# Cholestryl ester transfer protein and reoperative coronary artery surgery

*Kolesterol ester proteini ve reoperatif koroner arter cerrahisi*

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***Background:*** The activity of cholesteryl ester transfer protein (CETP) has been assessed in patients with occluded grafts following coronary artery bypass grafting (CABG).

***Methods:*** Twenty patients undergoing re-operative CABG (group 1) between June, 2003 and November, 2004 were prospectively compared with control groups (20 patients undergoing primary, isolated CABG -group 2 and 20 patients undergoing isolated non-ischemic valvular procedures-group 3) for CETP activity, pre-, peri- and postoperative data including hospital mortality and mortality. For statistical reason, groups 2 and 3 were denominated as 'group B' which delineates progressive atherosclerosis in some evaluations.

***Results:*** Cholesteryl ester transfer protein activity was highest in group 1 (14.28±3.87; 5.42±3.59; 7.08±3.87 in groups 1-3, respectively; $p<0.05$). 50% of patients in group 1 had a three-graft CABG (2.85±0.99 grafts/patient). One patient expired in group 1; two of three cases of perioperative myocardial infarction were from group 1. Cholesteryl ester transfer protein activity higher than 9.34 was recognized as the limit of progressive atherosclerosis. Area under the receiver operator characteristic curve (ROC) was 0.085 indicating that the analysis was very good.

***Conclusion:*** Screening younger patients for CETP activity may predict middle and long term prognosis and the use of "athero-resistant" grafts (e.g. arterial grafts) may be particularly important in those patients with a CETP activity above the cut-off point of 9.34.

*Key words:* Cholesterol ester/metabolism; coronary arteriosclerosis; coronary artery bypass; reoperation.

***Amaç:*** Koroner arter bypass cerrahisi sonrası greftleri tıkanmış olan hastalarda, kolesterol ester transfer proteininin (KETP) aktivitesi değerlendirildi.

***Çalışma planı:*** Haziran 2003 Kasım 2004 tarihleri arasında koroner arter bypass tekrar cerrahisi geçiren 20 hasta (grup 1) ile kontrol grupları (primer koroner bypass cerrahisi geçiren 20 hasta [grup 2] ve iskemik nedenlere bağlı olmayan kalp kapak ameliyatı geçiren 20 hasta [grup 3]) KETP aktivitesi, hastaların özellikleri ve hastane mortalite/morbiditesi açısından karşılaştırıldı. İstatistiksel inceleme açısından grup 2 ve 3 bazı değerlendirmelerde progresif aterosklerozu gösterdiği öngörülen "grup B" olarak adlandırıldı.

***Bulgular:*** En yüksek KETP aktivitesi grup 1'de bulundu (sırasıyla 14.28±3.87; 5.42±3.59; 7.08±3.87- grup 1'le karşılaştırıldığında $p<0.05$). Grup 1 hastalarının yarısında daha önce üç greft kullanıldığı belirlendi (2.85±0.99 greft/hasta). Kaybedilen tek hasta ve belirlenen üç peroperatif miyokard infarktüsü olgusundan ikisi grup 1'de idi. Kolesterol ester transfer proteinin aktivitesi açısından 9.34 değeri progresif aterosklerozun başladığı sınır olarak belirlendi. Kullanılan ROC (receiver operating characteristic curve) analizinde eğri altında kalan alan 0.085- çok iyi olarak bulundu.

***Sonuç:*** Genç hastalarda KETP aktivitesinin taranması, bu hastaların orta ve uzun dönem prognozu hakkında bilgi verebilir ve özellikle KETP aktivitesi sınırın üzerindeki hastalarda "aterorezistan" (örn. arteryel) greftlerin tercihi önem kazanmaktadır.

*Anahtar sözcükler:* Kolesterol ester/metabolizma; koroner arterioskleroz; koroner arter bypass; reoperasyon.

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In modern cardiac surgery, the majority of a cardiac surgeon's everyday practice consists of aortocoronary bypass grafting (CABG) procedures. As the history of CABG operations have reached 40 years and the late results of primary or re-operations have been reported, a better insight into the primary pathology and methods to refine the results have been sought. Among these issues, premature atherosclerosis (i.e. coronary artery disease at age younger than 40 years) and the atherosclerotic saphenous vein graft disease still pose a significant challenge in this field.

