Effects of Intravenous Apolipoprotein A-I/Phosphatidylcholine Discs on LCAT, PLTP, and CETP in Plasma and Peripheral Lymph in Humans

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Objective—We have previously shown that intravenous apolipoprotein A-I/phosphatidylcholine (apoA-I/PC) discs increase plasma pre-β HDL concentration and stimulate reverse cholesterol transport (RCT) in humans. We have now investigated the associated changes in the following 3 HDL components that play key roles in RCT: lecithin:cholesterol acyltransferase (LCAT), cholesteryl ester transfer protein (CETP), and phospholipid transfer protein (PLTP).

Methods and Results—apoA-I/PC discs (40 mg/kg over 4 hours) were infused into 8 healthy men. Samples of blood and prenodal peripheral lymph were collected for 24 to 48 hours. At 12 hours, plasma LCAT concentration had increased by 0.40±0.90 mg/L (+7.8%; mean±SD; P<0.05), plasma cholesterol esterification rate by 29.0±9.0 nmol/mL per h (+69.5%; P<0.01), plasma CETP concentration by 0.5±0.2 mg/L (+29.7%; P<0.01), and plasma PLTP activity by 1.45±0.67 μmol/mL per h (+23.9%; P<0.01). In contrast, plasma PLTP concentration had decreased by 4.4±2.7 mg/L (−44.8%; P<0.01). The changes in PLTP were accompanied by alterations in the relative proportions of large lipoproteins containing inactive PLTP and small particles containing PLTP of high specific activity. No changes were detected in peripheral lymph.

Conclusions—Nascent HDL secretion may induce changes in PLTP, LCAT, and CETP that promote RCT by catalyzing pre-β HDL production, cholesterol esterification in HDLs, and cholesteryl ester transfer from HDLs to other lipoproteins.

Key Words: apolipoprotein A-I ▪ phospholipid transfer protein ▪ lecithin ▪ cholesterol acyltransferase ▪ cholesteryl ester transfer protein

The inverse relationship between plasma HDL cholesterol concentration and incidence of coronary heart disease (CHD) is well documented.1,2 Although the mechanism of the antiatherogenic effect of HDLs is unclear, their role in reverse cholesterol transport (RCT) seems to explain at least part of the effect.1 The HDLs are composed of numerous subpopulations that undergo continuous remoulding by enzymes and lipid transfer proteins that are associated with the particles. These include lecithin:cholesterol acyltransferase (LCAT), cholesteryl ester transfer protein (CETP), and phospholipid transfer protein (PLTP).3–6

During RCT, small lipid-poor apolipoprotein (apo) A-I containing pre-β HDLs in tissue fluid take up free cholesterol (FC) from peripheral cells. The FC is esterified in plasma by LCAT, and the resultant cholesteryl esters (CEs) enter the cores of spheroidal αHDLs.7 In some species (including humans), some CEs are transferred from αHDLs to apoB-containing lipoproteins by CETP and are then taken up by hepatocytes as a consequence of receptor-mediated catabolism of remnant and LDLs. Other CEs in αHDLs are transferred directly to hepatocytes via SR-BI receptors.8

Phospholipid transfer protein is thought to play an important role in RCT by catalyzing the transfer of phospholipids to αHDLs from triglyceride-rich lipoproteins and by inducing fusion of αHDLs, generating pre-β HDLs in the process.9–11 Increased potential for pre-β HDL production has been described in mice with stable or transient adenovirus-mediated expression of human PLTP.12,13

The extent to which the actions of PLTP, LCAT, and CETP might be coordinately regulated to facilitate RCT is not known. Nor is there information on the degree to which they are influenced by variations in nascent HDL secretion rate.

