Aminophylline Decreases Myocardial Injury and Suppresses the Anticardiolipin Antibody Expression During Coronary Artery Bypass Grafting

AMİNOFİLİN KORONER ARTER BYPASS AMELİYATLARINDA MİYOKARDİYAL HASARI AZALTMAKTADIR VE ANTİKARDİYOLİPİN ANTİKOR EKSPRESYONUNU BASKILAMAKTADIR

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Abstract

Objective: Increased serum anticardiolipin antibody (aCL, IgM and IgG) levels were found to be a marker of myocardial injury and a risk factor for thromboembolic cardiovascular events in patients. The aim of the present study was to evaluate the serum aCL levels and if aminophylline could serve as a potential myocardial protector during coronary bypass surgery.

Material and Methods: Twenty patients were randomly divided into two groups. Ten patients received aminophylline (200 mg orally per day for 3 days preoperatively, aminophylline group, AG), and 10 patients received placebo (control group, CG). Blood samples were collected before induction of anesthesia (T0), at 30 min of aortic cross clamping (ACC) (T1), and at 1 (T2), 2 (T3) and 7 (T4) days postoperatively. Serum concentrations of aCL and creatine kinase-MB (CK-MB) were measured. Cardiac hemodynamics were investigated.

Results: Hemodynamics and baseline serum aCL levels were similar. aCLs concentration started to increase after T1 and peaked at T4 in both groups (IgM:1,76 ± 0.63 vs. 0.91 ± 0.48 MPL/Unit, and IgG: 2.37 ± 0.56 vs. 1.05 ± 0.44 GPL/Unit in CG and AG respectively, p< 0.001). aCL levels were significantly lower at T2, T3 and T4 in AG (p< 0.05). The CK-MB levels of both groups were consistent with aCL levels and supported these results. Echocardiographic data were non-significantly better in treatment group. Fewer patients needed inotropic support (1 vs. 3 patients) (p= 0.6) and experienced atrial fibrillation (AF) (1 vs 4 patients) (p= 0.3) in the AG after surgery.

Conclusions: aCL levels were changed in a parallel manner with CK-MB levels. There was no statistically valid evidence to indicate that aCLs were associated with adverse events and aminophylline improved clinical outcome in this study. However, several biochemical endpoints such as consistent reduction of aCL and CK-Mb levels in the treatment group, suggested that aCL could be a marker of myocardial injury and aminophylline reduced Ischemia/Reperfusion (I/R) damage at the cellular level and such subtle improvement could be clinically significant in high-risk patients (prone to postoperative cardiovascular adverse events).

Key Words: Aminophylline, coronary artery bypass grafting, ischemia-reperfusion injury, heart, anticardiolipin antibody

Özet

Amac: Kanda antikardiyolipin antikorların varlığının miyokard hasarı için bir marker ve tekrarlayan kardiyovasküler tromboembolik olaylar içinde bir risk faktörü olduğu gösterilmiştir. Bu çalışmanın amacı: koroner bypass ameliyatı olan hastalarda antikardiyolipin düzeylerinini belirlemek ve aminofilinin bu hastalarda miyokardı koruyucu bir etkisinin olup olmadığını araştırmaktır.

Gereç ve Yöntemler: Çalışmaya alınan 20 hasta gelişigüzel olarak eşit iki gruba ayrıldı. 10 hastaya ameliyat öncesi 3 gün oral olarak 200 mg aminofilin verildi (aminofilin grubu, AG), diğer 10 hastaya plasebo uygulandı (kontrol grubu, CG). Hastalardan; anestezi öncesi (T0), kros-klempin 30'uncu dakikasında (T1), ameliyattan sonraki 1, 2 ve 7'inci günlerde kan örnekleri alındı ve örneklerde aCL antikor (IgM ve IgG) ve kreatin kinaz-MB (CK-MB) serum düzeyleri çalışıldı. İlave olarak hastalarda kardiyak hemodinamikler araştırıldı.

