

Effect of Cardiopulmonary Bypass on Plasma Levels of Lipoprotein (a) in Hypercholesterolemic Patients

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SUMMARY

Increments of lipoprotein (a) (Lp (a)) concentration during cardiopulmonary bypass (CPB) have not been justified in the literature yet. We have investigated whether Lp (a) levels remain constant or increase during CPB and if high plasma levels of low density lipoprotein (LDL; containing apolipoprotein (apo) B) in hypercholesterolemic patients affect the assembly of Lp (a) (containing apoB: Apo (a)).

In this study, the change in plasma lipid and lipoprotein levels of 40 patients with hypercholesterolemia and 40 patients who have normal cholesterol values were determined and compared during CPB, and in the postoperative early stage. In our study, lipid and lipoproteins, except Lp (a), showed a falling trend and paradoxically, Lp (a) statistically showed a significant rising trend, like the acute phase reactant in two groups ($p=0.011$ for LDL, $p=0.016$ for high density lipoprotein (HDL) and $p<0.001$ for the others, in 80 patients). Concentrations of Lp (a) in plasma increased more sharply in the hypercholesterolemic group than the normocholesterolemic group during CPB. This difference was significant at the 60th minute of cardiopulmonary bypass with a nonparametric test ($p<0.05$ Mann-Whitney U test). High density lipoprotein values showed more decline in the hypercholesterolemic group patients than in the normocholesterolemic group patients ($p<0.05$). In conclusion, lipoprotein (a) levels increased more pronounced in patients with hypercholesterolemia during CPB. On the other hand, high LDL levels in hypercholesterolemic patients accelerated Lp (a) formation in the acute phase. (Jpn Heart J 2001; 42: 563-574)

Key words: Lipoprotein (a) (Lp(a)), Low density lipoprotein (LDL), Cardiopulmonary bypass (CPB), Acute phase reactant, Hypercholesterolemia, Lipids and lipoproteins, Coronary artery bypass grafting (CABG)

PREVIOUS studies have shown a decrease in plasma concentrations of total cholesterol, HDL and LDL-cholesterol following major surgical operations without using extracorporeal circulation and hemodilution.¹⁻⁴ Decreases in apoAI and apoB have also been reported with concomitant increases in acute phase proteins such as oromucoid, α -1 antitrypsin, ceruloplasmin and C-reactive protein, following surgical procedures.^{2,5} On the other hand, in the study of Maeda, *et al* Lp

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(a) levels showed a significant rise similar to the acute phase proteins reaching maximum concentrations almost 3-4 days after major surgical procedures and then returning to basal levels within one month.⁴⁾ Finlayson and coworkers investigating the changes in plasma proteins during CPB for coronary artery bypass grafting (CABG) demonstrated a fall in plasma lipoprotein levels very similar to that of proteins.¹⁾ Sgoutas, *et al* examined the changes in lipids, lipoproteins and apolipoproteins in greater detail in patients within minutes of going on bypass and compared them with the changes in the immediate postoperative period.²⁾ Their results showed that at the onset of CPB significant falls in total cholesterol, triglyceride, HDL, LDL, and very low density lipoprotein (VLDL) (except Lp (a)) occurred. They determined that dilution alone did not adequately explain the persistent low levels during CPB. Indeed, values corrected for dilution suggested a progressive reduction in lipoprotein and apolipoprotein concentration paralleling the reduction of albumin²⁾ and other serum proteins denatured due to exposure to a foreign surface within the heart-lung machines. It was quite possible that lipoproteins including Lp (a) were similarly changed due to denaturation.²⁾ In the immediate period following CPB all lipid, lipoprotein and apolipoprotein concentrations except Lp (a) remained significantly lower than the preoperative concentrations, in close agreement with results previously reported for major surgery,^{2,6)} infections,^{2,7)} burn injuries,^{2,8)} and myocardial infarction.^{2,9)} In that respect, CPB did not differ from major surgery and the effect of extracorporeal circulation and hemodilution on lipid metabolism several hours after the operation was minimal. The striking result of their study was the rise in Lp (a) levels at the initial period and throughout CPB.²⁾ Some earlier reports have already shown parallel concentration changes between Lp (a) and acute phase protein such as oromucoid, α -1 antitrypsin, ceruloplasmin and C-reactive protein during the course of the acute phase response in postoperative periods. Sgoutas, *et al* compared the changes in plasma concentrations between Lp (a) and C-reactive protein at the initial period of CPB and found that in most cases, Lp (a) was the best single protein for demonstrating the presence or absence of an acute phase response.²⁾ This effect of CPB on Lp (a) levels could not have been shown statistically. Contrary to this, some recent studies reported that Lp (a) levels were not affected by CPB and remained constant.¹⁰⁻¹²⁾ Previous studies have been carried out in normocholesterolemic, nondiabetic and euthyroid patients.^{2,10-12)}