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In previous studies we have used intravenous infusion of apoA-I/phosphatidylcholine (PC) discs to mimic a rise in nascent HDL secretion rate in humans. We have shown that the infusion induced rapid increases in plasma pre-β apoA-I and HDL cholesterol concentrations, followed by increases in HDL CE and apoA-I in large αHDLs. We subsequently showed that the infusion raised pre-β HDL concentration in peripheral tissue fluid and enhanced cholesterol flux through the RCT pathway, leading to increased bile acid synthesis. We have now tested the hypothesis that the infusion also induces a coordinated response of LCAT, CETP, and PLTP that facilitates the increase in RCT.

### Methods

#### Subjects

Eight healthy males aged 22 to 36 years were studied (Table). None was taking a special diet or medication. Alcohol was avoided for at least 48 hours before and during the study. The study was approved by the local ethics committee, and all subjects gave informed consent.

#### Clinical Procedures

The study was conducted in a metabolic ward with the subjects consuming a solid isocaloric low-fat diet. Each subject was given a polyethylene cannula inserted into a vessel in the lower leg, consuming a solid isocaloric low-fat diet. The study was conducted in a metabolic ward with the subjects consuming a solid isocaloric low-fat diet.

#### Laboratory Procedures

All assays were performed in duplicate. Total cholesterol (TC), triglyceride (TG), and phospholipids (PLs) were quantified as previously described. apoA-I was quantified by radioimmunoassay or rocket immunoelectrophoresis. Plasma cholesterol esterification rate (CER) was assessed by incubation of whole plasma at 37°C. LCAT concentration was measured by a sandwich ELISA (Daiichi Pure Chemicals). Concentrations of CETP and PLTP were measured by sandwich ELISAs. Plasma CETP concentration by our assay is strongly correlated with CETP activity. Plasma PLTP activity was assayed with a PC liposome-HDL₃ system, in which PC transfer rate is not influenced by CETP. The interassay coefficients of variation (n=8) were 5.1% for LCAT concentration, 5.9% for CETP concentration, 7.1% for PLTP activity, and 6.9% for PLTP concentration.

#### Size Exclusion Chromatography

Plasma samples (1.0 mL) were applied to a fast protein liquid chromatography system consisting of 2 Superose 6HR 10/30 columns (Amersham Pharmacia Biotech) equilibrated with TBS, pH 7.4. Flow rate was 0.25 mL/min; 0.5-mL fractions were collected.

#### SDS-PAGE and Nondenaturing Polyacrylamide Gradient Gel Electrophoresis

SDS-PAGE was performed in a 5% to 20% gradient polyacrylamide gel (ATTO). The samples (0.5 to 1.0 μL) were treated with 125 mmol/L Tris-HCl (pH 6.8), 10% (wt/vol) glycerol, 2.3% (wt/vol) SDS, and 0.01% bromphenol blue with 5% (vol/vol) 2-mercaptoethanol. Native polyacrylamide gradient gel electrophoresis (PAGGE) was performed in a 5% to 20% gradient polyacrylamide gel (ATTO). The samples (0.5 to 1.0 μL) were treated with 40% (wt/vol) sucrose and 0.05% bromphenol blue. Electrophoresis and immunoblotting were performed as previously described.

#### Electron Microscopy of Lipoproteins

Blood was collected at 0, 2, 4, and 8 hours into iodoacetate (final concentration, 5.0 mmol/L) in addition to EDTA-Na₂ to inhibit LCAT. The total lipoprotein fraction was isolated by preparative ultracentrifugation at d=1.21 g/mL and separated by Superose 6 size-exclusion chromatography into 4 fractions corresponding to medium-sized plus small HDLs, large HDLs plus small LDLs, medium-sized LDLs, and particles larger than LDLs, as previously described. The fractions were concentrated by centrifugal ultrafiltration and shipped to San Francisco on ice, where aliquots were examined by electron microscopy after negative staining with potassium phosphotungstate.

#### Statistical Analyses

Changes were analyzed by Mann-Whitney U test, repeated-measures ANOVA, and Fisher’s protected least-squares difference. P<0.05 was regarded as statistically significant.