Bulgular: Her iki grubun hemodinamik bulguları ile bazal aCL düzeyleri benzerdi. Her iki grupta da aCL düzeyleri T1 döneminden itibaren artmaya başlamış ve T4 döneminde en üst seviyeye ulaşmıştır (CG ve AG gruplarında aCL antikor düzeyleri sırasıyla; IgM:1.76 ± 0.63 karşın 0.91 ± 0.48 MPL/Unit, ve IgG: 2.37 ± 0.56'ya karşın 1.05 ± 0.44 GPL/Unit olarak bulunmuştur, p< 0.001). AG'de T2, T3 ve T4 zamanlarındaki aCL düzeyleri istatistiksel yönden anlamlı olacak şekilde düşüktü (p< 0.05). Her iki grubun CK-MB düzeyleri aCL düzeyleri ile uyumlu ve aCL düzeylerini destekler mahiyetteydi. İstatistiksel olarak anlamlı olmamakla birlikte, ekokardiyografik verilerin aminofilin tedavisi alan hastalarda daha olumlu olduğu bulundu. Aminofilin grubu hastalarda daha az atrial fibrilasyon gelişmiştir (1'e karşın 4, p= 0.3) ve daha az hastada inotropik desteğe gereksinim olmuştur (1'e karşın 3, p= 0.6).

Sonuç: Serum aCL düzeyleri CK-MB düzeyleri ile paralel bir seyir gösterecek şekilde değişmiştir. Bu çalışmada aminofilinin hastaların klinik durumlarında iyileşme sağladığına ve aCL düzeylerinin hastalarda olumsuz olaylarla ilişkilendirilebileceğine dair istatistiksel bir kanıt bulunamamakla birlikte, aminofilin alan hastalarda aCL ve CK-MB düzeylerinin birbiri ile uyumlu olacak şekilde düşük bulunması gibi bazı biyokimyasal parametreler, serum aCL düzeylerinin miyokard hasarının değerlendirilmesinde bir marker olarak kullanılabileceğini ve aminofilinin iskemi/reperfüzyon (İ/R) hasarını hücresel düzeyde azaltabileceğini, bu olumlu etkinin özellikle yüksek riskli hastalarda klinik yönden önemli olabileceğini düşündürmektedir.

Anahtar Kelimeler: Aminofilin, koroner arter bypass, iskemi-reperfüzyon hasarı, kalp, antikardiyolipin antikor

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A complex group of antibodies, binding to anionic phospholipids such as cardiolipin, are associated with a clinical syndrome characterized in particular by venous and arterial thrombosis, recurrent abortion, and thrombocytopenia.[1.] Although the pathogenic mechanisms of anticardiolipin antibodies (aCL) are not clear, a complex relation between aCL and coro-

nary artery and valvular disease was suggested recently in various studies.[2-9] Klemp et al.[2] reported an association between elevated levels of aCL and ischemic heart disease; high titers of aCL appeared to serve as a marker of high risk for recurrent cardiovascular events. Ciocca et al. reported that patients with circulating aCL were prone to excessive postoperative morbidity and mortality after cardiovascular surgical procedures.[3] Furthermore, they reported that the presence of aCL might be a marker of increased risk of complications after cardiovascular surgery.[3] Bulckaen et al. reported that patients with severe valvular heart disease and aCLs had an increased risk for developing thromboembolic events.[4,]Thus, in accordance with these findings, it is commonly suggested that raised serum aCL levels in patients with cardiovascular diseases, such as myocardial injury or infarction might be a marker of myocardial injury and recurrent adverse cardiovascular events. However, the effect of isolated coronary artery bypass grafting (CABG) surgery using extracorporeal circulation on the aCL levels and the risk associated with aCL in these patients is unknown at present.

