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# Changes in Plasma LDL and HDL Composition in Patients Undergoing Cardiac Surgery

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**Abstract**  Changes of lipoprotein composition have been mainly reported in conditions of sepsis. This study characterized compositional changes in LDL and HDL during the acute phase response following cardiac surgery with cardiopulmonary bypass. Twenty-one patients undergoing cardiac surgery were included in this study. Blood samples were drawn before operation and on day 2 post-surgery. In parallel to plasma lipids and antioxidant status, lipoproteins were analyzed for lipid, apolipoprotein (apo), hydroperoxide and alpha-tocopherol content. Beyond decreases in lipid concentrations and antioxidant defenses, cardiac surgery induced substantial modifications in plasma lipoproteins. ApoB decrease in LDL fraction (–46%; $P < 0.0001$) reflected a marked reduction in the circulating particle number. LDL cholesteryl ester content relative to apoB concentration remained unchanged post-surgery while triglyceride (+113%; $P < 0.001$), free cholesterol (+22%; $P < 0.05$) and phospholipid (+23%; $P < 0.025$) were raised relative to apoB indicating increased particle size. In HDL, an abrupt rise of apoSAA ($P < 0.05$) was observed together with a decrease of apoA1 (–22%; $P < 0.005$). Cholesteryl ester content in HDL fraction decreased in parallel to apoA1 concentration while triglycerides, free cholesterol and phospholipids increased relative to apoA1. In contrast to unchanged alpha-tocopherol content, hydroperoxide content was increased in LDL and HDL. By comparison to sepsis, cardiac surgery induces a comparable reduction in circulating LDL but a more limited decrease in HDL particles. Furthermore, in contrast, cardiac surgery induces an increase in polar and non-polar lipids, as well as of particle size in both LDL and HDL.

**Keywords**  Acute phase response · Cardiac surgery · Cardiopulmonary bypass · LDL · HDL · Lipids · Alpha-tocopherol · Oxidative stress · Particle size

**Abbreviations**

| | |
|---|---|
| Apo | Apolipoproteins |
| CE | Cholesteryl ester |
| FC | Free cholesterol |
| HDL | High density lipoproteins |
| LDL | Low density lipoproteins |
| PON | Paraoxonase |
| SAA | Serum amyloid A |
| TC | Total cholesterol |
| TG | Triglycerides |
| TAOS | Total antioxidant status |

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## Introduction

Various pathological conditions, such as severe sepsis, major surgery or accidental trauma and myocardial infarct, may induce an acute phase response. Such a systemic inflammatory reaction involves multiple metabolic

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adaptations induced by hormonal changes and the production of inflammatory cytokines to fight the infection and/or facilitate tissue repair. The acute phase response is characterized by the hepatic synthesis of several acute phase proteins but also by profound alterations in plasma lipid and lipoprotein metabolism [1–3]. In man, plasma concentration of total cholesterol (TC), LDL-cholesterol and HDL-cholesterol decreases within the first 48 h following infectious or non-infectious insults with variable changes in plasma triglyceride (TG) levels [4, 5]. The extent of alterations in the concentration of plasma lipids notably depends on the type and severity of the insult [4]. The reduction of cholesterol-rich lipoproteins may result from reduced secretion, increased catabolism and from increased sequestration of lipoproteins in extra-vascular compartments. A negative correlation has been reported between TC as well as HDL-cholesterol levels and clinical outcome in critically ill and septic patients [4, 6, 7].

The composition of plasma lipoproteins has been mainly studied in conditions of sepsis with severe inflammation and substantial changes have been documented in LDL and HDL [8–11]. Alterations in lipoprotein lipid and apolipoprotein composition may enhance pro-inflammatory and pro-atherogenic properties of LDL and convert HDL from anti- into pro-inflammatory particles with reduced antioxidant functions [9, 12].

Major surgical injury also induces a severe acute phase response with postoperative decreases of plasma (as well as LDL and HDL) cholesterol concentration as reported after cardiac surgery [5, 7, 13, 14]. In contrast to sepsis, which is a very heterogeneous condition, cardiac surgery with cardiopulmonary bypass follows strict routine procedures and represents a fairly standardized insult. In addition to surgical trauma, contact of blood cells and plasma components with artificial membranes of the extracorporeal circuit, and ischemia–reperfusion are responsible for the severe systemic inflammation observed after cardiac surgery with cardiopulmonary bypass [15–17]. Since the composition of plasma lipoproteins has not been investigated in depth after surgery, we questioned whether the acute phase response induced by major cardiac surgery would affect plasma LDL and HDL composition differently as compared to previous observations in severely septic patients. Further, since such operations are associated to substantial oxidative stress and reduced plasma levels of vitamin E (alpha-tocopherol) [18], lipoprotein fractions were also used to determine whether decreased levels of vitamin E are due to a decreased number of lipoprotein carriers or to a reduced content of alpha-tocopherol. Improved knowledge on compositional changes occurring in plasma LDL and HDL after surgery may be important to better define strategies preventing pro-inflammatory changes.

## Materials and Methods

### Study Group Selection

The study group included 21 ASA 3 (American Society of Anesthesiologists class 3) patients undergoing elective cardiac surgery (coronary artery bypass or mitral valve replacement) with cardiopulmonary bypass. Clinical characteristics of the patients are shown in Table 1.

Major exclusion criteria were: patients on steroids or with body mass index >30 kg/m$^2$, plasma creatinine concentration >1.5 mg/dl, altered liver function tests, or diabetes mellitus. None of the patients received corticosteroids in the perioperative period. Patients were not on statin treatment before surgery, except for three of them in whose statins were not reinitiated during the immediate postoperative period of the study protocol. The patients were allowed nothing per os from the evening before the operation until day 1 post-surgery. The study was approved by the Ethical Committee of Erasme Hospital (Université Libre de Bruxelles, Brussels, Belgium) and all participating patients received complete information and signed a written consent form.

### Anesthesia and Cardiopulmonary Bypass

Anesthesia was induced and maintained with a target-controlled infusion of remifentanil and propofol with cisatracurium. All patients received a full-dose of aprotinin ($2 \times 10^6$ KIU at induction, followed by $5 \times 10^5$ KIU/h until the end of surgery and $1 \times 10^6$ KIU in the cardiopulmonary bypass). Cardiopulmonary bypass was performed under mild systemic hypothermia (>35°C). After cross-clamping of the ascending aorta, anterograde cold hyperkalemic cardioplegia was induced, followed by intermittent retrograde cold hyperkalemic cardioplegia whenever necessary. Mean aortic cross-clamp and cardiopulmonary bypass time as well as data on blood transfusion are shown in Table 1.