### Results

The subjects experienced no symptoms, developed no rashes, and showed no significant changes in pulse rate, blood

### Table: Plasma Lipids, Enzymes, and Lipid Transfer Proteins Before apoA-I/PC Infusion

<table>
<thead>
<tr>
<th>Subject</th>
<th>TC, mmol/L</th>
<th>TG, mmol/L</th>
<th>PL, mmol/L</th>
<th>HDL-C, mmol/L</th>
<th>apoA-I, mg/dL</th>
<th>CER, nmol/mL per h</th>
<th>LCAT, μg/mL</th>
<th>CETP, μg/mL</th>
<th>PLTP, Activity, μmol/mL per h</th>
<th>PLTP, μg/mL</th>
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<td>1.86</td>
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<td>2.32</td>
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<td>ND</td>
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<td>1.13</td>
<td>2.32</td>
<td>1.12</td>
<td>93</td>
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<td>0.5</td>
<td>0.9</td>
<td>2.2</td>
</tr>
</tbody>
</table>

ND indicates not determined.
pressure, or body temperature. Nor were there any changes in routine clinical chemistry or hematology. Preinfusion values in plasma are given in Table.

### Plasma Lipids and Apolipoproteins

Changes in plasma TC, TG, PL, non-HDL cholesterol, HDL cholesterol, non-HDL cholesterol, and apoA-I concentrations relative to preinfusion values are shown in Figure 1. As previously observed, all increased during the infusion, although the change in plasma TG was not statistically significant. By the end of the infusion, plasma apoA-I concentration had increased by 73.9±10.9 mg/dL (mean±SD, P<0.01). At 24 hours, it was approximately 50 mg/dL above baseline. After reaching peak concentration at 4 hours, by 16 hours, plasma PL concentration had decreased to near baseline. The increment in total HDL cholesterol reached a maximum of 0.65±0.17 mmol/L (P<0.01) at 8 hours. Initially the increase was more rapid in HDL FC than in HDL CE. After the infusion, HDL CE continued to rise, whereas HDL FC returned toward baseline.

### Plasma Enzymes and Lipid Transfer Proteins

These results appear in Figure 2. Plasma CER increased throughout the infusion and reached 29.0±9.0 nmol/mL per h (+69.5%, P<0.05) above baseline at 12 hours. Plasma LCAT concentration did not change during the infusion but increased thereafter. At 12 hours it was 0.40±0.90 mg/L above baseline (+7.8%, P<0.05). Plasma CETP concentration increased from the start of the infusion to 12 hours and remained elevated thereafter at approximately 0.45 μg/mL (+30%) above baseline. Plasma PLTP concentration decreased throughout the infusion, reaching a nadir approximately 4.5 mg/L (−45%, P<0.01) below baseline at 12 hours. In contrast, PLTP activity increased, reaching 1.45±0.67 μmol/mL per h (+23.9%, P<0.01) above baseline at 12 hours.

### PLTP Particle Size Distribution

Plasma PLTP exists in 2 types of PLTP-bearing particles, 1 catalytically active and the other inactive. Those carrying inactive PLTP are large particles associated with apoA-I, and those carrying active PLTP are smaller particles containing less lipid. Therefore, we studied the effects of the disc infusion on plasma PLTP particle size. As previously described, before the infusions, plasma PLTP-containing particles by native PAGGE were widely distributed in size ranging from 8.0 to 17.0 nm (Figure 3). During the infusion, the smallest PLTP particles (8.0 to 11.0 nm) disappeared, and

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Figure 1. Changes from baseline in plasma TC, PL, TG, HDL cholesterol, non-HDL cholesterol, and apoA-I concentrations during and after a 4-hour intravenous infusion of apoA-I/PC discs. For ΔHDL cholesterol, results for FC (Δ), CE (●), and TC (○) are shown. Data are presented as mean±SD. Mean baseline concentrations appear in the Table. *P<0.01, **P<0.05.