Despite well-established procedures, inadequate myocardial protection in patients undergoing CABG operation still contributes to overall hospital morbidity and mortality.[10] Reperfusion following ischemia, so called ischemia-reperfusion injury (I/R), significantly impairs myocardial recovery after aortic cross clamping (ACC) during open-heart operations.[11] Currently, I/R injury remains the most uncontrolled phenomenon during cardiac operations. Because of this, various methods and pharmacologic approaches have been examined to discover a drug capable of preserving the myocardium and preventing the incidence of postoperative adverse events. Aminophylline, an anti-ischemic drug, is a xanthine derivative and is widely used in the treatment of cardiovascular and respiratory diseases due to its broncodilative and putative anti-inflammatory effects.[12] It is an anti-ischemic and anti-anginal drug that has cardioprotective effects. These effects have been assessed both experimentally,[13] and clinically.[14-19]

In the past several decades, serum levels of cardiac enzymes and isoenzymes have become the final arbiters by which myocardial damage is diagnosed or excluded. Cardiac troponins, TnI and TnT and creatine kinase-MB (CK-MB) are highly specific and sensitive markers of myocardial injury; release of these enzymes and proteins into the circulation indicates various degrees of myocardial cell damage.[20] Currently, in clinical practice, determination of these enzymes and proteins provide the highest diagnostic efficiency for detecting myocardial cell necrosis. The aim of the present study was to determine the plasma aCL (immunoglobulin M, IgM and immunoglobulin G, IgG) levels in patients who underwent isolated CABG operation and to investigate the potential protective role of aminophylline treatment on myocardium and on aCL levels during CABG operations. Furthermore, the aim of this study was to see in addition to other markers, whether aCL could serve as a diagnostic marker for myocardial injury and a prognostic marker for adverse events in these patients.

Material and Methods

Patients

A cardioplegic-arrested heart during open-heart surgery was the model of myocardial ischemia. We designed a prospective, randomized, placebo-controlled trial to determine the efficacy of aminophylline on I/R injury after CABG operations. Twenty patients, selected from the waiting list, with coronary artery disease (CAD) who had elective, isolated, primary CABG operation in our institution were randomly assigned by a random number generator to aminophylline (n= 10) or placebo (n= 10). Patients with rhythm defects detected by electrocardiography (ECG) and patients receiving dipyridamole, xanthine products, β-adrenergic blocking agents, bacterial or viral infections, known systemic lupus, exposure to drugs that can induce aCL antibodies (phenothiazine, hydralazine, quinidine and valproic acid) and positive serum aCL levels were excluded from the study. All patients had normal ventriculographic findings and no known associ-

ated cardiac or noncardiac disorders. The institutional review board approved the study and written informed consent was obtained from all patients. Aminophylline, (Aminocardol, Novartis, Istanbul) was administered to 10 patients 200 mg orally per day for 3 days (Aminophylline Group, AG), and placebo was given to the remaining 10 cases (Control Group, CG). Serum concentration of aminophylline was measured daily in all patients and it was 5.12 ± 1.28 μg/ml in the AG just before the operation, but was not detectable in the CG. The reported potential side effects of the aminophylline were not observed. In the AG, there were 4 females and 6 males with a mean age of 60.7 ± 9.8 years. In the CG, there were 2 females and 8 males with a mean age of 57.2 ± 9.8 years (Table 1).

Operative procedures: Anesthesia, Cardiopulmonary Bypass, and Surgical Technique

Anesthetic management was uniform in all patients. Midazolam was used for premedication, and the anesthetic agent consisted of a combination of fentanyl, midazolam, and pancuronium. After intubation, mechanical ventilation was started with oxygen and nitrogen. Anesthesia was maintained with midazolam, vecuronium, and inhaled sevaflurane.

Patients were operated on by the same surgical team. CABG was performed with moderate hypothermia (28°C) and intermittent, cold, anterograde crystalloid cardioplegia (15 ml/kg, Plegisol, Abbott Laboratories, Abbott Park, IL). Topical cooling with cold saline was applied only once at the beginning of cardioplegic arrest. Half dose of cardio-

Table 1. Patients' demographic, surgical, and postoperative data.[a, b]