### Study Protocol

In order to ensure that measurements of lipoprotein composition are made during the acute phase response (and the resulting changes in plasma lipids), measurements of inflammatory proteins, of selected apolipoproteins, and of plasma lipid parameters were performed before surgery and on postoperative day 2 in the first six patients. Assessment of antioxidant status, of vitamin E and of PON was also performed in these patients. In addition, alpha-tocopherol content was analyzed in platelets, white blood

**Table 1** Patients clinical characteristics

| Variable | Patients ($n = 21$) |
|---|---|
| Mean age (range) | 69 ± 3 (42–83) |
| Gender (M:F) | 19:2 |
| CABG:mitral valve replacement | 15:6 |
| CPB (min) | 108 ± 5 |
| Aortic clamping (min) | 83 ± 4 |
| Patients requiring blood products | 8 |
| Number of patients transfused PRBC (mean units of PRBC transfused) | 6 (3 ± 1) |
| Number of patients transfused FFP (mean units FFP transfused) | 5 (4 ± 1) |
| Number of patients transfused platelets (mean units platelets transfused) | 3 (2 ± 1) |

*CABG* Coronary artery bypass graft, *CPB* cardiopulmonary bypass, *PRBC* packed red blood cells, *FFP* fresh frozen plasma

cells and red blood cells isolated from fresh blood samples [19]. In the 15 following patients, plasma lipoprotein fractions were isolated and analysed, before surgery and on postoperative day 2, for their content in lipid components, apolipoproteins, alpha-tocopherol as well as hydroperoxides. Preoperative concentrations of the different biological variables did not significantly differ from values recently measured in a control population from the same region of comparable age and gender with no known coronary heart disease [20, 21].

## Blood Sampling

Blood samples were drawn at the time of anesthesia induction (baseline) and again on day 2 post-surgery. Blood was collected in tubes with EDTA (1 mg/mL) for plasma separation and without EDTA for serum separation. Plasma and serum were immediately separated by low speed centrifugation at 3,500*g* (4 °C; 15 min) in a J2.21 centrifuge (Beckman Instruments, Fullerton, CA, USA).

## Separation of Lipoproteins

Plasma LDL and HDL fractions were isolated by sequential ultracentrifugation [22] in a L8–55 ultracentrifuge using a 50–4Ti rotor (Beckman, Palo Alto, CA, USA). Plasma density was adjusted by addition of solid KBr at density ranges 1.019–1.063 g/ml and 1.063–1.210 g/ml for separation of LDL and HDL, respectively. Plasma was centrifuged at 227,000*g* (5 °C) during 20 h for LDL and 40 h for HDL. LDL and HDL fractions were then either kept at 4 °C for immediate lipid and protein measurements or at –70 °C for vitamin E analysis performed within

2 weeks. EDTA and salts present in the LDL and HDL fractions were removed by filtration on PD10 Sephadex columns (Amersham Pharmacia, Uppsala, Sweden) prior to hydroperoxide measurements by the FOX-2 method [23] or to evaluation of LDL resistance to *ex vivo* oxidation according to Esterbauer et al. [24].

## Analytical Measurements

TC and TG were measured in plasma, LDL and HDL fractions using enzymatic kits CHOD-PAP (Roche Diagnostics GmbH, Mannheim, Germany) and Triglycerides Glycerol blanked (Roche Diagnostics GmbH), respectively. Free Cholesterol (FC) and phospholipid concentrations were determined using enzymatic kits CHOD-PAP (Sopachem, Brussels, Belgium) and PAP 150 (Biomérieux, Lyon, France), respectively. Cholesteryl ester (CE) concentration was calculated by subtracting FC from TC.

Alpha-tocopherol was analysed in plasma and lipoprotein fractions by reverse-phase HPLC (Merck-Hitachi Ltd, Tokyo, Japan) using a Lichrospher column 100 RP 18 (5 μm; 125 × 4 mm, L × ID) with a mobile phase of methanol:water (95/5, w/w) at a flow rate of 1.5 ml/min; alpha-tocopherol was monitored by a UV detector at 292 nm [25]. In cells, alpha-tocopherol concentration was expressed relative to cell phospholipid content.

Plasma total antioxidant status (TAOS) was determined by the capacity to inhibit the peroxidase-mediated formation of the ATBS (2,2'-azinobis-3-ethylbenzothiazoline-6-sulfonic acid) radical [26]. In parallel, paraoxonase (PON) activity was determined spectrophotometrically at 270 nm by measuring the hydrolysis of phenyl acetate [27].

Total protein concentration was determined in plasma fractions using bovine serum/globulin solution as standard [28]. Apolipoproteins (apo) B and A1, as well as serum amyloid A (SAA) were measured in plasma and lipoprotein fractions by ELISA using rabbit polyclonal antibodies for apo A1, B or SAA, respectively [29].

CRP level was determined in plasma using high sensitive CRP immuno-turbidimetric method [30].

## Calculation of LDL and HDL Particle Size

Assuming a spherical configuration, LDL and HDL radii were determined by calculating both particle core volume and surface area. Calculations of core volume were based on the molar content of CE and TG per particle; values of 1.068 and 1.556 nm$^3$ were used for the molecular volume of CE and TG, respectively [31]. Total particle radius was obtained by adding surface monolayer thickness (2.02 nm) to core radius [32]. Calculations of surface area were based

on the molar content of phospholipids and FC per particle; values of 0.310 and 0.685 nm$^2$ were used for the molecular surface area of phospholipids and FC, respectively [31].

Statistical Analysis

All results are expressed as mean values ± SEM. Statistical significance of differences between pre- and postoperative values was assessed by the paired Student's $t$-test.

## Results

Measurements of Selected Plasma Proteins, Apolipoproteins, Lipids and Antioxidants

Pre- and postoperative measurements of plasma parameters in the first six subjects are shown in Table 2 (statistical significance of tabulated results refers to the paired difference in pre- and postoperative absolute values, whilst in the text it often refers to the paired difference in percent changes relative to preoperative baseline values). Total protein concentration decreased by 15.7 ± 3.4% on post-operative day 2 ($P < 0.025$). In contrast, CRP concentration increased from 0.41 ± 0.18 mg/dl (preoperative) to 13.90 ± 3.90 mg/dl ($P < 0.005$) and SAA concentration from 0.22 ± 0.06 to 25.40 ± 5.77 mg/dl ($P < 0.005$) on postoperative day 2. Plasma concentration of apoB and apoA1 decreased by, respectively, 41.3 ± 6.0% ($P < 0.01$) and 31.2 ± 1.1% ($<0.0001$) post-surgery. This decrease of plasma apoB and apoA1 was

more marked than that of total plasma proteins. Indeed, apoB/total protein ratio decreased by 30.6 ± 6.6% ($P < 0.01$) on postoperative day 2 [from 14.5 ± 2.8 to 9.8 ± 1.7 mg/g ($P < 0.05$)]. Similarly, apoA1/total protein ratio decreased by 17.8 ± 3.2% ($P < 0.005$) post-surgery [from 28.0 ± 2.7 to 22.9 ± 2.2 mg/g ($P < 0.05$)].