Figure 2. Changes from baseline in plasma LCAT, PLTP, and CETP concentrations, plasma CER, and plasma PLTP activity (PC transfer activity) during and after a 4-hour intravenous infusion of apoA-I/PC discs. Results for CER are from 4 subjects only. Data are presented as mean±SD. Mean baseline concentrations appear in the Table. *P<0.01, **P<0.05.
PLTP particles larger than any present before the infusion appeared. Thereafter, the number of small PLTP-bearing particles increased and the number of large particles decreased. No change in the molecular weight of PLTP was seen by SDS-PAGE under nonreducing or reducing conditions (Figure 3).

We additionally analyzed plasma PLTP-containing particles by size-exclusion chromatography (Figure 4). Before the infusion, PLTP concentration was distributed mostly between LDLs and HDLs, whereas PLTP activity was mostly confined to particles the size of HDLs, as previously described. During the infusion, mean PLTP particle size increased slightly. The distribution of PLTP activity shifted toward both larger and smaller particles, the former change occurring during the infusion and the latter after the infusion. PLTP activity became measurable in very small particles, in which none had been detectable initially, and in which PLTP concentration was below the limit of detection.

**Electron microscopy**

No discoidal particles were seen at any time point in a thorough examination of the 4 lipoprotein fractions (not shown).

**CETP, PLTP, and LCAT in Peripheral Lymph**

The apoA-I/PC disc infusion had no detectable effects on the concentrations of LCAT, CETP, or PLTP in peripheral lymph (data not shown). This was also true when the results were expressed relative to albumin concentration to adjust for variations lymph flow rate.

**Discussion**

We have previously shown that infusion of apoA-I/PC discs in humans rapidly increased the plasma concentrations of pre-β HDLs and HDL FC, followed by increases in those of large αHDLs and HDL CE and by a rise in the CE/apoB ratio of non-HDLs. In a subsequent study, increases were ob-

**Figure 3.** Size distribution of plasma PLTP-containing particles. Plasma samples were subjected to native PAGGE (A), reduced SDS-PAGE (B), and nonreduced SDS-PAGE (C) (5% to 20% gels). After electrophoresis, the proteins were electrotransferred to a PVDF membrane and immunoblotted with monoclonal anti-PLTP antibody (Mab 113). Representative results from 1 subject (No. 6). Numbers at the top of each lane give the number of hours relative to the start of the infusion.

**Figure 4.** Distribution of PLTP concentration and activity in plasma by size exclusion chromatography. Plasma samples taken at 0 (A), 2 (B), 4 (C), 6 (D), 8 (E), and 12 (F) hours relative to the start of the infusion were applied to 2 Superose 6HR columns connected in series. Fractions were collected and analyzed for PLTP concentration (●) and PC transfer activity (○). Details of the procedure are provided in the Methods section. Representative results from 1 subject (No. 6).
served in pre-β HDL concentration, the size of αHDLs, the cholesterol content of lipoproteins, and the specific radioactivity of cholesterol in prenodal lymph.13 Plasma CER and fecal bile acid excretion also increased. These results indicated that the infusion stimulated the extravascular, intravascular, and intracellular stages of RCT, at least in part by increasing pre-β HDL production rate. We have now investigated the associated changes in LCAT, CETP, and PLTP.

The increase in plasma CER occurred from the beginning of the infusion, reached its peak at 12 hours, and then declined toward baseline. In contrast, plasma LCAT concentration showed no increase until after the infusion had finished. In addition to this difference in time course, there was a large quantitative difference in the 2 effects. The increment in plasma CER in vitro averaged approximately 70% relative to baseline at 12 hours, whereas in plasma LCAT concentration averaged less than 10%. This suggests that the initial rapid rise in CER was attributable mostly to the removal of an inhibitory effect on LCAT activity or to increased availability or quality of its substrate. Of these possibilities, the latter is likely to provide at least a partial explanation, because plasma HDL FC concentration also increased from the outset. Furthermore, discoidal apoA-I/PC discs are better substrates for LCAT in vitro than are native plasma αHDLs, as also are nascent discoidal HDLs from rat liver perfusates.26–28 The contribution of discs as LCAT substrates to the increased CER values in vitro might not have been great, however, because electron microscopy failed to visualize any discoidal particles, suggesting that they had already been converted into αHDLs or had fused with circulating αHDLs in vivo before the blood samples were collected.