Cholesteryl ester transfer protein (CETP), a glycoprotein responsible for transferring cholesteryl esters from high density lipoproteins (HDL) to triglyceride-rich lipoproteins (e.g. low density lipoprotein-LDL, chylomicrons), have been studied extensively for a causative or therapeutic relationship.[1-3] Cardioprotective effects of HDL have been shown to be affected by altered expression or activity of this enzyme.[4-7]

CABG at an early age has been emphasized to be a significant risk factor for a future reoperation.[8] Studies have shown an approximately 30% occlusion rate in addition to another 30% stenosis rate for saphenous vein grafts in 10 years; a 17% rate of re-intervention need for these grafts has also been suggested.[9-11]

In this preliminary study, we aimed to determine the importance of CETP and other known characteristics of the patients undergoing reoperative CABG.

## PATIENTS AND METHODS

***Patient selection and diagnostic criteria.*** Patients undergoing re-operative CABG (group 1) between June 2003 and November 2004 were prospectively included in the study. As control groups, 20 patients undergoing primary, isolated CABG at an age older than 40 years (group 2) and 20 patients undergoing isolated non-ischemic valvular procedures (group 3) were randomly chosen from authors' patient pool so that the primary surgeons were the same in a double-blinded fashion. Institutional review and ethics committee approval and informed consents from all patients regarding the surgical procedure and the study were obtained. To emphasize CETP's effect on atherosclerosis in group 1, a time limit of at least 5 years between the primary and re-operation was chosen. Patients deemed to undergo a re-operation before 5 years were excluded. All patients underwent standard median sternotomy and cardiopulmonary bypass with aortic clamping. The proximal coronary anastomoses in all patients were done using a partial occluding aortic clamp. In all patients in group 1, femoral artery and vein were prepped surgically for a possible cannulation. Pre- and peri-operative data as well as procedural records of primary operation for patients in group 1 were acquired to be able to elaborate on the nature of the disease. All patients with a history of familial hyperlipidemic syndromes or endocrinological disorders other than diabetes mellitus were excluded from the study, but no patient was excluded from any of the patient groups for such a reason. All perioperative data such as aortic clamp times, cardiopulmonary bypass (CPB) duration, failure to wean from CPB, perioperative use of inotropic agents or intraaortic balloon counterpulsation as well perioperative adverse events were recorded. Changes in CKMB in the perioperative course of all patients were followed as CKMB0: at postoperative 30th minute; CKMB1: at postoperative 24th hour; CKMB2: at postoperative 48th hour; CKMB3: on postoperative 7th day. Mortality was noted as in-hospital mortality; perioperative myocardial infarction was diagnosed in accordance with ACC/AHA guidelines; neurological adverse events were diagnosed and managed by a clinical neurologist using the Modified Rankin Scale. Myocardial creatine kinase levels (IU/lt) were determined at postoperative 30th minute, 24th and 48th hours as well as on the 7th day. Hospital and intensive care unit stay durations for each patient were noted.

***CETP analysis.*** All serum samples taken preoperatively after a 12-hour fasting period were stored at -20 °C until analyzed with scintillation proximity assay (CETP [3H] SPA, human, TRKQ7005-25 µCi kit, Amersham Biosciences, NJ, USA) which is based on the transfer of [3H] cholesteryl esters from high density lipoproteins (HDL) to biotinylated low density lipoproteins (LDL) and its measurement following incubation of donor and acceptor particles in the presence of partially purified CETP. Analysis of the scintillation was done using a gamma counter (Isocomb I Multiwell Gamma Counter, GMI Instrumentation Inc., MN, USA) and was standardized using incubation period-effect and transfer-amount of plasma curves which provided a linear expression of ester transfer process. Based on these data, scintillation counts outside the range of 4 to 10 units (representing a change of 20-35% as suggested by the supplier) were accepted as hyper- or hypoactivity.

***Statistical analysis.*** For statistical analysis, patients were divided into A (groups 1 - progressive atherosclerosis) and B groups (groups 2 and 3). Statistical procedures were performed by SPSS 10.0 (SPSS Inc, Chicago, Ill) and MedCalc 7.0.0.4 (MedCalc Statistical Software for Biomedical Research, 2002 Frank Schoonjans, Mariakerke, Belgium). Data are expressed as means ± standard deviation. A p value of less than 0.05 was considered to indicate statistical significance. "Fischer's exact test", "Levene's f-test", and "Independent-samples t-test" as well as "Mann-Whitney U-test" and "receiver operating characteristic