Increased Lp (a) levels are associated with an increased incidence of disease based on atherosclerosis, namely ischemic heart disease. Another effect of Lp (a) is its competition with plasminogen resulting in decreases in fibrinolysis and thrombogenic activity. Lp (a) is a plasma protein, consisting of apo (a), linked by a covalent disulfide bond with the apoB100 particle. Recent studies have demonstrated that apoB100 binds noncovalently to apo (a) too: Increasing evidence sug-

gests that the assembly of Lp (a) proceeds in two steps. In the first step, non-covalent interactions between apo (a) and apoB of LDL form a dissociable apo (a): LDL complex. In the second step, a covalent disulfide linkage forms the stable Lp(a) particle.¹³⁻¹⁵⁾

Forty hypercholesterolemic patients who had high LDL levels according to NCEP criteria took part as study group. Their alterations in concentrations of plasma lipids and lipoproteins were compared with 40 normocholesterolemic patients. Our aim was to show that Lp (a) was an acute phase reactant during CPB in large numbers of patients (80 patients) and high levels of LDL accelerated Lp (a) formation in hypercholesterolemic patients.

MATERIALS AND METHODS

Eighty patients undergoing aortocoronary bypass surgery were included in this study. Groups were established according to preoperative cholesterol levels. There are two groups of patients, one (40 patients; group A) with normal plasma total cholesterol levels (below 200 mg/dl) and the other (40 patients; group B) with high plasma total cholesterol levels (above 200 mg/dl which is the cut off value for normal total cholesterol suggested by NCEP). These groups statistically have different total cholesterol levels. None of them received lipid lowering medications. There was no difference between the two groups with respect to age or body mass index (BMI). Eighty patients who did not have hypertension, diabetes mellitus, the other endocrine diseases and had normal renal function were included. All of the patients were on CPB for at least 60 minutes. In these two groups of patients, total cholesterol, triglycerides, LDL, HDL, VLDL, and Lp (a) levels in plasma were measured after the induction phase of anesthesia, at the 20, 40, and 60th minutes, and on the postoperative first day, and plasma levels of total cholesterol, triglycerides, LDL, VLDL and lipoprotein (a) were measured and the levels compared between the two groups.

Samples drawn during CPB were diluted to the expected degree by the priming solution. The degree of hemadilution was estimated by the reduction in hematocrit in the absence of visible hemolysis. In the present study we evaluated changes in plasma lipids and lipoproteins during CPB by comparing values before and after CPB as corrected for changes in hemodilution for both groups. Hematocrit was measured by standard procedures (Coulter Counter, STKR, Hialeath, FL).

Total cholesterol and total triglycerides were determined enzymatically. Enzymatic colorimetric test was used for triglycerides and total cholesterol (BM/Hitachi 747/737, Boehringer Mannheim GmbH, Mannheim, Germany and Roche/Hitachi 747/737, Roche Diagnostics GmbH, D-68298, Mannheim, Ger-

many, respectively).

HDL-cholesterol was determined enzymatically with the same method for total cholesterol after precipitation of LDL and VLDL with phosphotungstic acid (Roche/Hitachi 747/737, Roche Diagnostics GmbH). Lipoprotein (a) was measured with a turbidimetric method (Lp (a) reagent: P/N 465360, Beckman ARRAY® Analyzers and Lipoprotein (a) Calibrator (LPA Cal), Beckman Instruments, Inc. Galway, Ireland).

The anesthetic contained midazolam hypnomidate and the muscle relaxant vecuronium. Propofol was not used because it depresses steroidogenesis. CPB employed a hollow fiber membrane oxygenator (Polystan, Bentley, Baxter) primed with a buffered electrolyte solution (2000 ml Ringer's lactate). Hypothermia was induced to 26-28°C.