Plasma concentration of TC and TG decreased by, respectively, 35.5 ± 4.3% ($P < 0.001$) and 23.7 ± 9.5% ($P < 0.06$) from initial values. Plasma alpha-tocopherol concentration decreased by 34.9 ± 5.6% postoperatively ($P < 0.005$). Of interest, alpha-tocopherol/TC ratio was not significantly modified after surgery ($P > 0.25$). Postoperative alpha-tocopherol content in red blood cells and platelets (expressed in relation to phospholipid content) remained unchanged on postoperative day 2 ($P > 0.4$). However, alpha-tocopherol content in white blood cells, (also expressed relative to phospholipid content), decreased by 20.5 ± 6.1% ($P < 0.03$) on postoperative day 2 (Table 3).

A dramatic fall in plasma TAOS was observed postoperatively, from 19.0 ± 3.9 to 3.2 ± 2.8% ($P < 0.01$). Similarly, serum PON activity was decreased by 21.7 ± 2.4% ($P < 0.0001$) after surgery.

Measurements of LDL and HDL Parameters

In 15 other subjects, plasma CRP concentrations increased from 0.41 ± 0.14 mg/dl (preoperative) to a postoperative value of 12.04 ± 1.95 mg/dl ($P < 0.001$), these changes being comparable to those found in the first six patients ($P > 0.6$). Results of pre- and postoperative measurements of LDL and HDL parameters are given in Tables 4 and 5.

*Apolipoproteins*

LDL apoB concentration was decreased by 45.5 ± 5.7% ($P < 0.0001$) on postoperative day 2. This reflects a substantial reduction in the number of circulating LDL particles after cardiac surgery.

Likewise, HDL apoA1 concentration decreased by 21.8 ± 6.5% ($P < 0.005$) on postoperative day 2. This may

**Table 2** Plasma concentration of selected proteins, apolipoproteins, lipids and antioxidant measurements

| Biological variables | Preoperative ($n = 6$) | Postoperative ($n = 6$) |
|---|---|---|
| Protein (g/l) | 67.3 ± 2.0 | 56.0 ± 2.5[a] |
| CRP (mg/dl) | 0.41 ± 0.18 | 13.90 ± 3.90[c] |
| SAA (mg/dl) | 0.22 ± 0.06 | 25.40 ± 5.77[c] |
| ApoB (mg/dl) | 94.8 ± 17.3 | 54.5 ± 10.1 [a] |
| ApoA1 (mg/dl) | 183.8 ± 14.8 | 126.4 ± 10.0[d] |
| TC (mmol/l) | 5.17 ± 0.43 | 3.31 ± 0.31[b] |
| TG (mmol/l) | 1.42 ± 0.34 | 0.97 ± 0.17 |
| α-Tocopherol (μmol/l) | 33.76 ± 3.43 | 22.30 ± 3.44[b] |
| PON (μmol/min ml) | 84.5 ± 7.3 | 66.8 ± 7.6[e] |
| TAOS (%) | 19.0 ± 3.9 | 3.2 ± 2.8[a] |

*CRP* C-reactive protein, *SAA* serum amyloid A, *apoB* apolipoprotein B, *apoA1* apolipoprotein A1, *TC* total cholesterol, *TG* triglycerides, *PON* paraoxonase, *TAOS* total antioxidant status

Values are expressed as mean ± SEM. $P$ values were calculated by paired Student $t$ test. [a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.005$, [d]$P < 0.001$, [e]$P < 0.0001$ versus preoperative value

**Table 3** Alpha-tocopherol content in blood cells (μmol/mmol PL)

| Biological variables | Preoperative ($n = 5$) | Postoperative ($n = 5$) |
|---|---|---|
| Red blood cells | 8.03 ± 0.91 | 8.22 ± 1.06 |
| White blood cells | 17.27 ± 1.89 | 13.50 ± 1.45[a] |
| Platelets | 17.04 ± 2.20 | 16.39 ± 1.75 |

Values are expressed as mean ± SEM. $P$ values were calculated by paired Student $t$ test. [a]$P < 0.03$ versus preoperative value

*PL* Phospholipids

**Table 4** LDL and HDL absolute values

| Biological variables | Preoperative (n = 15) | Postoperative (n = 15) |
|---|---|---|
| LDL-apoB (mg/dl) | 71.5 ± 9.5 | 43.2 ± 8.7[e] |
| HDL-apoAI (mg/dl) | 142.4 ± 12.3 | 108.5 ± 11.2[c] |
| HDL-apoSAA (mg/dl) | 0.5 ± 0.2 | 39.2 ± 17.2[a] |
| LDL-TC (mmol/l) | 2.67 ± 0.15 | 1.52 ± 0.17[e] |
| LDL-CE (mmol/l) | 1.98 ± 0.11 | 1.09 ± 0.13[e] |
| LDL-FC (mmol/l) | 0.69 ± 0.04 | 0.43 ± 0.04[e] |
| HDL-TC (mmol/l) | 0.97 ± 0.10 | 0.79 ± 0.07[b] |
| HDL-CE (mmol/l) | 0.78 ± 0.08 | 0.60 ± 0.05[c] |
| HDL-FC (mmol/l) | 0.19 ± 0.02 | 0.19 ± 0.02 |
| LDL-TG (mmol/l) | 0.20 ± 0.02 | 0.19 ± 0.02 |
| HDL-TG (mmol/l) | 0.08 ± 0.01 | 0.07 ± 0.01 |
| LDL-PL (mmol/l) | 0.80 ± 0.04 | 0.50 ± 0.05[e] |
| HDL-PL (mmol/l) | 0.77 ± 0.06 | 0.73 ± 0.05 |
| LDL-hydroperoxides (μmol/l) | 14.1 ± 4.3 | 15.5 ± 4.4 |
| HDL-hydroperoxides (μmol/l) | 10.5 ± 2.0 | 13.8 ± 4.6 |
| LDL-α-tocopherol (μmol/l) | 11.3 ± 0.7 | 6.6 ± 0.6[e] |
| HDL-α-tocopherol (μmol/l) | 8.3 ± 1.0 | 6.3 ± 0.6[d] |

Values are expressed as mean ± SEM. *P* values were calculated by the paired Student *t* test. [a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.005$, [d] $P < 0.001$, [e] $P < 0.0001$ versus preoperative value

*apoB* Apolipoprotein B, *apoA1* apolipoprotein A1, *TC* total cholesterol, *FC* free cholesterol, *TG* triglycerides, *PL* phospholipids

correspond to a decrease in the number of HDL particles if an unchanged mean number of apoA1 molecules per HDL particle is assumed. The HDL apoSAA concentration increased markedly post-surgery, from 0.5 ± 0.2 to 39.2 ± 17.2 mg/dl ($P < 0.05$).