**Table 1. Preoperative characteristics of patients in groups 1-3**

| | Group A | | Group B | | | | *p* |
|---|---|---|---|---|---|---|---|
| | Group 1 | | Group 2 | | Group 3 | | |
| | n | % | n | % | n | % | |
| Age (years) | 65.35±6.88 | | 58.4±8.56 | | 48.15±15.17 | | 0.4 |
| Smoking | 9 | 45 | 13 | 65 | 8 | 40 | 0.5 |
| Hypertension | 9 | 45 | 10 | 50 | 3 | 15 | <0.05 |
| Hyperlipidemia | 9 | 45 | 2 | 10 | 0 | 0 | <0.05 |
| Cholesterol lowering drug use | 12 | 60 | 1 | 5 | 0 | 0 | <0.05 |
| Preoperative myocardial infarction | 19 | 95 | 16 | 80 | 2 | 10 | <0.05 |
| Preoperative serum creatinine (mg/dL) | 0.97±0.18 | | 0.98±0.26 | | 0.78±0.11 | | 0.2 |
| Diabetes mellitus | 4 | 20 | 6 | 30 | 1 | 5 | 0.7 |

(ROC) curve analysis" were used for the statistical evaluation of data.

The predictive power of CETP activity for progressive atherosclerosis was tested using ROC analysis. For each serum CETP value of a patient, likelihood ratio, positive and negative predictive values, 95% confidence interval (CI) were determined. An overall analysis of these values and likelihood ratios yielded a critical CETP activity with minimal false negative and false positive values; and thus assisted in commenting on the role of CETP in prediction of progressive atherosclerosis in regard to vein graft atherosclerosis and premature coronary artery disease. A further analysis was done so as to elaborate on the probability of a higher CETP level from a randomly chosen patient in progressive atherosclerosis group than another randomly chosen patient from group B. Based on Hosmer and Lemeshow tests, CETP's power for discrimination between progressive atherosclerosis and the control group was assessed and commented as the following: area under the ROC curve (AUC) = 0.5: no difference, 0.5<AUC<0.7: test with an insignificant discriminatory power, 0.7<AUC< 0.8: acceptable discriminatory power, 0.8<AUC< 0.9: very good and 0.9 < AUC: perfect.

## RESULTS

Between June 2003 and November 2004, 24 patients were re-operated for occluded/stenotic coronary artery grafts. All except four, had their primary operation at least 5 years before the date of re-operation. These 4 patients were not included in the study because of possible cause other than atherosclerosis (e.g. intimal hyperplasia, thrombosis). Thus, the analysis was applied to 60 patients all operated by the same primary surgeon. Table 1 shows preoperative characteristics of the patients. Preoperative history of previous myocardial infarction, hypertension, hyperlipidemia, use of lipid-lowering drugs were significantly higher in group A ($p<0.05$). Of note, group 1 had higher number of patients with high serum lipid levels. Since patients in group 4 were chosen from patients with documented normal coronary artery anatomy, risk factors as hyperlipidemia, use of lipid lowering drugs or hypertension were not as significant. Preoperative total cholesterol and triglyceride levels in group 1-3 were noted as 188.25±40.78 / 119.25±54.41; 174.25±26.20 / 126.45±54.39; 161.05±49.17 / 90.25±56.91 mg/dl, respectively. Table 2 demonstrates all four groups with CETP activities and Cleveland-Higgins scores. Patients in group 1 had significantly higher CETP values than patients in group 2 ($p<0.05$). Patients in group 1 also had significantly higher Cleveland-Higgins scores ($p<0.05$). CETP activity values were highest in group 1 (groups 1-3: 14.28±3.87; 5.42±3.59; 7.08±3.87, respectively). A cut-off level for CETP where it has the highest specificity and sensitivity was determined as 9.34 with 95% CI, a value that would indicate a higher tendency for "progressive atherosclerosis" (Fig. 1). A further analy-

**Table 2. Cholesteryl ester transfer protein activity values and Cleveland-Higgins scores of group 1-3**

| | Group 1 | Group 2 | *p* |
|---|---|---|---|
| CETP (count units/ml) | 14.28±3.87 | 5.42±3.59 | <0.05 |
| Cleveland-Higgins score | 4.85±0.81 | 1.71±0.64 | <0.05 |
| CETP (count units/ml) | 14.28±3.87 | 7.08±3.87 | <0.05 |
| Cleveland-Higgins score | 4.85±0.81 | 1.15±1.04 | <0.05 |

sis was applied using ROC analysis and the AUC was 0.085 (Fig. 2) indicating that the previous analysis was very good, almost perfect for discriminating between progressive atherosclerosis and the controls.

It is important to mention that no surgical complication in regard to resternotomy occurred in group 1 patients necessitating prompt onset of CPB with cannulation from surgically prepped femoral vessels.