Blood samples were collected in EDTA tubes for hematological examinations and for lipid and lipoprotein. Blood samples were drawn through a radial artery catheter. Basal samples were drawn prior to the beginning of CABG and after the induction of anesthesia. Five samples were drawn in a sequence at the 20, 40 and 60th minutes after the start of CPB, and one sample on the first postoperative day.

The statistical significance of the results was evaluated with a repeated measures analysis of variance. Statistical significances in the changes in values in time are shown with the Friedman test, except HDL values. Hoselings test was used for HDL values. Differences between the two groups were analyzed with Hoselings and Mann-Whitney U tests (nonparametric tests). A *p* value <0.05 was accepted as statistically significant.

The statistical significance of the change in values in time intervals was tested with the Student *t* test for HDL, for the others the Wilcoxon test was used and a *p* value <0.005 was considered as statistically significant (Bonferroni correction was performed).

RESULTS

There were no surgical complications, including postoperative infections, in these patients and there was no clinically evident hemolysis. The lipid and lipoprotein values for the preoperative, CPB (corrected for hemodilution) and postoperative periods are shown in Table I for group A patients and Table II for group B patients. No differences were observed between the two groups (*p*>0.05) (Student *t* test) for the parameters of BMI, age, aortic clamping time, CPB period and numbers of grafts.

Significant decreases were observed in total cholesterol, triglycerides, LDL, HDL, and VLDL values. Tables I and II show the variation in total cholesterol,

Table I (Group A). Change in Lipids and Lipoproteins over Time for the Normocholesterolemic Patients

Concentrations of Plasma Lipids and Lipoproteins (Mean±SD)						
Time	T CHOL mg/dl	TG mg/dl	LDL mg/dl	HDL mg/dl	VLDL mg/dl	Lp(a) mg/dl
After the Induction Phase (0 th min.)	168±9	134±41	82±14	31±4	28±7	45±26
20 th minute on CPB	150±15	81±27	85±13	30±3	18±5	48±29
40 th minute on CPB	150±7	86±25	90±14	31±3	19±6	72±34
60 th minute on CPB	146±13	81±28	88±16	31±3	18±5	65±23
Postoperative first day	143±12	104±31	65±8	31±4	23±6	73±24

Table II (Group B). Change in Lipids and Lipoproteins Time for the Hypercholesterolemic Patients*

Concentrations of Plasma Lipids and Lipoproteins (Mean±SD)						
Time	T CHOL mg/dl	TG mg/dl	LDL mg/dl	HDL mg/dl	VLDL mg/dl	Lp(a) mg/dl
After the Induction Phase (0 th min.)	280±55	173±25	171±49	33±4	36±5	48±23
20 th minute on CPB	195±31	118±25	157±48	25±3	22±5	68±29
40 th minute on CPB	196±32	103±21	153±37	32±6	19±4	79±27
60 th minute on CPB	213±35	102±21	152±39	28±4	21±4	95±23
Postoperative first day	187±22	140±20	122±14	30±4	26±3	88±24

CPB=cardiopulmonary bypass; HDL=high density lipoprotein; Lp (a)=lipoprotein (a); LDL=low density lipoprotein; T CHOL=total cholesterol; TG=triglyceride; VLDL=very low density lipoprotein.

*Tables I and II show the variations in T CHOL, LDL, HDL, VLDL, Lp (a) levels over time as Mean±SD. The increase in the level of Lp (a) over time was statistically significant (in 80 patients: $p<0.001$). Decreases in the levels of T CHOL, TG, LDL, HDL, and VLDL were statistically significant, in 80 patients: $p<0.05$ for LDL and HDL, $p<0.001$ for the other). The differences between two groups were not statistically significant, except for T CHOL, HDL, and at the 60th minute for Lp (a).

triglycerides, LDL, HDL, VLDL, and Lp (a) levels over time and the differences in these values for the two groups (A, B) were assessed by analysis of variance. The results showed the increase in the level of Lp (a) and the decreases in the levels of total cholesterol, triglycerides, LDL, HDL, and VLDL in time were statistically significant ($p=0.011$ for LDL, $p=0.016$ for HDL and $p<0.001$ for the others) in the 80 patients. In the hypercholesterolemic group, the decreases in the HDL and total cholesterol levels occurred earlier than that of the normocholesterolemic group during CPB and the first postoperative day. The differences in the

total cholesterol and HDL values between two groups were statistically significant in all periods ($p=0.001$ and $p=0.037$, respectively).