### Cholesterol

CE concentration in the LDL fraction decreased from 1.98 ± 0.11 to 1.09 ± 0.13 mmol/l ($P < 0.0001$), corresponding to a decrease of 45.9 ± 4.4% ($P < 0.0001$) from initial values. This fall in LDL-CE was comparable to the decrease in LDL-apoB. FC concentration in the LDL fraction decreased by 38.1 ± 4.5% ($P < 0.0001$) on postoperative day 2. The FC/CE and FC/apoB molar ratios in LDL increased by, respectively, 16.9 ± 4.4% ($P < 0.002$) and 21.6 ± 9.5% ($P < 0.05$) after cardiac surgery.

Comparable postoperative changes of CE and FC content were observed in the HDL fraction. HDL-CE decreased from 0.78 ± 0.08 to 0.60 ± 0.05 mmol/l ($P < 0.005$), i.e., by 18.9 ± 6.6% ($P < 0.02$) from preoperative values. In contrast, FC concentration in the HDL fraction remained unchanged after surgery ($P > 0.8$). Thus, the FC/CE ratio in the HDL fraction increased by 36.3 ± 8.3% ($P < 0.001$) post-surgery. HDL CE/apoA1

ratio was not significantly modified post-surgery ($P > 0.31$), while FC/apoA1 increased by 42.9 ± 7.1% compared to preoperative values ($P < 0.0001$).

### Triglycerides

In sharp contrast to cholesterol, TG concentration in the LDL fraction remained unchanged post-surgery ($P > 0.6$). Hence, the TG/CE ratio in LDL increased by 101.5 ± 18.9% ($P < 0.0001$) on postoperative day 2. Similarly, TG/apoB ratio in LDL increased by 112.9 ± 26.2% ($P < 0.001$) after surgery.

Likewise, TG concentration in the HDL fraction was not significantly modified after surgery ($P > 0.5$). TG/CE and TG/apoA1 ratios in the HDL fraction, however, increased by 31.3 ± 16.9% ($P=0.08$) and 34.3 ± 15.2% ($P < 0.05$), respectively. Thus, TG content relative to either CE or apoA1 tended to be or increased in HDL but to a lesser extent than in LDL fraction.

### Phospholipids

Phospholipid concentration in the LDL fraction decreased by 37.6 ± 4.5% ($P < 0.0001$) on postoperative day 2. In contrast, phospholipid/apoB ratio in LDL increased by 22.5 ± 8.6% ($P < 0.025$) post-surgery.

Phospholipid concentration in the HDL fraction was not significantly modified after surgery ($P > 0.9$). Hence, phospholipid/apoA1 ratio increased by 30.2 ± 6.1% ($P < 0.001$) on postoperative day 2 compared to preoperative values.

In fair agreement with current knowledge [32], FC/phospholipid molar ratio was, before surgery, about four times higher in LDL (0.86 ± 0.02 mmol/mmol) than in HDL (0.23 ± 0.01 mmol/mmol). This ratio was unaffected by surgery in LDL but increased by 17.6 ± 7.4% ($P < 0.05$) in HDL.

### Calculation of LDL and HDL Particle Size

Before surgery, LDL particle radius calculated from the sum of core lipid molecule volumes averaged 9.98 ± 0.29 nm, in fair agreement with current knowledge [32] and also with LDL radius calculation from surface area molecules (including one apoB molecule), which averaged 9.60 ± 0.34 nm. After surgery, unchanged CE and increased TG content (+113%) per LDL particle imply an increase in the size of LDL particles. Consistently, FC/apoB and phospholipid/apoB ratios increased by 21.6 ± 9.5 and 22.5 ± 8.6%, respectively ($P < 0.05$) after surgery;

**Table 5** LDL and HDL ratios

| Biological variables | Preoperative ($n = 15$) | Postoperative ($n = 15$) |
|---|---|---|
| LDL-CE/apoB (mmol/g) | 3.30 ± 0.33 | 3.46 ± 0.46 |
| LDL-FC/apoB (mmol/g) | 1.18 ± 0.14 | 1.46 ± 0.21[a] |
| LDL-FC/CE (mmol/mmol) | 0.35 ± 0.01 | 0.41 ± 0.02[c] |
| HDL-CE/apoA1 (mmol/g) | 0.59 ± 0.06 | 0.62 ± 0.07 |
| HDL-FC/apoA1 (mmol/g) | 0.14 ± 0.01 | 0.20 ± 0.02[d] |
| HDL-FC/CE (mmol/mmol) | 0.23 ± 0.01 | 0.31 ± 0.02[d] |
| LDL-TG/apoB (mmol/g) | 0.34 ± 0.04 | 0.75 ± 0.12[d] |
| LDL-TG/CE (mmol/mmol) | 0.10 ± 0.01 | 0.20 ± 0.02[e] |
| HDL-TG/apoA1 (mmol/g) | 0.06 ± 0.01 | 0.08 ± 0.01 |
| HDL-TG/CE (mmol/mmol) | 0.11 ± 0.01 | 0.14 ± 0.02 |
| LDL-PL/apoB (mmol/g) | 1.36 ± 0.16 | 1.71 ± 0.24[b] |
| LDL-PL/CE (mmol/mmol) | 0.41 ± 0.01 | 0.48 ± 0.02[d] |
| LDL-FC/PL (mmol/mmol) | 0.86 ± 0.02 | 0.86 ± 0.02 |
| HDL-PL/apoA1 (mmol/g) | 0.57 ± 0.05 | 0.75 ± 0.08[d] |
| HDL-PL/CE (mmol/mmol) | 0.98 ± 0.06 | 1.18 ± 0.06[a] |
| HDL-FC/PL (mmol/mmol) | 0.23 ± 0.01 | 0.26 ± 0.01[a] |
| LDL-hydroperoxides/TC (μmol/mmol) | 6.40 ± 2.45 | 17.27 ± 7.17 |
| LDL-hydroperoxides/apoB (μmol/g) | 22.45 ± 7.98 | 55.58 ± 16.32[b] |
| HDL-hydroperoxides/TC (μmol/mmol) | 10.87 ± 1.70 | 16.50 ± 3.94 |
| HDL-hydroperoxides/apoA1 (μmol/g) | 8.26 ± 1.51 | 15.03 ± 4.85 |
| LDL-α-tocopherol/TC (μmol/mmol) | 4.32 ± 0.25 | 4.59 ± 0.27 |
| LDL-α-tocopherol /apoB (μmol/g) | 18.99 ± 2.05 | 22.62 ± 2.97 |
| LDL-α-tocopherol/FC+PL (μmol/mmol) | 7.69 ± 0.44 | 7.27 ± 0.34 |
| HDL-α-tocopherol/TC (μmol/mmol) | 8.63 ± 0.37 | 7.94 ± 0.30[a] |
| HDL-α-tocopherol/apoA1 (μmol/g) | 6.21 ± 0.67 | 6.41 ± 0.72 |
| HDL-α-tocopherol/FC+PL (μmol/mmol) | 8.61 ± 0.40 | 6.74 ± 0.26[d] |