Variable	Aminophylline Group (n= 10)	Control Group (n= 10)
Characteristic		
Mean age (y)	60.7 ± 9.8	57.2 ± 9.8
Female (n)	4	2
Body surface area (m^2)	1.8 ± 0.1	1.8 ± 0.1
Body weight (kg)	76.9 ± 13.6	85.1 ± 5.3
Canadian Class 1/2/3/4 (n)	0 / 2 / 4 / 4	0 / 3 / 2 / 5
NYHA Class 1/2/3/4 (n)	0 / 0 / 4 / 6	0 / 0 / 6 / 4
Systemic hypertension (n)	6	4
EF (%), preop/postop	58.3 ± 6.9, 66.4 ± 5.0	64.3 ± 9.6, 59.1 ± 4.9
LVEDL (cm) preop, postop	5.4 ± 0.5, 5.2 ± 0.5	5.4 ± 0.3, 5.6 ± 0.2
LVESL (cm) preop, postop	3.5 ± 0.5, 3.5 ± 0.4	3.6 ± 0.7, 4.1 ± 0.4
Mean LVEDP (mmHg)	13.3 ± 5.1	14.1 ± 4.4
Cardiac output preop, postop (ml)	89.6 ± 14.5, 96.2 ± 15.9	96.9 ± 13.6, 90.3 ± 9.4
CI preop/postop ($L/m^2/min$)	3.73 ± 0.35, 3.95 ± 0.23	3.87 ± 0.25, 3.81 ± 0.14
No of vessels diseased, 2/3	3 / 7	4 / 6
Left main stenosis > 50 % (n)	2	1
Distal anstomoses (n)	3.0 ± 0.7	3.3 ± 1.1
Aortic cross-clamp time (min)	34.0 ± 7.4	36.8 ± 9.9
Bypass time (min)	70.5 ± 20.8	68.0 ± 16.0
Left internal thoracic artery graft (n)	10	10
Postoperative low cardiac output (n)	1	3
Postoperative atrial fibrillation (n)	1	4
Mechanical ventilation time (h)	4.8 ± 1.0	6.8 ± 2.3
Intensive care unit stay (days)	2.0 ± 0.5	2.5 ± 0.8
Postoperative hospital stay (days)	8.8 ± 0.9	9.1 ± 0.6

[a] Data are shown as mean ± standard deviation,
[b] P value was > 0.05 for all variables.
MI= Myocardial infarction; CI= Cardiac index; EF= Ejection fraction; LVEDL: Left ventricle end-diastolic length; LVESL: Left ventricle end-systolic length; LVEDP= Left ventricular end-diastolic pressure; CPB= Cardiopulmonary bypass; NYHA=New York Heart Association.

plegia was repeated with 20 min intervals as needed. The distal anastomoses were constructed during a single period of total aortic occlusion, and proximal anastomoses were constructed with partial clamping of the aorta. Left internal thoracic artery to left anterior descending artery was used in all cases and additional saphenous vein grafts were used when needed.

If there were no contraindications, the patients were extubated within 4 hours after surgery. Postoperative analgesia was maintained with metamisole or meperidine. When there was low cardiac output state, dopamine was used as the first choice inotropic agent. In the case of a new onset AF, amiodarone was used as the first choice antiarrhythmic agent.

Hemodynamic Measurements

Standard radial and central venous catheters were inserted preoperatively. Hemodynamic data including heart rate (HR) and blood pressure (BP) were recorded every 2 hours for about 3 days preoperatively and 5 days postoperatively. Central venous pressure (CVP) was measured every 2 hours for the first two postoperative days. A serial 12-lead ECG was obtained every 12 hours for 3 days preoperatively and once prior to discharge. Cardiac index (CI) and ejection fraction (EF) were assessed preoperatively just before the operation and 5 to 7 days after surgery using two-dimensional echocardiography (GE, Vingmed, Harten, Norway). Cardiac output (CO), CI, and EF were determined by the method (area length algorithms) described previously.[21] A cardiologist, blinded to the patient's clinical history and biochemical information performed all echocardiographic studies and interpreted ECG findings.