Lp (a) showed a significant rise during the CPB period, peaking at the 40th minute for Group A and the 60th minute for Group B, after the beginning of CPB. The increase in the mean value of Lp (a) was higher in group B than in group A and this difference was not significant when tested with parametric tests. It was significant using a nonparametric test (Mann-Whitney U test, $p<0.05$) only at the 60th minute. For the group B patients the increase in Lp (a) level in plasma for all of the time intervals was statistically significant ($p<0.005$), but for the group A, this occurred only for two intervals (0-40th minute, 0-1st postoperative day) ($p<0,005$). Due to the large variation in plasma levels (see SD in tables), these values are presented in the figures as a percentage of the basal plasma level. The changes in the levels of cholesterol, triglycerides, LDL, HDL, VLDL and Lp (a) for both groups for all of the intervals are presented in Figures 1 to 6, successively.

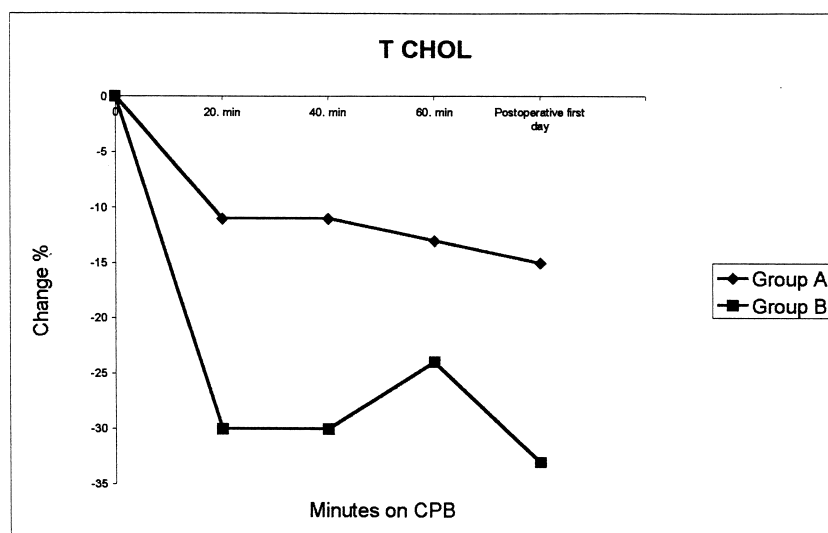


Figure 1. Percent change from basal levels of cholesterol on CPB in the two groups corrected for hemodilution. (the decrease was significant in 80 patients: $p<0.001$). The difference between the two groups was statistically significant ($p=0.001$).

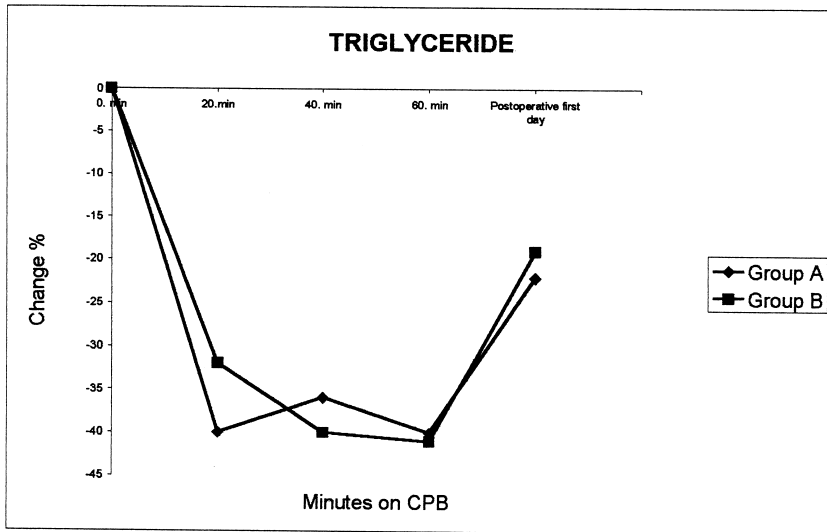


Figure 2. Percent change from basal levels of triglyceride on CPB in the two groups corrected for hemodilution (the decrease was significant in 80 patients; $p < 0.001$). The difference between the groups was not statistically significant ($p > 0.05$).