CKMB levels during the postoperative course of the patients at CKMB0 to CKMB3 were as 24.2±5.96, 72.45±41.11, 76.1±110.98, 28.55±7.51 IU/L for group 1; 27.9±47.4, 60.95±29.82; 54.95±36.67, 30.6±12.39 IU/L for group 2 and 16.8±4.34, 96.1±43.37, 77.7±50.8, 36.9±29.9 IU/L for group 3, respectively. More significant increases in CKMB1 and CKMB2 activities were observed in group 1. When CKMB activities were compared between group A and B, only CKMB3 levels were noted to be significantly higher in group A ($p<0.05$).

Analysis of group 1 patients for their previous operation showed that 50% of them had a three-graft CABG (2.85±0.99 grafts/patient for the whole group). In all patients but one, indication for a re-operation was considered due to intractable chest-pain with documented regional ischemia and occlusion of the graft to the LAD coronary artery. In only one patient, all three saphenous vein grafts were occluded in circumflex and right coronary artery territories although ITA graft to LAD was well patent. Indication for this latter patient was intractable chest-pain with documented ischemia in a large territory mainly supplied by the occluded grafts.

Group 1 needed more inotropic agents perioperatively with three cases of low cardiac output state (group 1 vs. 2: 11 vs. 2 patients; p=0.03; group 1 vs. 3: 11 vs. 11 patients; p=0.9). One of these patients represent the single case of mortality among all 80 patients. In addition to two cases in group 1, another patient in group 3 had a perioperative myocardial infarction (groups A and B, p=0.2). A single patient in group 3 was allocated to permanent pacemaker program due to complete heart block postoperatively. In groups 1-3, only one patient experienced a paroxysmal atrial fibrillation resuming to sinus rhythm with amiodarone.

ICU stay in groups 1-3 was found as 2.75±5.99, 1.1±0.3 and1.15±0.49 days. A comparison of ICU stay between groups A and B showed no difference (p=0.2). Hospital stay in group A was significantly higher (groups 1-3:10.45±6.26, 7.7±0.92 and 7.7±1.34 days, respectively; p=0.03).

## DISCUSSION

With more than 500.000 operations every year worldwide, CABG procedures still stand as the heaviest bulk of a cardiac surgeon's practice. Cardiac mortality and morbidity, being a major burden on the patients, their families and the society are closely related to the results of the surgical procedures as common as CABG. Coronary artery disase as the major target of many investigators have been studied in patients at younger age and in those who had a previous CABG operation. According to the results of "the European Coronary Surgery Study Group", CABG procedures have not yielded as good long-term results for younger patients

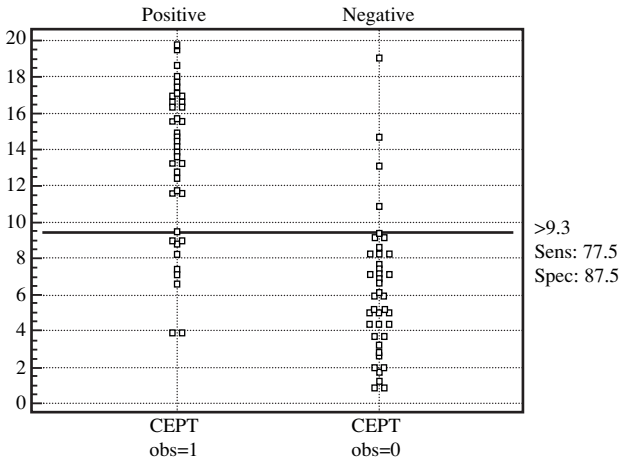


**Fig. 1.** CETP activity with highest sensitivity and specificity was found to be 9.34 (count units/ml); a cut-off value where atherogenesis increases significantly.

