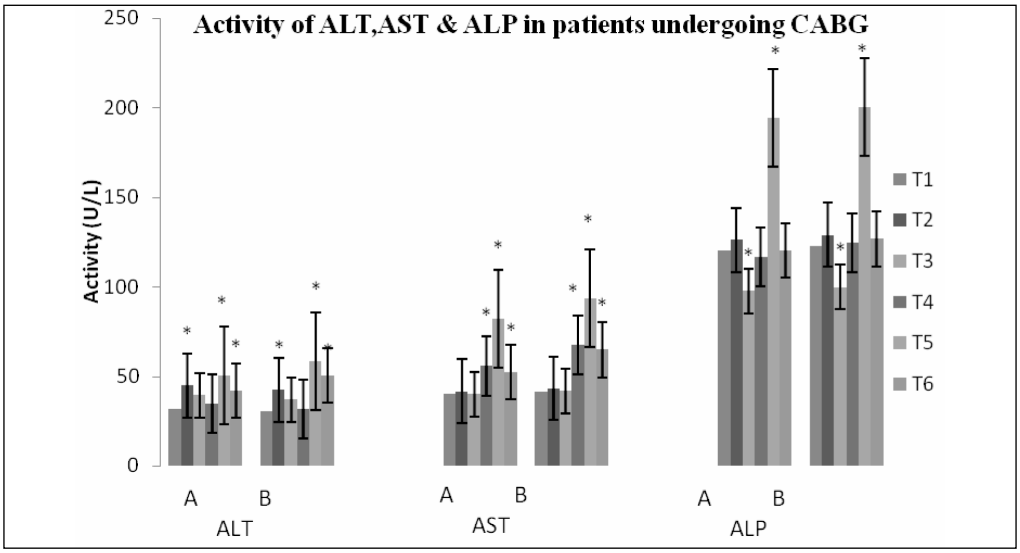

*Figure 1: Each data point represents the mean ± SEM. Activity is expressed as U/L for ALT, AST and ALP. *P<0.05 compared with T1.*

fusion injury and appeared to be an independent predictor of mortality in patients with angiographically proven coronary artery disease [16]. The peri-operative component like uric acid showed a significant increase during late phase of ischemia and persists in the late phase of reperfusion especially during re-warming stage. Increased levels of uric acid appear to be the consequence of oxidative stress in certain diseases and clinical conditions [17]. Indeed, uric acid also has antioxidant properties because it scavenges peroxyl and hydroxyl radicals and binds metal ions to prevent them from catalysing free radical reactions [18]. The other component such as creatinine also showed much similar patterns of increase during late phase of revascularization even though no significant change was observed. Impaired renal function after coronary artery bypass graft (CABG) surgery is a key risk factor for in-hospital mortality. Lassnigg and his co-worker reported that a 0.5 mg/dL change in creatinine from pre-operation to post-operation was indicative of acute renal failure and associated with an 18-fold risk of 30-day mortality [19]. The improved uric acid and creatinine levels of magnesium-treated patients as compared to magnesium-untreated patients emphasize the protective nature of magnesium (fig 2).

Several factors such as surgical trauma, inadequate myocardial protection, coronary artery embolism, graft occlusion or other complications of the procedure can trigger the release of the specific markers of the myocardial injury, i.e. serum aspartate transaminase, creatine kinase, creatine kinase, myocardial isoenzyme, cardiac troponin I [20]. In the present study, serum markers of myocardial damage were higher during the phase of revascularization in both magnesium-treated and untreated patients. However the extent of injury was more in Mg-untreated patients (fig 3,4 & 5). Even the arterial blood sample taken after 48hr post-operation showed elevated cardiac markers (fig 6) suggesting post operative complications and were observed to be declined in Mg-treated patients. Similar type of findings were reported early in the literature suggesting the beneficial effect of magnesium in patients with acute myocardial infarction where they preserved left ventricular ejection fraction, decreased infarct size and limited mortality [21].