Metabolic Studies

Serial venous blood samples were collected before induction of anesthesia (T0), after 30 min of aortic cross clamping (ACC) (T1), and at 1 (T2), 2 (T3), and 7 (T4) days postoperatively. The samples taken for CK-MB and aminophylline measurement were drawn into tubes without an anticoagulant agent and the samples obtained for aCL measurement were drawn into tubes including 4% EDTA and 2000KIU aprotinin. Then all samples were kept at room temperature for 20 minutes to allow clotting. The samples were centrifuged at 3,000 rpm for 10 minutes and then stored in aliquots at a minimal temperature of (-) 20 °C until analysis. All measurements were made at all time points and there were no missing data. Serum levels of enzymes and aCL were determined for all samples by biochemists unaware of the patient's histories. CK-MB mass concentrations were assayed by an electrochemiluminescence immunoassay (ECLIA, Roche, Mannheim, Germany) using an Elecsys 1010 System analyzer (Roche, Mannheim, Germany). aCL (IgG and IgM) levels were determined by Enzyme-Linked Immunosorbent Assay (ELISA) (Clark Lab. Inc. NY, USA) in the same samples. Titers of IgG and IgM isotypes of aCL antibodies were expressed in standardized units, according to international recommendations;[22] GPL units for the IgG isotype and MPL units for the IgM isotype. Plasma concentrations of theophylline were determined according to a previously described method with a modified fluorescence polarization immunoassay (TDx analyzer, Abbott, IL, USA).[23] The upper reference limits for the normal ranges were set at CK-MB mass 5.0 ng/ml, and theophylline 20 μg/ml.

Statistical Analysis

All data were expressed as mean ± standard deviations. Statistical significance between the two groups was determined using unpaired Student's t-test and analysis of variance (ANOVA). CK-MB enzyme and aCL levels were compared at different time points using ANOVA (Bonferroni) to test for interactions. Data were considered significant when the p-value was less than 0.05.

Results

There were no hospital mortalities, perioperative myocardial infarctions or cerebrovascular thromboembolic events in either group. The clinical, operative, and postoperative characteristics of both groups are shown in Table 1. There were no significant differences in these variables between the two groups. Postoperative atrial fibrillation (AF) occurred in 1 patient in the AG and in 4 pa-

tients in the CG (p= 0.3). There were no substantial elevations in the CK-MB enzyme and aCL levels of these patients postoperatively. They were treated with amiodarone and they converted to sinus rhythm within the first 24 hours of onset, and were discharged from the hospital with sinus rhythm. No significant changes in ECGs (ST changes, new Q-wave) except AF were detected in any of the patients. One patient in the AG and 3 patients in the CG received dopamine postoperatively (p= 0.6). The mean duration of mechanical ventilation and hospital stay was shorter in the AG (p> 0.05) (Table 1). There were no significant intergroup differences for echocardiographic values, CI, EF, (Table 1) or any other hemodynamic data such as HR, BP, and CVP during the perioperative period.

Serum levels of aCL IgM and IgG at several sampling times in the groups are presented in Table 2 and changes in their serum levels are shown in Figure 1A and 1B. Serum aCL, IgM and IgG, were absent in both groups preoperatively. However, serial measurements of aCLs increased significantly in both groups over time postoperatively; concentration of both aCLs started to increase gradually by the time after T1, and peaked at T4 in both groups (IgM: 1.76 ± 0.63 vs. 0.91 ± 0.48 MPL/Unit, and IgG: 2.37 ± 0.56 GPL/Unit vs. 1.05 ± 0.44 GPL/Unit in CG and AG respectively, p< 0.001). In this study, measured serum aCL levels in the AG group were less than those of the CG throughout the entire postoperative measurement period (p< 0.001); however, aCL IgM and IgG levels were significantly lower at T2, T3 and T4 in AG (p< 0.05). These results demonstrate that myocardial reperfusion after CPB significantly enhanced the expression of aCLs in both groups, and this increment was significantly suppressed by amonophylline treatment.

Table 2. Mean serum concentrations.[a]

Study Period	Aminophylline Group (n= 10)			Control Goup (n= 10)		
	aCL IgG (GPL/Unit)	aCL IgM (MPL/Unit)	CK-MB (ng/mL)	aCL IgG (GPL/Unit)	aCL IgM (MPL/Unit)	CK-MB (ng/mL)
Preoperative	0.00 ± 0.00	0.00 ± 0.00	0.94 ± 0.92	0.00 ± 0.00	0.00 ± 0.00	1.69 ± 0.74
30 min of ACC	0.00 ± 0.00	0.17 ± 0.53	4.13 ± 2.16*	0.21 ± 0.36	0.23 ± 0.48	9.99 ± 4.63
Postoperative day 1	0.26 ± 0.35*	0.22 ± 0.38*	29.12 ± 9.57*	1.25 ± 0.93	1.13 ± 0.58	42.83 ± 16.3
Postoperative day 2	0.53 ± 0.49*	0.67 ± 0.46*	11.94 ± 8.78	1.64 ± 1.01	1.55 ± 0.60	23.54 ± 15.7
Postoperative day 7	1.05 ± 0.44*	0.91 ± 0.48*	5.46 ± 3.84	2.37 ± 0.56	1.76 ± 0.63	6.41 ± 2.74

