Cholesteryl ester transfer protein and coronary artery surgery in young patients

Genç hastalarda kolesterol ester proteini ve koroner arter baypas cerrahisi

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In modern cardiac surgery, the majority of a cardiac surgeon's daily 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 (coronary artery disease at age younger than 40 years) poses 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 (low density lipoprotein-LDL, chylomicrons), have been studied extensively for a causative or therapeutic relationship (1-3).

The CABG at an early age has been emphasized to be a significant risk factor for a future re-operation (4). Studies have shown 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 (4,5).

In this preliminary study, we aimed to compare the patients undergoing primary CABG at an age younger than 40 years (Group 1, n=20) with older CABG patients (Group 2, n=20) and with those with documented normal coronary anatomy, undergoing isolated valvular procedures (Group 3, n=20) to determine the importance of CETP.

All patients and controls were randomly chosen from the hospital operation schedule charts between June 2003 and November 2004 upon local ethics committee approval. Group 1 and 2 patients underwent standard coronary artery bypass surgery with cardiopulmonary bypass (CPB) with aortic clamping, and Group 3 patients underwent isolated valvular procedures with CPB and aortic clamping. Pre-, peri- and postoperative data were recorded prospectively for each patient. Changes in myocardial creatine kinase (CKMB) in peri-operative course of all patients were recorded: CKMB0 - at postoperative 30th minute, CKMB1 - at postoperative 24th hour, CKMB2 - at postoperative 48th hour and CKMB3 - on postoperative 7th day. Mortality was noted as in-hospital mortality; peri-operative myocardial infarction was diagnosed in accordance with ACC/AHA guidelines (6). All serum samples taken preoperatively for CETP analysis after a 12-hour fasting period and were stored at -20°C until analyzed with scintillation proximity assay (CETP [3H] SPA, human, TRKQ7005-25μCi kit, Amersham Biosciences, NJ, USA) which is based on the transfer of [3H] cholesteryl esters from HDL to biotinylated low density lipoproteins and its measurement was done with a standardized gamma counter (Isocomb I Multiwell Gamma Counter, GMI Instrumentation Inc., MN, USA). Based on this 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 procedures were performed with SPSS 10.0 (SPSS Inc, Chicago, Il) and MedCalc 7.0.0.4 (MedCalc Statistical Software for Biomedical Research, 2002 Frank Schoonjans, Mariakerke, Belgium) using analysis of variances (ANOVA) and receiver operator curve (ROC) analysis. Table 1 shows preoperative characteristics of the patients. Preoperative history of previous myocardial infarction, hypertension, hyperlipidemia, use of lipid-lowering drugs were found significantly higher in group 1 ($p<0.05$). Preoperative total cholesterol and triglycerides levels were significantly higher in groups 1 and 2 as compared with group3 ($p<0.05$). Patients groups did not differ by Cleveland-Higgins scores ($p>0.05$). Patients in group 1 had significantly higher CETP values than patients in groups 2 and 3 (12.58±4.34, 5.42±3.59 and 7.08±3.87 U/ml, $p<0.05$). A cut-off level for CETP, where it has the highest specificity and sensitivity, was determined as 9.34 U/ml with 95% CI, a value that would indicate a higher tendency for "progressive atherosclerosis". A further analysis was applied using ROC analysis and the AUC was 0.885 (Fig. 1) indicating that accuracy of the test was high and acceptable (standard error=0.039, 95% CI, 0.794 to 0.945, $p<0.001$) for discriminating between progressive atherosclerosis and the controls. The CKMB levels (IU/L) during the postoperative course of the patients at CKMB0 to CKMB3 were as 21.15±11.53, 56.3±16.64, 36.25±11.96, and

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23.35±8.17 for group 1; 27.9±47.4, 60.95±29.82; 54.95±36.67, 30.6±12.39 for group 2 and 16.8±4.34, 96.1±43.37, 77.7±50.8, 36.9±29.9 for group 3, respectively. More significant increases at CKMB1 and CKMB2 were observed in group 1 as compared with group 2 and 3. When a comparison of CKMB levels between group 1 and 2 was performed, only CKMB3 levels were significantly higher in group 1 (p<0.05). Analysis of all patients for operative charts and peri-operative low cardiac output states yielded similar results for all three groups except that group 1 had shorter CPB times than group 3 (77.2±38.75 min vs. 99.8±29.38 min, p=0.02). No single case of mortality was observed in 60 patients; however, only one patient in group 2 had a peri-operative myocardial infarction. No differences were found between groups in intensive care unit stay and hospital stay durations (p>0.05) (Table 1).