Values are expressed as mean ± SEM. $P$ values were calculated by the paired Student $t$ test. [a]$P < 0.05$, [b]$P < 0.025$, [c]$P < 0.01$, [d]$P < 0.001$, [e]$P < 0.0001$ versus preoperative value

*CE* Cholesteryl ester, *FC* free cholesterol, *TG* triglycerides, *PL* phospholipids, *apoB* apolipoprotein B, *apoA1* apolipoprotein A1

comparable changes were found for LDL-FC/CE (+16.9 ± 4.4%) and LDL phospholipid/CE ratios (+18.0 ± 3.9%) after surgery. These ratios suggest a postoperative increase of surface area and of particle radius by 14 ± 5% ($P < 0.03$) and 6 ± 2% ($P < 0.03$), respectively.

Before surgery, the HDL core volume corresponded to a core radius of 2.56 ± 0.09 nm and a total particle radius of 4.58 ± 0.09 nm, in fair agreement with current knowledge [32, 33]. Calculations from the sum of surface components (assuming a mean of 3 apoA1 molecules per HDL particle) correspond to a core radius of 3.02 ± 0.05 nm, in fair agreement with the HDL calculated core radius from core volume. The unchanged CE content and increased TG content in postoperative HDL particles imply an increase in core lipid molecules and volume. Accordingly, both FC/apoA1 and phospholipid/apoA1 ratios increased in HDL post-surgery, with a mean increase of, respectively, 42.9 ± 7.1% ($P < 0.001$) and 30.2 ± 6.1% ($P < 0.001$). Comparable percentages were obtained for HDL-FC/CE (36.3 ± 8.3%) and HDL-phospholipid/CE ratios (23.6 ± 6.7%). This suggests an increase of HDL area by 31 ± 6% ($P < 0.001$) and of HDL radius by 14 ± 3% ($P < 0.001$) after cardiac surgery. Note that calculations of

HDL size are underestimates since the molecular volume of apoSAA is not taken into account.

### Hydroperoxides

The hydroperoxide concentration in the LDL fraction was not significantly modified after surgery ($P > 0.3$). However, hydroperoxide/apoB and hydroperoxide/TC ratios increased by, respectively, 189.1 ± 83.0 and 191.3 ± 89.2% on postoperative day 2 ($P < 0.05$).

Similarly, the hydroperoxide concentration in the HDL fraction was not significantly modified ($P > 0.5$) post-surgery but, when expressed relative to TC content, the hydroperoxide/TC ratio in HDL increased by 62.4 ± 29.3% ($P < 0.03$) after surgery.

### Alpha-tocopherol

In the LDL fraction, alpha-tocopherol concentration decreased by 41.0 ± 3.9% ($P < 0.0001$) on postoperative day 2. However, alpha-tocopherol content relative to apoB

or TC content in the LDL fraction was not decreased by surgery. Similarly, the alpha-tocopherol/FC+phospholipid ratio was not modified after surgery.

In the HDL fraction, alpha-tocopherol concentration had decreased by $21.6 \pm 4.4\%$ ($P < 0.001$) on postoperative day 2. Alpha-tocopherol content relative to apoA1 or TC content was not or little affected after surgery. In contrast, the alpha-tocopherol/FC+phospholipid ratio had decreased by $20.5 \pm 2.9\%$ ($P < 0.001$) after surgery.

Notice that alpha-tocopherol/TC ratio was two times higher ($P < 0.001$) in HDL versus LDL in pre- and post-operative conditions.

### LDL Peroxidation

LDL resistance towards oxidative stress, reflected by the lag phase preceding the generation of conjugated dienes from LDL exposed to $CuSO_4$, did not significantly decrease after surgery ($73 \pm 3$ vs. $71 \pm 3$ min; NS). The propagation slope decreased slightly after surgery (by $10.4 \pm 4.0\%$; $P < 0.025$). This coincided with a trend towards a lower maximal value for the generation of conjugated dienes, with a postoperative/preoperative ratio for dienes averaging $91.8 \pm 4.5\%$ ($P < 0.09$).

### Discussion

The present study was aimed at characterizing changes in plasma lipoprotein composition induced by cardiac surgery with cardiopulmonary bypass, notably in comparison to alterations reported in sepsis. Indeed, most current data on LDL and HDL alterations occurring in acute phase reactions comes from observations in patients with severe septic conditions [8, 9].

Analyses of plasma lipid parameters are in agreement with prior observations on the effect of surgical stress, i.e., decreased levels of TC, TG and alpha-tocopherol [5, 14, 34, 35]. An important decrease of apoB and apoA1 level was also observed in the present study that largely exceeded the reduction of total plasma protein concentration. The marked increase of SAA levels paralleled and even exceeded that of CRP. Reduced TAOS indicates decreased antioxidant defenses and/or consumption of antioxidant scavengers in response to oxidative stress as previously described after cardiac surgery with cardiopulmonary bypass [36]. Furthermore, the activity of the antioxidant enzyme PON, largely associated to HDL particles, was decreased post-surgery; this may substantially reduce protection against LDL oxidation [12]. Such alterations in antioxidant parameters have also been described in sepsis [37–39]. In this study, alpha-tocopherol content in blood

cells was analysed to evaluate whether the decreased antioxidant defenses and more specifically whether the marked reduction in circulating alpha-tocopherol level are associated to impaired alpha-tocopherol delivery to cells. Indeed, apart from one study reporting unchanged alpha-tocopherol content in erythrocytes after surgery [40], no data is currently available on alpha-tocopherol content in blood cells of surgical or septic patients. Since blood cell counts are modified after surgery, alpha-tocopherol content was expressed relative to cell phospholipid concentration, which to our knowledge, is not affected by the operative procedure, Alpha-tocopherol content was unchanged in erythrocytes and platelets on postoperative 2, but was decreased in leukocytes. This may reflect increased consumption by white blood cells or an impaired alpha-tocopherol uptake, or both; after surgery, another possibility is that, leukocytes released in great number in the circulation after surgery have a lower alpha-tocopherol content.