[a] Data are shown as mean ± standard deviation.
aCL= anticardiolipin; CK-MB = creatine phosphokinase-MB; ACC = aortic cross-clamping.

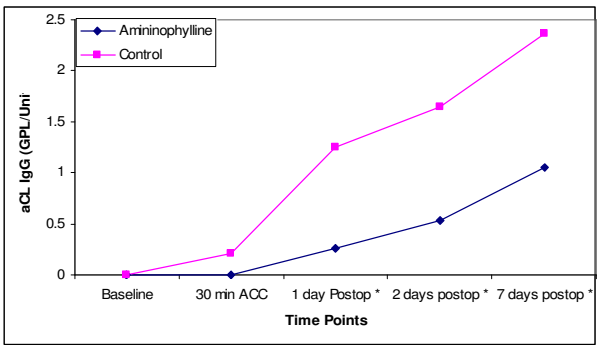

Figure 1A. Comparisons of aCL IgG levels between aminophylline and control groups. p< 0.05 at 1, 2 and 7 days postoperatively (unpaired Student's t-test and ANOVA) and p< 0.001 for Bonferroni.

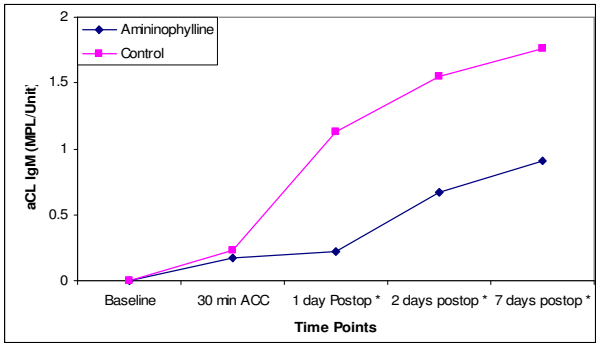

Figure 1B. Comparisons of aCL IgM levels between aminophylline and control groups. p< 0.05 at 1, 2 and 7 days postoperatively (unpaired Student's t-test and ANOVA) and p< 0.001 for Bonferroni.

The preoperative serum concentrations of CK-MB were similar (p> 0.05). Serum levels at several sampling times in the groups are presented in Table 2 and enzyme changes are shown in Figure 2. In the serial measurements, CK-MB level increased significantly in both groups over time compared with baseline measurements. Especially, myocardial reperfusion after CPB showed significantly elevated release of CK-MB enzyme in the groups. In both groups, baseline CK-MB concentrations increased at 30 min of ACC, and peaked at 1 day after declamping, followed by a progressive decline until postoperative day 7 (Table 2 and Figure 2). In this study, measured enzyme levels in both groups were significantly higher than preoperative values all through the postoperative study period (p< 0.001). These levels were less in the AG group than those of the CG throughout the entire measurement period. However, CK-MB levels in the AG were significantly lower at T1 and T2 postoperatively than those of the CG (p< 0.001) (Figure 2).