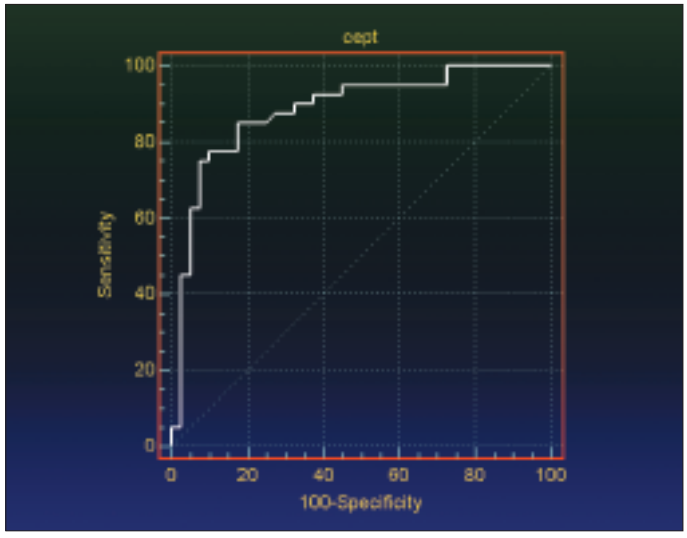

Figure 1. Receiver operator curve for CETP activity. Area under the curve (AUC) values indicates that test accuracy was high and acceptable for determination of significance (AUC=0.88, standard error= 0.039, 95% CI, 0.794 to 0.945, p<0.001)

With more than 500.000 operations every year worldwide, CABG procedures still stand as the heaviest bulk of a cardiac surgeon's practice. According to the results of "the European Coronary Surgery Study Group", CABG procedures have not yielded as good long-term results for younger patients as the other patient populations (7). Long-term study of those patients showed significantly higher mortality, not particularly attributable to well-known risk factors as dyslipidemia, smoking and hypertension (8, 9). With the advance of surgical and medical therapy, 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 (4,5). Vasculitis may be a cause of coronary artery disease in younger patients. Demirkılıç et al. (10) in their review on CABG in very young patients (<30 years) found 9.5% incidence of a history of vasculitis (namely Behçet's disease) in 20 patients; we have not observed any patients with any history of vasculitis.

The CETP has been the focus of many researchers as a possible factor in atherosclerotic process. Kuivenhoven et al. (3) emphasized the importance of this protein and its genetic variants on the angiographic evolution of coronary artery atherosclerosis (3). 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.

High levels of CETP in group 1 in comparison to group 2 and 3 may suggest screening for younger CABG candidates. Surgeons operating younger patients may be encouraged to use grafts with longer patency rates (11). Presence of higher CETP levels in younger patients undergoing CABG suggests need for the screening of CETP activity and the use of "athero-resistant" grafts (arterial grafts) in this category of patients. Significance

Table 1. Preoperative characteristics of patients

	Group 1	Group 2	Group 3	p
Gender (male), n	20	14	12	
Age, years	37.9±2.7	58.4±8.5	48.1±15.1	NS
Preoperative Cleveland-Higgins Score	2.05±2.32	1.71±0.64	1.15±1.04	NS
Smoking, n/%	15/ 75	13/ 65	8/ 40	NS
Hypertension, n/%	15/ 75	10/ 50	3/ 15	<0.05
Hyperlipidemia, n/%	8/ 40	2/10	0/ 0	<0.05
Preoperative total cholesterol, mg/dl	171.30±58.07	174.25±26.20	161.05±49.17	<0.05
Preoperative triglyceride, mg/dl	156.05±95.68	126.45±54.39	90.25±56.91	<0.05
Cholesterol lowering drug use, n/%	4/ 20	1/ 5	0/ 0	<0.05
Preoperative myocardial infarction, n/%	13/ 65	16/ 80	2/ 10	<0.05
Preoperative serum creatinine, mg/dl	0.89±0.12	0.98±0.26	0.78±0.11	NS
Diabetes Mellitus, n/%	4/ 20	6/ 30	1/5	NS
CETP, U/Lt	12.58±4.34	5.42±3.59	7.08±3.87	<0.05
CPB period, minutes	77.2±38.75	94±39.85	99.8±29.38	<0.05
ICU stay, days	1.15±0.37	1.1±0.3	1.50±0.49	NS
Hospital stay, days	7.75±1.61	7.7±0.92	7.7±1.34	NS

CETP- Cholesteryl ester transfer protein; CPB- Cardiopulmonary bypass; ICU- Intensive care unit, NS- nonsignificant

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 (a possible indicator of accelerated atherosclerosis), where sensitivity and specificity is maximal, is close to our upper limit of 10, which is coherent with the large AUC. Heterogeneous patient cohorts and the use of different CETP analysis kits in various studies may hinder conclusive results. This present study poses some limitations as it includes limited number of patients; however its prospective and randomized nature may partly eliminate the potential for surgeon/investigator bias.

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