Analyses of lipoprotein fractions in 15 subjects characterize the effect of cardiac surgery on changes in the number, composition, and size of circulating particles.

LDL-cholesterol markedly decreased (–45%) after surgery. Such a decrease in LDL cholesterol is commonly observed after surgery [5, 14, 34] and in other types of acute phase reactions, including sepsis [11, 41, 42] and acute myocardial infarct [43]. In the later condition, however, cholesterol production and secretion appear not to be reduced but are rather augmented [44]. If this was also the case in the surgical acute phase, the lower LDL-cholesterol level would largely result from increased particle disposal (endocytosis via LDL B, E and scavenger receptors, and possible margination of LDL particles outside the plasma compartment).

ApoB concentration in the LDL fraction also substantially decreased (–46%) after cardiac surgery. Since LDL particles contain one single apoB molecule, this change reflects a proportional reduction of the number of circulating LDL particles. Lipid content per LDL particle was reflected by the concentration of each component relative to LDL-apoB (Fig. 1). CE content per LDL particle remained unchanged after cardiac surgery, while TG content was increased (+113%) together with surface components FC (+22%) and phospholipids (+23%). Such increase of both core and surface lipid components strongly suggests an increased LDL particle size postoperatively. This is in sharp contrast with changes observed during sepsis where the decrease in LDL number is associated with the appearance of small sized and denser LDL particles, in which an increased TG content is largely compensated for by a reduced CE content [45, 46]. Such small dense LDL particles are more sensitive to peroxidative damage, are more cytotoxic, and have an increased
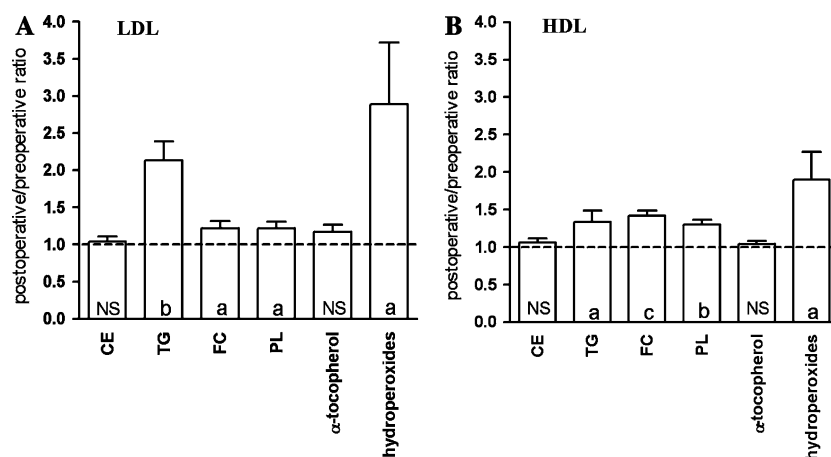
**Fig. 1** Postoperative changes in LDL (*A*) and HDL (*B*) composition. LDL and HDL lipid components are expressed relative to LDL-apoB and HDL-apoA1, respectively. The figure shows an unchanged cholesteryl ester (*CE*) content in LDL and HDL particles, an increased triglyceride (*TG*) content (particularly in LDL) together with an increase in surface components [free cholesterol (*FC*) and phospholipids (*PL*)]; in spite of unchanged alpha-tocopherol content, LDL and HDL showed increased hydroperoxide content. Values are expressed as mean ± SEM. *P* values were calculated by paired Student *t* test. [a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.005$, [d]$P < 0.001$, [e]$P < 0.0001$ versus preoperative value

atherogenic potential [47]. Of interest, alpha-tocopherol content per LDL particle remained unchanged after surgery and no difference of susceptibility to peroxidation was observed between pre- and postoperative circulating LDL particles when subjected *ex vivo* to copper oxidative stress. Still, as reported in sepsis [47], an increased hydroperoxide content was measured in circulating LDL particles after cardiac surgery, suggesting that the (unchanged) alpha-tocopherol content in postoperative LDL particles could not completely prevent the oxidative stress associated to cardiac surgery with cardiopulmonary bypass. From current data it is difficult to speculate whether these changes in LDL composition and size can modulate properties of LDL and influence (in one or another direction) the inflammatory response.

In contrast to LDL particles, which are characterized by the presence of one single apoB molecule, HDL particles contain 2 to 4 apoA1 molecules in physiological conditions [33]. In addition, HDL apolipoprotein composition is substantially modified during the acute phase reaction, notably by a massive increase of SAA [48, 49]. While high SAA concentrations had previously been suggested to displace apoA1 from HDL particles, apoA1 decrease during acute phase response seems to result mainly from an increased catabolic rate, which parallels that of HDL particles [50]. If one assumes that the mean number of apoA1 molecules in HDL is not appreciably modified by cardiac surgery, the number of circulating HDL particles would decrease by 20% on postoperative day 2. Such a decrease in HDL particles is lower than that observed for LDL and it is not as marked as in patients with sepsis [42, 51]. Of interest,

HDL-CE decreased by 18.9 ± 6.6% ($P < 0.02$) postoperatively so that HDL-CE/apoA1 ratio remained virtually unchanged (Fig. 1). As indicated by the increased HDL-TG/apoA1 (+34%) and HDL-TG/CE (+31%) ratios, TG content in HDL particles increased after surgery, but to a lesser extent than in LDL particles. Such an increase in LDL- and HDL-TG content on postoperative day 2 contrasts with a lower plasma TG concentration. Lower plasma TG concentrations do not usually induce cholesteryl ester transfer protein-mediated exchanges of core lipids between TG-rich and CE-rich lipoproteins [52, 53]. Hence, TG enrichment in LDL and HDL may result from reduced hepatic lipase activity as reported in conditions of sepsis and inflammation [41]. The increase of core lipid molecules in postoperative HDL is associated to an increase of surface components, as indicated by increased FC/apoA1 and phospholipid/apoA1 ratios (Fig. 1). All together these changes and the presence of SAA molecules in HDL surface indicate an increased particle size after cardiac surgery. Changes in the balance between HDL surface lipid components were also observed after surgery with a higher FC relative to phospholipid content. This is in agreement with observations in septic patients where reduced lecithin:cholesterol acyltransferase activity is associated with an increased FC content in HDL particles [54, 55]. Finally, the alpha-tocopherol level decreased in the HDL fraction after cardiac surgery in close relation to the reduced number of circulating HDL particles. The hydroperoxide content in HDL increased after surgery but to a lesser extent than in LDL particles. The global reduction of alpha-tocopherol transport by LDL and

HDL may affect alpha-tocopherol delivery to cells and organs in a condition (ischemia–reperfusion) characterized by oxidative stress.