Discussion

Various studies demonstrated that aCL antibodies in cardiovascular surgery patients were involved in complications associated with arterial or venous thrombotic events affecting the heart. aCL antibodies were observed in nonautoimmune patients who experienced thromboembolic (TE) complications such as stroke[24] and cardiac complications.[2,9] These antibodies also were detected in recipients of renal, cardiac, and hepatic allografts who subsequently experience TE complications.[8,25,26] Fastenau et al observed an increased incidence of aCL antibodies in left ventricular assist system recipients.[5] Vaarala et al reported that, in a prospective cohort of healthy middle-aged men, the presence of a high aCL antibody level was an independent risk factor for myocardial infarction or cardiac death.[6] Hamsten et al. observed an increased prevalence of patients with elevated aCL antibody levels in a highly selected series of young patients with myocardial infarction.[9] Furthermore, high titers of these antibodies appeared to serve as a marker of high risk for recurrent cardiovascular events. In accordance with this, Klemp et al.[2] reported an association between elevated levels of aCL antibodies and ischemic heart disease. Boullanne et al. found a high prevalence of aCL antibodies in patients referred for heart valve replacement compared with matched control subjects in their studies.[7] However, in the latter study, no increased risk was demonstrated in the patients with aCL antibodies.[7] Ciocca et al. reported that patients with circulating aCL antibodies were prone to excessive postoperative morbidity and mortality after cardiovascular surgical procedures.[3] Bulckaen et al. reported that patients with severe valvular heart disease and aCLs had an increased risk for developing TE events.[4] Reports indicate that serum aCL antibodies may be a marker of increased risk of complications after cardiovascular surgery. However, the link between isolated CABG surgery using extracorporeal circulation and the level of aCL antibodies and the significance of the presence of aCL in patients who underwent CABG surgery is unknown. In this study, we examined the aCL levels in CABG patients and observed changes parallel to the level of CK-MB suggesting the possibility that they could be a diagnostic marker for myocardial injury. Although it was statistically non-significant, fewer patients needed inotropic support (1 vs. 3 patients) and experienced AF (1 vs. 4 patients) in the AG, whose aCL and CK-MB levels were lower compared with the control group during the recovery period.

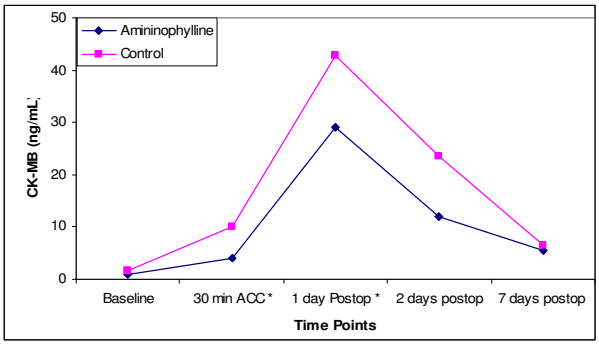

Figure 2. Comparisons of CK-MB levels between aminophylline and control groups. p< 0.05 at 30 min of ACC and 1 day postoperatively (unpaired student's t-test and ANOVA) and p< 0.001 for bonferroni.

Aminophylline is a methylxanthine derivative, widely used in the treatment of cardiovascular and respiratory diseases. Bioavailability of oral aminophylline is as high as 70% to 90%.[12] Clinical effects of aminophylline include relaxation of smooth muscles, stimulation of the central nervous system, increase in respiratory drive, decrease in peripheral vascular resistance, and inotropic and chronotropic effects.[12] The primary pharmacological effects of aminophylline are that, it increases intracellular cyclic adenosine monophosphate (cAMP) concentration by inhibiting cyclic nucleotide phosphodiesterase activity, influences and decreases the translocation of intracellular calcium by acting on membranes of the sarcoplasmic reticulum, acts as a competitive inhibitor of the adenosine receptor, and increases plasma catecholamine concentrations.[12]