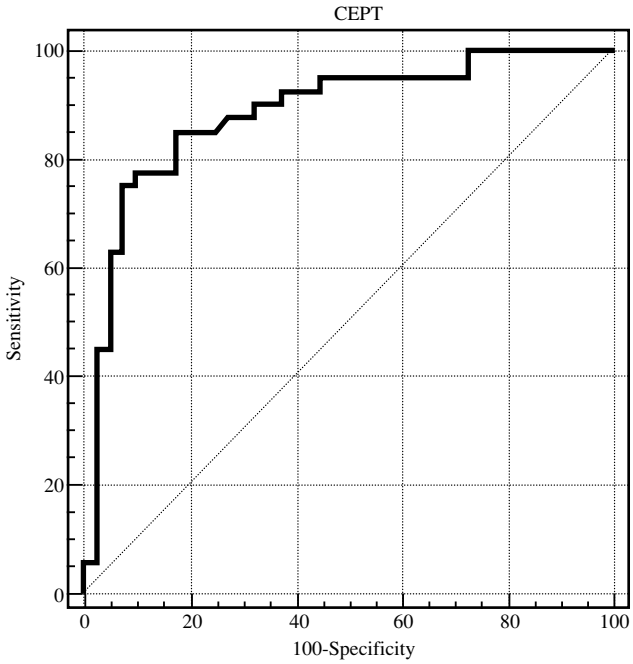


**Fig. 2.** Receiver operator curve for CETP activity. Area under the curve was found to be 0.885; a finding to indicate that test was "very good" for determination of significance.

as the other patient populations.[12] Long-term study of those patients showed significantly higher mortality, not particularly attributable to well-known risk factors as dyslipemia, smoking, hypertension.[13,14] In time, with the advance of surgical and myocardial preservation techniques as well as the development of various drugs that are effective on left ventricular remodelling and platelet activity, short- and long-term survival of these patients may have been prolonged; however, up to one third of vein grafts is subject to atherosclerotic occlusion/stenosis in 10 years.[15-17] In years, many factors including high levels of homocysteine and low density lipoproteins have been accused of both primary coronary artery and the graft atherosclerosis.[18-20]

Being discovered somehow accidentally in Japanese families whose members show a significant tendency to have high HDL levels and be spared from atherosclerosis, CETP has been the focus of many researchers.[4-6,20-22] Kuivenhoven et al and others emphasized the importance of this protein and its genetical variants on the angiographic evolution of coronary artery atherosclerosis.[5,23,24] Authors realize that the present study may be the first to assess the importance of CETP among surgical patients so that we may elaborate more on the fate of our grafts.

It is not surprising that group 1 patients presented a higher preoperative MI rate since they were subjected to longer periods of coronary artery disease and experienced highs and lows of CABG. It is known that the graft disease consists of fragile lesions with tendency to rupture and thromboembolism. Serum lipid concentrations of the patients in group 3 is significantly lower than the serum lipid levels in group 1, but similar to those in group 2. Patient medical history of high cholesterol levels (45%, 10% and 0% in groups 1-3, respectively) along with the serum lipid profiles are coherent with CETP profile of the patients in all four groups. At CKMB0 and CKMB3, CKMB activities were found to be similar in all four groups; however, group 1 patients demonstrated a significant increase in CK-MB1 and CK-MB2, a finding attributable to more tissue resection and higher risk of myocardial ischemia in this group of patients. The use of inotropic agents and perioperative MI rate were higher in group 1, too. Not surprisingly, group 3 patients were found to have high CKMB activities due to resection of cardiac tissues. The Society of Thoracic Surgeons data reported a 6.95% mortality rate for reoperative CABG,[25] it is noteworthy that the only mortality and 2 of 3 cases with perioperative MI were observed in group 1, which was considered to be due to fragility of atherosclerotic grafts. As expected, the preoperative risk scores were significantly higher in this group, too.

High activities of CETP in group 1 in comparison to group 2 and 3 may imply the benefit of screening for CETP activity in younger CABG candidates. Surgeons operating younger patients with particularly higher CETP activities may be encouraged to use grafts with longer patency rates. This argument may be supported by the finding that CETP activities in group 1 patients were similar and higher than in groups 2 and 3. The significance of these findings was further augmented by the ROC analysis. Area under the curve was found as 0.885, signifying a good quality of testing. The cut-off level of 9.34 for CETP activity, where sensitivity and specificity is maximal, is close to our upper limit of 10, which is coherent with the large AUC. This limit of 9.34 may be an indicator of accelerated atherogenesis, depicted in this study as saphenous vein graft occlusion or severe coronary artery disease necessitating surgery before the age of 40. Larger cohorts are required to assess CETP's impact on graft occlusion and reoperation rates. Heterogenous patient cohorts and the use of different CETP analysis kits in various studies may hinder conclusive results.

The present study poses some limitations as it includes limited number of patients and it is not a randomized study. Patients in control groups were, however, randomly chosen in a double-blind fashion from the general operation pools of the same surgeons that operated the study groups so that the potential for surgeon/investigator bias is partly eliminated. Analysis of CETP activity yielded a cut-off level of 9.34 for increased atherogenesis. These findings may suggest the benefit of screening younger patients undergoing CABG for CETP activity and the use of "athero-resistant" grafts (e.g. arterial grafts) in particularly those with high CETP activity.

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