Part of the early increase in CER might also have been a consequence of the rapid rise in the plasma concentration of small pre-β HDLs, which are good substrates for LCAT,29 which has been shown to occur during apoA-I/PC disc infusion.14 However, whereas the effect of disc infusion on pre-β HDLs is transient, diminishing as soon as the infusion is stopped,14 the rise in CER continued for an additional 8 hours.

The continued rise in CER that occurred after the infusion may have been partly a consequence of the delayed increase in plasma LCAT concentration during this time. The mechanism of the increase in LCAT concentration is not apparent from our data. Possibilities include increased synthesis in liver, reduced catabolic rate, and redistribution between the intravascular and extravascular compartments. Our measurements of LCAT in lymph provided no evidence for the third mechanism.

We have previously reported that intravenous infusion of apoA-I/PC discs increased the CE content of apoB-containing lipoproteins and attributed this to the transfer of some of the CEs generated in the HDLs.14 Our present findings show that this was accompanied by a progressive increase in plasma CETP concentration, which continued for several hours after the infusion was stopped. Because values for plasma CETP concentration by our assay are strongly correlated with CETP activity,19 this may have contributed to the enrichment of apoB-containing particles with CEs. Our results suggest that there may exist a physiological mechanism for regulating plasma CETP concentration in vivo in accordance with the demand for the disposal of HDL CEs. Oliveira et al30 have shown that the CETP gene has sterol-responsive elements.

It is also possible that the rise in plasma triglycerides that occurred during and after the infusion was associated with an increase in the transfer of CEs from HDLs to triglyceride-rich lipoproteins, leading to increased plasma CER as a secondary phenomenon.31 However, this is unlikely to have been the major factor, because the increase in triglycerides was small and its time course differed from that in CER.

In contrast to the changes in plasma LCAT and CETP concentrations, plasma total PLTP concentration decreased during and after the infusion. This did not seem to result from transfer of PLTP from plasma to tissue fluid, because lymph PLTP concentration showed no discernible change. Despite the decrease in plasma PLTP concentration, plasma PLTP activity in vitro, quantified as PC transfer activity, increased throughout the infusion and continued to do so for an additional 8 hours. This corresponded to more than a 2-fold increase in plasma PLTP specific activity over 12 hours. It is noteworthy in this context that the disc preparation itself contains no PC transfer activity and that our assay for plasma PC transfer activity is unaffected by plasma CETP concentration.20 Because PLTP catalyzes remodeling and fusion of αHDLs to generate pre-β HDLs,11,13 the increase in plasma PLTP activity may contribute to the rise in pre-β HDL concentration that is induced by apoA-I/PC disc infusion.14

Increased PLTP activity in association with decreased PLTP concentration occurs in acute-phase patients.32,33 This is unlikely to have been the mechanism in the present study, however, because we observed no clinical signs of an acute-phase reaction and have shown that intravenous infusion of the apoA-I/PC disc preparation or of lipid-free apoA-I had no effect on acute-phase reactants in plasma or blood leukocyte count.14,16