There are some limitations that need to be addressed regarding this study. First, it does not allow one to distinguish between the impact of surgical trauma, that of cardiopulmonary bypass and that of anesthesia on the inflammatory response and more particularly on the changes in plasma lipoproteins and oxidative stress. Second, measurements reflect changes in circulating LDL and HDL particles, but more profound alterations may occur in those lipoproteins that marginate outside the plasma compartment. Third, measurements were performed at two time points, i.e., before (=baseline) and at 48 h after surgery, the latter corresponding to the peak of the inflammatory response but not to the peak of systemic oxidative stress, which takes place during surgery (after reperfusion) and in the immediate postoperative period [56]. Finally, since the measured postoperative alterations of lipoprotein composition probably last over a limited period of time, their impact on the functional properties of circulating plasma lipoproteins remains to be determined.

In summary, the present study indicates that the acute phase response that occurs after major cardiac surgery induces profound alterations not only in the concentration but also in the composition of circulating LDL and HDL particles. Several of these surgery-induced alterations in the lipid composition of LDL and HDL particles differ from changes previously observed in sepsis. Thus acute phase reactions caused by different conditions may affect the properties of plasma lipoproteins differently and should be considered specifically. Although the increase in LDL and HDL particle size probably limits the pro-inflammatory risk, additional experiments are required to fully determine the impact of postoperative modifications on the roles and function of circulating lipoproteins. Reduced levels of circulating lipoproteins post-surgery may also affect the delivery to cells and tissues of substrates such as alpha-tocopherol.

# References

1. Gabay C, Kushner I (1999) Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 340:448–54
2. Carpentier YA, Scruel O (2002) Changes in the concentration and composition of plasma lipoproteins during the acute phase response. Curr Opin Clin Nutr Metab Care 5:153–8
3. Feingold KR, Staprans I, Memon RA, Moser AH, Shigenaga JK, Doerrler W, Dinarello CA, Grunfeld C (1992) Endotoxin rapidly induces changes in lipid metabolism that produce hypertriglyceridemia: low doses stimulate hepatic triglyceride production while high doses inhibit clearance. J Lipid Res 33:1765–76
4. Fraunberger P, Schaefer S, Werdan K, Walli AK, Seidel D (1999) Reduction of circulating cholesterol and apolipoprotein levels during sepsis. Clin Chem Lab Med 37:357–62
5. Akgun S, Ertel NH, Mosenthal A, Oser W (1998) Postsurgical reduction of serum lipoproteins: interleukin-6 and the acute-phase response. J Lab Clin Med 131:103–8
6. Chien JY, Jerng JS, Yu CJ, Yang PC (2005) Low serum level of high-density lipoprotein cholesterol is a poor prognostic factor for severe sepsis. Crit Care Med 33:1688–93
7. Gordon BR, Parker TS, Levine DM, Saal SD, Wang JC, Sloan BJ, Barie PS, Rubin AL, (2001) Relationship of hypolipidemia to cytokine concentrations and outcomes in critically ill surgical patients. Crit Care Med 29:1563–8
8. Hudgins LC, Parker TS, Levine DM, Gordon BR, Saal SD, Jiang XC, Seidman CE, Tremaroli JD, Lai J, Rubin AL (2003) A single intravenous dose of endotoxin rapidly alters serum lipoproteins and lipid transfer proteins in normal volunteers. J Lipid Res 44:1489–98
9. Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR, Grunfeld C (2004) Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. J Lipid Res 45:1169–96
10. Kitchens RL, Thompson PA, Munford RS, O'Keefe GE (2003) Acute inflammation and infection maintain circulating phospholipid levels and enhance lipopolysaccharide binding to plasma lipoproteins. J Lipid Res 44:2339–48
11. Hardardottir I., Grunfeld C, Feingold KR (1994) Effects of endotoxin and cytokines on lipid metabolism. Curr Opin Lipidol 5:207–15
12. Van Lenten BJ, Hama SY, de Beer FC, Stafforini DM, McIntyre TM, Prescott SM, La Du BN, Fogelman AM, Navab M (1995) Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response. Loss of protective effect of HDL against LDL oxidation in aortic wall cell cocultures. J Clin Invest 96:2758–67
13. Stephens CJ, Graham RM, Yadava OP, Leong LL, Sturm MJ, Taylor RR (1992) Plasma platelet activating factor degradation and serum lipids after coronary bypass surgery. Cardiovasc Res 26:25–31
14. Cunningham MJ, Boucher TM, McCabe CH, Horowtiz GL, Pasternak RC (1987) Changes in total cholesterol and high-density lipoprotein cholesterol in men after coronary artery bypass grafting. Am J Cardiol 60:1393–4
15. Levy JH, Tanaka KA (2003) Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 75:S715–20
16. Larmann J, Theilmeier G (2004) Inflammatory response to cardiac surgery: cardiopulmonary bypass versus non-cardiopulmonary bypass surgery. Best Pract Res Clin Anaesthesiol 18:425–38
17. Goudeau JJ, Clermont G, Guillery O, Lemaire-Ewing S, Musat A, Vernet M, Vergely C, Guiguet M, Rochette L, Girard C (2007) In high-risk patients, combination of antiinflammatory procedures during cardiopulmonary bypass can reduce incidences of inflammation and oxidative stress. J Cardiovasc Pharmacol 49:39–45
18. Coghlan JG, Flitter WD, Clutton SM, Ilsley CD, Rees A, Slater TF (1993) Lipid peroxidation and changes in vitamin E levels during coronary artery bypass grafting. J Thorac Cardiovasc Surg 106:268–74
19. Pouliot M, Fiset ME, Masse M, Naccache PH, Borgeat P (2002) Adenosine up-regulates cyclooxygenase-2 in human

granulocytes: impact on the balance of eicosanoid generation. J Immunol 169:5279–86

20. Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, Patsch W (2001) Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 104:1108–13

21. Nzuzi Tembo N, Bazelmans C, Dufourny G, Levèque A, Nève J, Carpentier YA (2006) Comparison of cardiovascular risk factors between different ethnic groups living in the region of Brussels. 28th ESPEN Congress, Istanbul (Turkey) Abstract