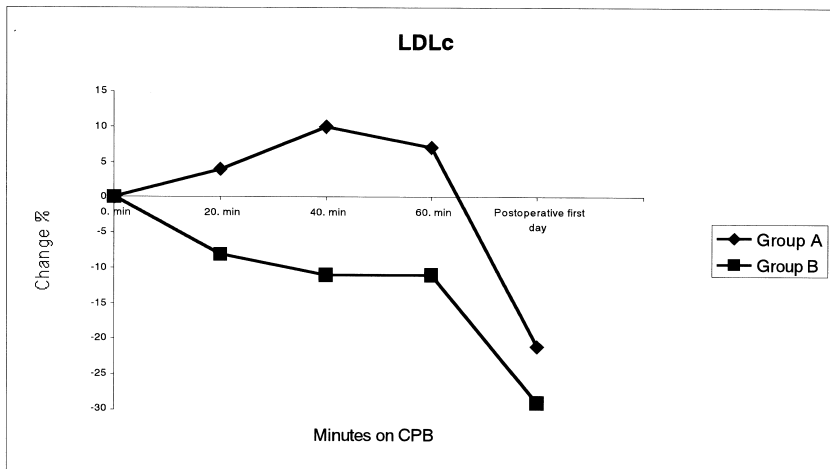


Figure 3. Percent change from basal levels of LDL on CPB in the two groups corrected for hemodilution (the decrease was significant in 80 patients; $p = 0.011$). The difference between the groups was not statistically significant ($p > 0.05$).

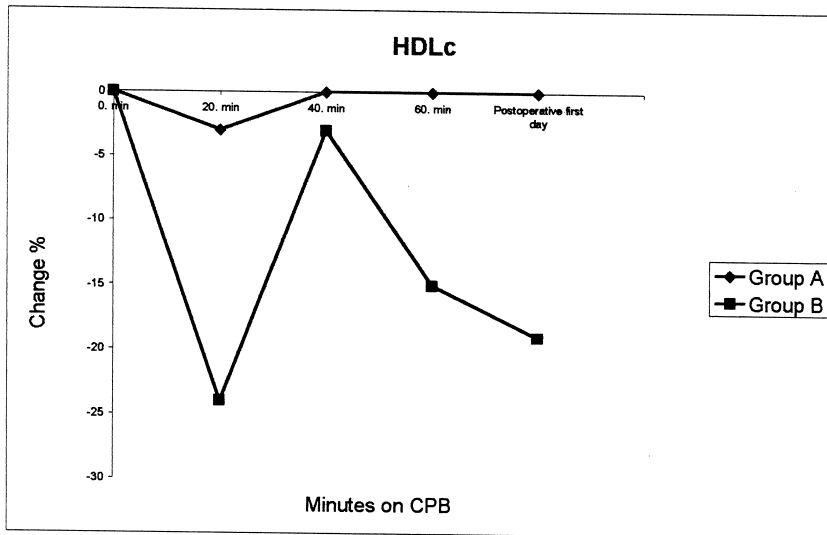


Figure 4. Percent change from the basal levels of HDL on CPB in the two groups corrected for hemodilution (the decrease was significant in 80 patients: $p=0.016$). The difference between the groups was statistically significant ($p=0.037$).

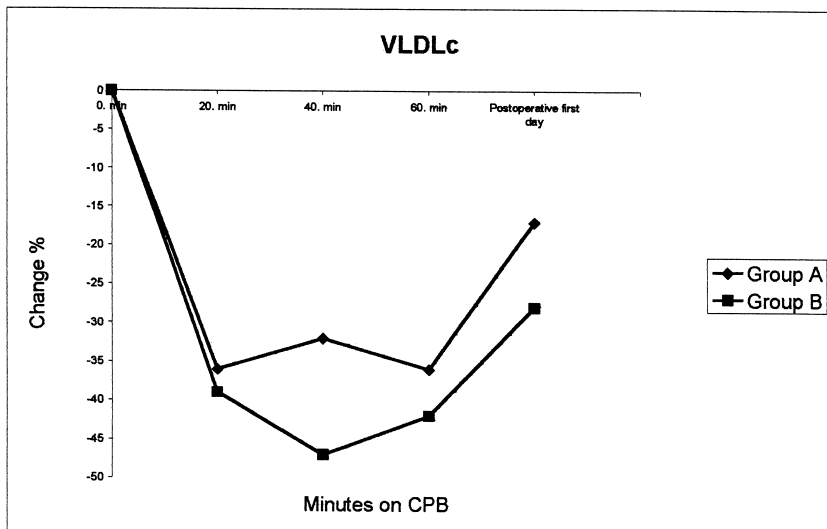


Figure 5. Percent change from the basal levels of VLDL on CPB in the two groups corrected for hemodilution (the decrease was significant in 80 patients: $p<0.001$). The difference between the groups was not statistically significant ($p>0.05$).