During cardiopulmonary bypass reactive oxygen species produced by activated neu-

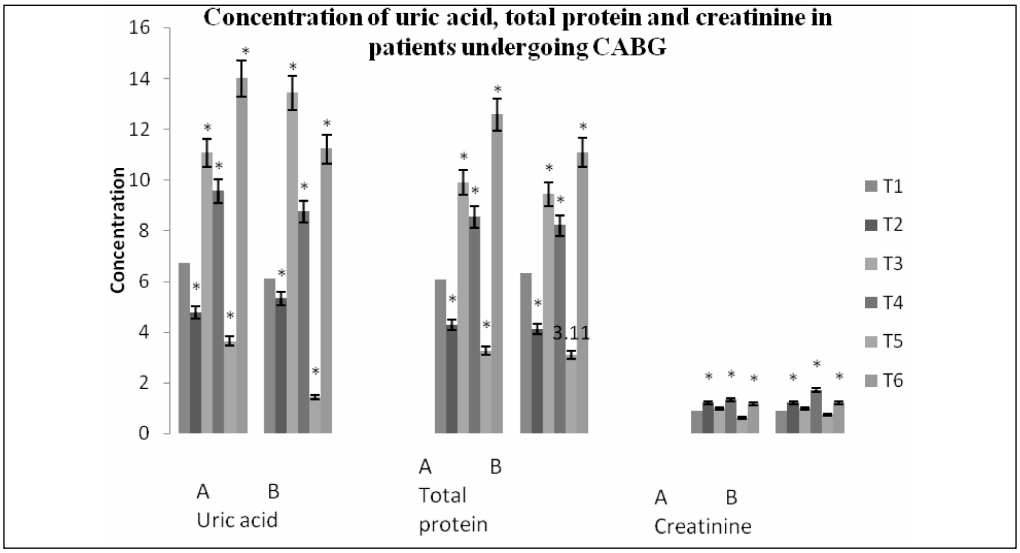

*Figure 2: Each data point represents the mean ± SEM. Activity is expressed as mg/dl for uric acid and creatinine; g/dl for total protein. *P<0.05 compared with T1.*