Despite surgical and pharmacological advances in myocardial preservation during CABG, myocardial I/R damage remains the most uncontrolled aspect of cardiac operations. Aminophylline may be beneficial in many ways. Katircioglu et al, found that aminophylline (3 mg/kg, IV) improved ventricular function and metabolism, and decreased leukocyte activation in CABG patients.[27] Other clinical studies showed that aminophylline improved exercise capacity in patients with angina pectoris, and reduced the extent of myocardial ischemia,[14,16-18] right atrial pressure, LVEDP, left ventricular end-diastolic volume, and myocardial contractility.[14] Studies also showed that aminophylline increased the time to onset of angina and exercise duration,[17,18] work tolerance, ischemic threshold in patients with CAD[16] and significantly reduced the severity of cardiac ischemic pain as well as myocardial lactate production.[18,28] Furthermore, we demonstrated that aminophylline reduced myocardial I/R injury and decreased cardiac troponin, TnI and TnT release in CABG patients.[19] The chronotropic and pressor response to aminophylline is dose-dependent.[15] However, the positive inotropic response to aminophylline is independent of the dose.[18] At very low concentrations (5 to 10 μg/ml), aminophylline did not change the HR and BP, but apparently enhanced cardiac contractility (positive inotropic response) and reduced preload.[15,18] In our study, the mean plasma concentration of aminophylline was 5.12 ± 1.28 μg/ml in the AG. Although it was statistically non-significant, fewer patients needed inotropic support (1 vs. 3 patients) and experienced AF (1 vs. 4 patients) in the AG during the recovery period. However, the echocardiographic data (CI and EF) in this study showed no significant improvement after treatment with aminophylline. In addition, aminophylline did not have a significant effect on the other hemodynamic variables in our study. No significant changes in ECGs (ST changes, new Q-wave) except AF were detected in any of the patients. Hence, in our study, patients with high aCL and CK-MB levels were more prone to develop AF and had a better CI and EF than the other group. However, the correlation between the aCL Ab expression and enzyme elevations, and electrocardiographic or hemodynamic outcomes of the patients who were treated with aminophylline was not significant. The evaluation of the aCL level and efficacy of aminophylline in this study was based on a small number of patients, small number of item measurements, and a limited observation period. Further studies on the prognostic efficacy of aCL in CABG patients and the therapeutic potency of aminophylline in these patients, with larger groups, are needed to clarify this issue.

The best model of myocardial I/R is the cardioplegic ischemic-arrested heart during open-heart operation. All study patients received preoperative oral aminophylline for myocardial protection. One limitation of our study related to the use of cold crystalloid cardioplegia and cold saline for myoprotection. Because blood cardioplegia is more effective than cold crystalloid cardioplegia, aminophylline could have been more beneficial for patients receiving blood cardioplegia than for those who received cooled crystalloid cardioplegia and topical saline. However, this should not be a major concern, as the end-point of the study was not the comparison of these two myoprotection methods, but the comparison of the enzyme levels in the patients.

In the past several decades, serum levels of cardiac enzymes and isoenzymes have become the

final arbiters by which myocardial damage is diagnosed or excluded. CK-MB measurement is highly sensitive in the diagnosis of myocardial injury and accurately detects even small amounts of myocardial necrosis.[10] For this reason, in our study, to detect the cytoprotective effect of aminophylline during I/R, we measured serum level of CK-MB and compared them with aCL levels. We observed a parallel increase in the aCL and CK-MB enzyme levels in both groups. We found significantly lower aCL and CK-MB levels in the AG postoperatively ($p< 0.001$). The fact that no patient developed MI as indicated by CK-MB enzyme, ECG and echocardiography in this study, may support the following hypothesis: virtually all patients had temporary myocardial ischemia that led to the release of membrane phospholipids and cytosolic molecules leaking from reversibly injured myocytes. Our study showed that the elevation of the serum aCL and release of cytosolic molecules from reversibly injured myocytes was significantly lower in the AG. In addition, our data clearly showed that when the cross clamp was applied to the aorta, the unfavorable ischemic effects of CPB were induced, and the aCL and enzymatic increment were significantly reduced in patients who received aminophylline therapy before CPB. With this study, we demonstrated the anti-ischemic and anti-inflammatory effect of aminophylline, confirmed by a reduction in the aCL and CK-MB levels of the aminophylline treated group, by using cardio-specific markers for I/R injury. However, we cannot explain its anti-inflammatory and anti-ischemic cellular mechanism based on our data.

In conclusion, aCL level increased consistently with CK-MB enzyme elevation in the CABG patients postoperatively. Although there was no statistically valid evidence to indicate that high serum aCL levels were associated with a postoperative adverse event and aminophylline improved clinical outcome in this study, several biochemical endpoints suggest that aminophylline reduced aCL expression and I/R damage at the cellular level, and such subtle improvement could be clinically significant in high-risk patients.

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