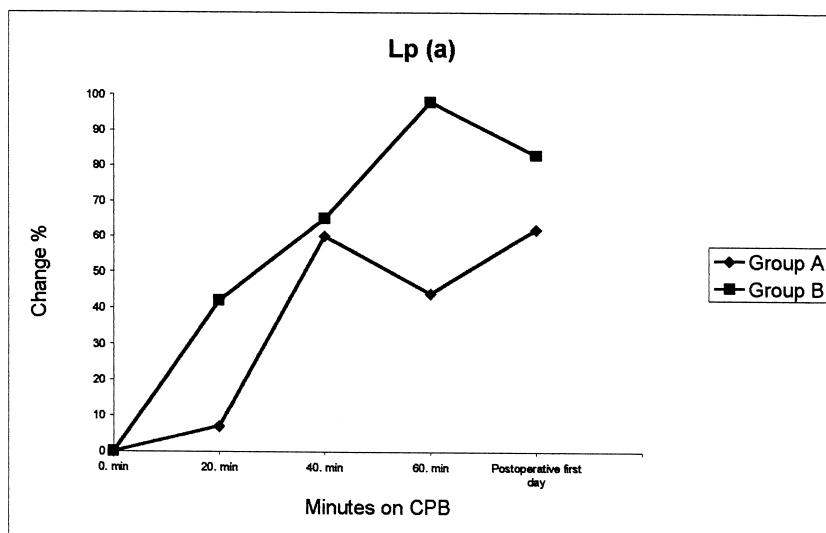


Figure 6. Percent change from the basal levels of Lp (a) on CPB in the two groups corrected for hemodilution (the increase was significant in 80 patients: $p < 0.001$). The difference between the groups was statistically significant only at the 60th minute ($p < 0.05$). In the hypercholesterolemic group a more rapid and significant increase in Lp (a) level (nearly 100% at 60th minute) was observed. Cholesterol: Total cholesterol, CPB: Cardiopulmonary bypass, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein, Lp (a): Lipoprotein (a).

DISCUSSION

In this study, a rapid secretion of Lp (a) was observed in plasma during CPB and this may be related to its thrombogenic properties.²⁾ An alternative explanation to the rapid secretion is the possibility of a sharp decrease in the degradation of Lp (a). It has already been documented²⁾ that although one of the protein components of Lp (a) is apoB100, the crucial structural component of VLDL and LDL, the second component is apo (a), a glycoprotein unique to Lp (a) that has the same repeated amino acid domain as plasminogen. Areas of kringle-4 in plasminogen are homologues with the areas of amino acids.¹⁷⁾ With this kringle, both plasminogen and Lp (a) bind to a fibrin in a competitive way and when Lp (a) is present in excessive amounts in blood, it inhibits enzymes like plasmin and tissue plasminogen activator of lysing thrombi. The effect of Lp (a) may be important in early graft thrombosis and restenosis. Increases in the plasma concentrations of thrombogenic substances⁹⁾ (which may include cardiolipins) during CPB have been reported previously and the underlying mechanisms are presently under investigation.²⁾ The previous studies have all included normocholesterolemic patients.