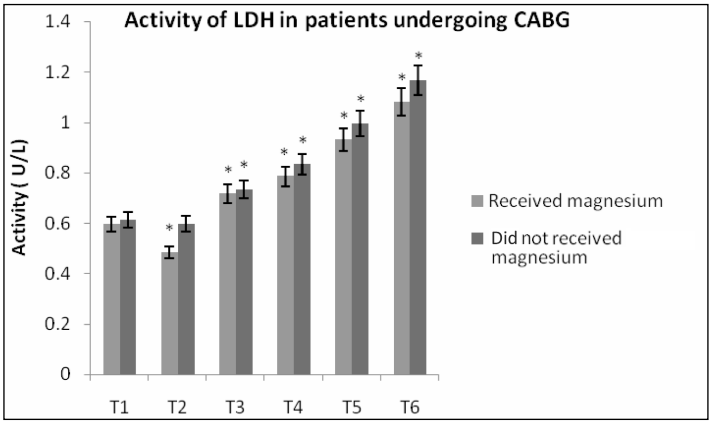

Figure 3: Each data point represents the mean ± SEM.
**P<0.05 compared with T1.*

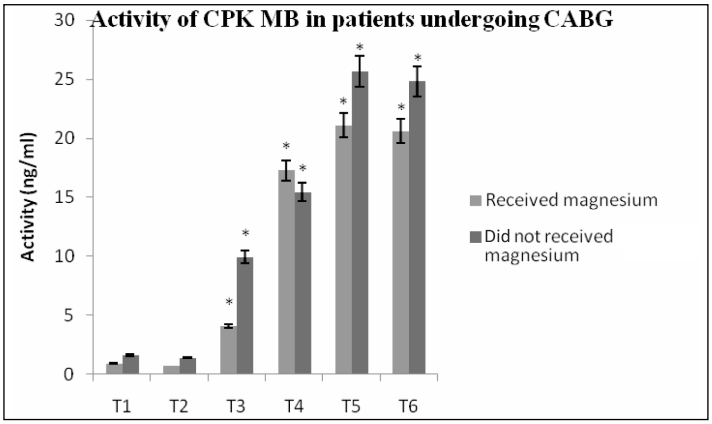

Figure 4: Each data point represents the mean ± SEM.
**P<0.05 compared with T1.*

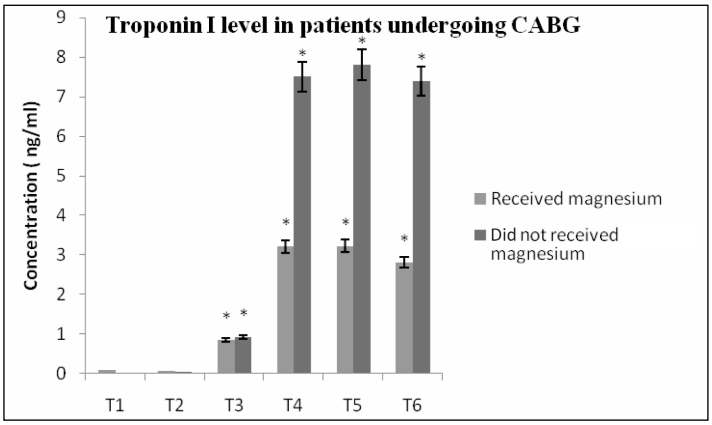

Figure 5: Each data point represents the mean ± SEM.
**P<0.05 compared with T1.*

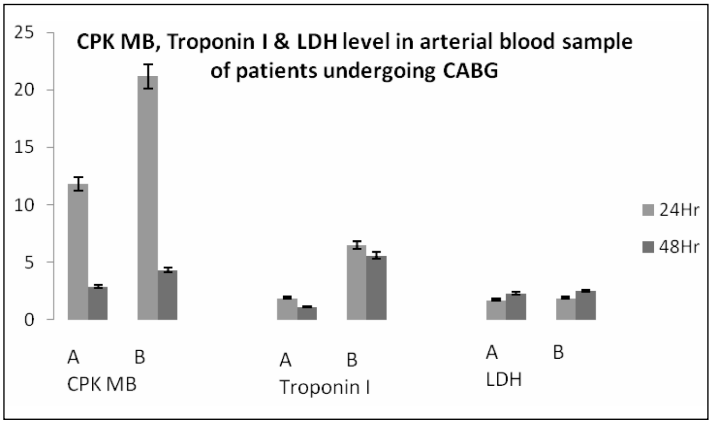

Figure 6: Each data point represents the mean ± SEM.

trophils or by tissue reperfusion injury may be involved in pathogenesis of diffuse damage in patients undergoing cardiac surgery [22]. Experimental evidence suggested an elevated lipid peroxidation during CABG [23]. However, antioxidant enzyme activities vary among different tissues, and environmental factors might affect the enzyme activities only in susceptible organs. Therefore, the activities found in erythrocytes do not necessarily reflect the antioxidant defense of the whole organism. But in this study, variations between individuals are substantially larger than within-subject variations, thus suggesting that the enzyme activity in a blood sample may reflect differences in the antioxidant defense. During ischemic reperfusion phase, significant increase in the erythrocyte TBARS were observed (Table 3). Indeed, magnesium-treated patients showed a better adaptation towards oxidative stress by CABG procedure as compared to Mg-untreated patients. In fact, experimental evidence by Afanas'ev et al. (1995) suggested free radical scavenging activity of Mg. But this effect is of minimal level as compared with other scavengers such as the transition metal manganese [24]. Thus, the mechanism exhibited by Mg in attenuating free radicals may be through inhibition of free radical production upon reperfusion and not by direct scavenging of radicals already present.