Plasma PLTP exists in active and inactive forms on particles of differing sizes.20,21,25 Because our PLTP ELISA quantifies plasma total PLTP concentration,20 we examined the effects of the disc infusion on the particle size distributions of PLTP concentration and activity. Native PAGE electrophoresis followed by immunoblotting with anti-PLTP antibody revealed an early shift in the distribution of PLTP concentration from smaller to larger particles. Subsequently, the number of small PLTP-bearing particles increased and the number of the large particles decreased. When lipoproteins were separated by size exclusion chromatography, a transient small shift in the particle size distribution of PLTP concentration was observed. PC transfer activity showed 2 changes, an early shift in the peak of activity toward larger particles during the infusion and a later increase in PC transfer activity associated with small particles, including those in which the PLTP concentration was below the limit of detection. Considered together, these results suggest that the decrease in plasma total PLTP concentration reflected reductions of both small and large particles and that the increase in PC transfer activity resulted largely from the appearance of PLTP of very high specific activity in small and very small particles.
Because the infusion increased mean apoA-I concentration by more than its normal within-subject variation,\textsuperscript{34} the question arises of whether the changes observed were physiological. Although it is not possible to be certain without additional experiments using lower infusion rates, the effects are likely to have been physiological for several reasons. First, in all subjects, plasma HDL cholesterol remained within the normal range. Second, the mean value for apoA-I concentration at the end of the infusion (164 mg/dL) was well within the normal range for white subjects, as exemplified by the Framingham Offspring Study of 1879 American men (134±23 mg/dL, mean±SD)\textsuperscript{35} and the WHO-IFCC standardized study of 83 112 Swedish men (136±22 mg/dL).\textsuperscript{36} Third, as shown in Figure 2, plasma CETP concentration and CER had already increased after 2 hours, by which time apoA-I had increased by only 36.6 mg/dL (or 39.6%). Although not statistically significant, an upward trend in PLTP activity and a downward trend in PLTP concentration were also evident at 2 hours.

The relations of the changes in CETP, PLTP, and LCAT to those in apoA-I were additionally explored by analyzing the data from subjects 1 through 4 and 5 through 8 separately. Because the baseline apoA-I concentrations in subjects 5 through 8 (66 to 81 mg/dL, mean 73.3, Table) were lower than those in subjects 1 through 4 (102 to 129 mg/dL, mean 111.8), the former also had also lower apoA-I concentrations throughout the infusion (2 hours, 91.0 versus 148.5 mg/dL; 4 hours, 139.7 versus 188.3 mg/dL). Plasma LCAT concentration did not change in subjects 5 through 8, but the changes in CETP concentration (mean increase at 12 hours, 0.43 μg/mL, PLTP concentration (mean decrease at 12 hours, 2.5 μg/mL), and PLTP activity (mean increase at 12 hours, 1.13 μmol/mL per h) were qualitatively similar to those in subjects 1 through 4 (+0.50 μg/mL, −6.3 μg/mL, and +1.78 μmol/mL per h, respectively).

It is not possible to determine from our data whether the changes observed were effects of the discs per se or of apoA-I or phosphatidylcholine acting alone. This can be partly addressed by considering the effects of dietary lipemia, when phospholipids enter blood in chylomicrons with little or no change in plasma apoA-I. During alimentary lipemia, mass transfer of CEs from HDLs to apoB-containing lipoproteins increases,\textsuperscript{31,37} but this seems to be secondary to an increase in CETP concentration (mean increase at 12 hours, 0.43 μg/mL per h). This can be partly explained by the fact that apoA-I concentrations in subjects 5 through 4 (102 to 129 mg/dL, mean 111.8), the former also had also lower apoA-I concentrations throughout the infusion (2 hours, 91.0 versus 148.5 mg/dL; 4 hours, 139.7 versus 188.3 mg/dL). Plasma LCAT concentration did not change in subjects 5 through 8, but the changes in CETP concentration (mean increase at 12 hours, 0.43 μg/mL, PLTP concentration (mean decrease at 12 hours, 2.5 μg/mL), and PLTP activity (mean increase at 12 hours, 1.13 μmol/mL per h) were qualitatively similar to those in subjects 1 through 4 (+0.50 μg/mL, −6.3 μg/mL, and +1.78 μmol/mL per h, respectively).

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