Our study compared the changes in the concentrations of plasma lipids and lipoproteins in normocholesterolemic and hypercholesterolemic patients during CPB and after CPB in CABG operations and showed that in the immediate period following CPB the levels of lipids and lipoproteins, except Lp (a), progressively decreased. The lipid and lipoprotein values, except Lp (a), remained significantly lower than the preoperative values in the early postoperative period, in close agreement with the results previously reported for major surgery and other conditions.^{2,7-9)} Paradoxically, Lp (a) levels increased at onset, doubled (or 60% increase) during CPB and remained elevated postoperatively in both of these groups. At the onset and during CPB a rapid and significant rise in Lp (a) was found to be statistically significant for the two groups ($p < 0.001$ in 80 patients). Moliterno, *et al* in contrast to our findings, found the Lp (a) concentration did not increase during CPB phase.¹²⁾ In their study, a hollow-fiber membrane oxygenator with a minimum host inflammatory response and plasma expanders with host defence reducing capability were used, and also a limited number of patients without lipid disorder were observed. These methodological differences may explain the difference between the results of the two studies. In the hypercholesterolemic group, it was observed that the decrease in the total cholesterol and HDL levels was statistically more significant than the other group ($p < 0.05$). On the other hand, the further decrease in the total cholesterol level of the hypercholesterolemic group during the CPB phase was not important, because the cholesterol level in the hypercholesterolemic group was higher on the absolute scale than the other group. However, a significant fall in HDL in the normocholesterolemic group may be important for the progress of the disease when we consider HDL to be an antiatherogenic lipoprotein. This significant decrease in HDL during reperfusion may increase the effect of Lp (a) and LDL on saphenous grafts and native coronaries. Some studies have shown that there is a relation between coronary artery disease and HDL. In particular, the apoAI component of HDL in coronary artery patients is low.^{18,19)}

Although the basal levels of Lp (a) in both groups were similar, the increase in Lp (a) plasma levels in group B patients was pronounced (nearly 100% increase) and then remained more stable than the mean values of Lp (a) plasma in group A patients during the CPB phase. Fluctuations in the mean values of Lp (a) plasma levels were observed in group A patients. In the postoperative period, the level of Lp (a) in group B patients was higher than the group A patients. This is important because the high Lp (a) levels increase the risk of atherosclerosis six times more in hypercholesterolemic patients. Some data support the notion that Lp (a) (apo (a)) and LDL (apo B) play significant roles in the atherosclerosis of saphenous veins.²⁰⁾ There is a correlation between the plasma and tissue (atherosclerotic vein grafts) concentrations of apo (a) and apoB in redoCABG patients.²¹⁾

This correlation is more pronounced with Lp (a) than with LDL because this lipoprotein contains apo (a) and apoB. ApoB is present with apo (a), which is localized at the atherosclerotic saphenous graft areas. ApoB is bonded to apo (a) with disulfide bonds. Under normal conditions apo (a) and apoB are not present at saphenous grafts.²¹⁾ In open heart surgery, during ischemia and reperfusion injury increasing permeability of endothelium causes the first influx of LDL and Lp (a) to the subendothelium.²²⁻²⁴⁾ However, this has not been clarified sufficiently. The cause of early restenosis and occlusion after CABG operation may be attributed to the thrombogenic and acute phase reactant property of Lp (a). The accumulation of Lp (a) in the subendothelium and the thrombogenic effect of hypertriglyceridemia together may decrease the graft patency. A recent study has demonstrated that factor XIIIa-mediated cross-linking of Lp (a) to fibrin effectively increases the local concentration of Lp (a) within fibrin clots.²⁵⁾

Basal values of LDL in the hypercholesterolemic group were higher than the normocholesterolemic group (more than twice, $p < 0.05$). Although the basal levels of Lp (a) in both groups were similar ($p > 0.05$), the Lp (a) value in the hypercholesterolemic group increased more significantly than the normocholesterolemic group. This may be attributed to the high plasma level of LDL, increasing Lp (a) formation with the high level of apo (a) binding. Also there is a competition between apoB and free apo (a) with LDL binding. LDL binds to both Lp (a) and apo (a) substrates with similar affinity.¹⁵⁾ These initial forms with non-covalent interactions transform to stable Lp (a) forms with covalent interactions between apoB100 and apo (a).^{14,15)}

LDL apheresis during CPB is an effective and reliable method with which to decrease the level of LDL and Lp (a) in plasma before reperfusion. This method can lower the influx of Lp (a) and LDL to the vessel wall.²²⁾

Conclusion: An increased passage of Lp (a) to the subendothelium as a result of increased endothelial permeability during ischemic and reperfusion period is speculated. Also, the thrombotic effect of Lp (a) may be important for early graft occlusion and restenosis. Therefore pre or intraoperative treatment modalities such as LDL apheresis may be of considerable value in hypercholesterolemic patients to prevent excessive Lp (a) formation. Further investigations are necessary and studies with different designs should be conducted.

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