Among the antioxidant enzymes evaluated, the present study showed a significantly decreased activity of GPx at the end of reperfusion phase (T6). On the other hand, SOD activity was found to be decreased in the early stages (T5) of revascularization. According

Table 3: Anti oxidants in erythrocytes

Anti oxidant enzymes	Received magnesium	Did not receive magnesium
TBARS (n mol/ml)		
T1	[a]1.055 ± 0.11	[a]0.99 ± 0.11
T2	[b]1.523 ± 0.13	[b]1.453 ± 0.11
T3	[c]2.153 ± 0.17	[c]2.087 ± 0.18
T4	[d]2.975 ± 0.19*	[d]3.302 ± 0.19*
T5	[e]2.438 ± 0.12*	[d]3.111 ± 0.17*
T6	[b]1.661 ± 0.13	[c]2.334 ± 0.14
Catalase (μM of H_2O_2 utilized /min/mg Hb)		
T1	[a]688.54 ± 20.93	[b]695.22 ± 20.10
T2	[b]978.89 ± 36.12	[b]987.68 ± 35.92
T3	[c]1047.41 ± 38.61	[c]1058.92 ± 39.11
T4	[c]1062.07 ± 38.14*	[c]1094.67 ± 38.56
T5	[b]954.87 ± 36.12*	[c]1001.12 ± 37.14
T6	[c]823.68 ± 34.23	[b]869.93 ± 33.72
Glutathione Peroxidase (U/g Hb)		
T1	[a]7.13 ± 1.1	[a]7.01± 1.2
T2	[b]5.85 ± 0.9	[b]5.74 ± 0.9
T3	[c]4.79 ± 0.8	[c]4.70 ± 0.8
T4	[a]6.45 ± 1.0*	[a]7.03 ± 1.1*
T5	[c]4.96 ± 0.8*	[d]6.55 ± 0.9*
T6	[b]5.77 ± 0.9	[b]5.84 ± 0.9
Super oxide Dismutase (U/g Hb)		
T1	[b]4372.8 ± 340	[a]4254.1 ± 323
T2	[b]2697.8 ± 235	[b]2621.6 ± 243
T3	[b]2834.8 ± 255	[b]2761.3 ± 233
T4	[c]1426.7 ± 241*	[c]1353.6 ± 255*
T5	[c]1504.1 ± 254*	[c]1397.9 ± 213*
T6	[d]1634.8 ± 222	[d]1527.9 ± 221
Glutathione Reductase (IU/g Hb)		
T1	[a]1.228 ± 0.18	[a]1.20 ± 0.17
T2	[b]1.702 ± 0.21	[b]1.70 ± 0.20
T3	[c]1.009 ± 0.10	[c]0.987 ± 0.10
T4	[d]0.473 ± 0.08*	[d]0.444 ± 0.08*
T5	[d]0.551 ± 0.09*	[d]0.476 ± 0.09*
T6	[e]0.831 ± 0.09	[e]0.756 ± 0.09

All values significantly differ from group 1 ($p< 0.05$)
The comparison between T2 vs T4 and T3 vs T4 are expressed as (*) $P < 0.05$.
Values not sharing a common superscript (a,b,c,d,e,f) differ significantly at $P<0.05$) when compared between the groups

to Blankenberg, glutathione peroxidase (GPx) activity was among the strongest univariate predictors of the risk of cardiovascular events, whereas superoxide dismutase activity had not much direct association with risk [25].

In summary, the biochemical changes accompanying CABG surgery observed in this report are in accordance with the free-radical theory. Unlike a recent report, that suggests a severe early ischemic liver injury after cardiac surgery [26], we found that the biochemical changes associated with both liver function and kidney function are near to the normal level especially in the magnesium-treated pa-

tients. The present study concluded that intravenous Mg has the ability to reduce biochemical abnormalities associated with distant organs during CABG procedure.

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