22. Havel RJ, Eder HA, Bragdon JH (1955) The distribution and chemical composition of ultracentrifugally separated lipoproteins in human serum. J Clin Invest 34:1345–53

23. Jiang ZY, Hunt JV, Wolff SP (1992) Ferrous ion oxidation in the presence of xylenol orange for detection of lipid hydroperoxide in low density lipoprotein. Anal Biochem 202:384–9

24. Esterbauer H, Dieber-Rotheneder M, Striegl G, Waeg G (1991) Role of vitamin E in preventing the oxidation of low-density lipoprotein. Am J Clin Nutr 53:314S–321S

25. Traber MG, Kayden HJ (1989) Preferential incorporation of alpha-tocopherol vs gamma-tocopherol in human lipoproteins. Am J Clin Nutr 49:517–26

26. Wong WM, Stephens JW, Acharya J, Hurel SJ, Humphries SE, Talmud PJ (2004) The APOA4 T347S variant is associated with reduced plasma TAOS in subjects with diabetes mellitus and cardiovascular disease. J Lipid Res 45:1565–71

27. Eckerson HW, Wyte CM, La Du BN (1983) The human serum paraoxonase/arylesterase polymorphism. Am J Hum Genet 35:1126–38

28. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ (1951) Protein measurement with the Folin phenol reagent. J Biol Chem 193:265–75

29. Dubois DY, Cantraine F, Malmendier CL (1987) Comparison of different sandwich enzyme immunoassays for the quantitation of human apolipoproteins A-I and A-II. J Immunol Methods 96:115–20

30. Cotton F, Thiry P, Hsain AB, Boeynaems JM (2001) Analyzer transfer of a broad range high-sensitivity C-reactive protein immunoassay. Clin Lab 47:405–9

31. Pruzanski W, Stefanski E, de Beer FC, de Beer MC, Ravandi A, Kuksis A (2000) Comparative analysis of lipid composition of normal and acute-phase high density lipoproteins. J Lipid Res 41:1035–47

32. Gotto AM Jr, Pownall HJ, Havel RJ (1986) Introduction to the plasma lipoproteins. Methods Enzymol 128:3–41

33. Eisenberg S (1984) High density lipoprotein metabolism. J Lipid Res 25:1017–58

34. Malmendier CL, Amerijckx JP, Bihain BE, Fischer ML (1985) Changes in apolipoprotein and lipids in patients after surgery. Biomed Pharmacother 39:192–5

35. Cavarocchi NC, England MD, O'Brien JF, Solis E, Russo P, Schaff HV, Orszulak TA, Pluth JR, Kaye MP (1986) Superoxide generation during cardiopulmonary bypass: is there a role for vitamin E? J Surg Res 40:519–27

36. McColl AJ, Keeble T, Hadjinikolaou L, Cohen A, Aitkenhead H, Glenville B, Richmond W (1998) Plasma antioxidants: evidence for a protective role against reactive oxygen species following cardiac surgery. Ann Clin Biochem 35(Pt 5):616–23

37. Goode HF, Cowley HC, Walker BE, Howdle PD, Webster NR (1995) Decreased antioxidant status and increased lipid peroxidation in patients with septic shock and secondary organ dysfunction. Crit Care Med 23:646–51

38. Wu A, Hinds CJ, Thiemermann C (2004) High-density lipoproteins in sepsis and septic shock: metabolism, actions, and therapeutic applications. Shock 21:210–21

39. Chuang CC, Shiesh SC, Chi CH, Tu YF, Hor LI, Shieh CC, Chen MF (2006) Serum total antioxidant capacity reflects severity of illness in patients with severe sepsis. Crit Care 10:R36

40. Ballmer PE, Reinhart WH, Jordan P, Buhler E, Moser UK, Gey KF (1994) Depletion of plasma vitamin C but not of vitamin E in response to cardiac operations. J Thorac Cardiovasc Surg 108:311–20

41. Sammalkorpi K, Valtonen V, Kerttula Y, Nikkila E, Taskinen MR (1988) Changes in serum lipoprotein pattern induced by acute infections. Metabolism 37:859–65

42. van Leeuwen HJ, Heezius EC, Dallinga GM, van Strijp JA, Verhoef J, van Kessel KP (2003) Lipoprotein metabolism in patients with severe sepsis. Crit Care Med 31:1359–66

43. Rosenson RS (1993) Myocardial injury: the acute phase response and lipoprotein metabolism. J Am Coll Cardiol 22:933–40

44. Pfohl M, Schreiber I, Liebich HM, Haring HU, Hoffmeister HM (1999) Upregulation of cholesterol synthesis after acute myocardial infarction—is cholesterol a positive acute phase reactant? Atherosclerosis 142:389–93

45. Feingold KR, Krauss RM, Pang M, Doerrler W, Jensen P, Grunfeld C (1993) The hypertriglyceridemia of acquired immunodeficiency syndrome is associated with an increased prevalence of low density lipoprotein subclass pattern B. J Clin Endocrinol Metab 76:1423–7

46. Grunfeld C, Pang M, Doerrler W, Shigenaga JK, Jensen P, Feingold KR (1992) Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. J Clin Endocrinol Metab 74:1045–52

47. Memon RA, Staprans I, Noor M, Holleran WM, Uchida Y, Moser AH, Feingold KR, Grunfeld C (2000) Infection and inflammation induce LDL oxidation in vivo. Arterioscler Thromb Vasc Biol 20:1536–42

48. Coetzee GA, Strachan AF, van der Westhuyzen DR, Hoppe HC, Jeenah MS, de Beer FC (1986) Serum amyloid A-containing human high density lipoprotein 3. Density, size, and apolipoprotein composition. J Biol Chem 261:9644–51

49. Clifton PM, Mackinnon AM, Barter PJ (1985) Effects of serum amyloid A protein (SAA) on composition, size, and density of high density lipoproteins in subjects with myocardial infarction. J Lipid Res 26:1389–98

50. Hosoai H, Webb NR, Glick JM, Tietge UJ, Purdom MS, de Beer FC, Rader DJ (1999) Expression of serum amyloid A protein in the absence of the acute phase response does not reduce HDL cholesterol or apoA-I levels in human apoA-I transgenic mice. J Lipid Res 40:648–53

51. Gordon BR, Parker TS, Levine DM, Saal SD, Wang JC, Sloan BJ, Barie PS, Rubin AL (1996) Low lipid concentrations in critical illness: implications for preventing and treating endotoxemia. Crit Care Med 24:584–9

52. Eisenberg S, Gavish D, Oschry Y, Fainaru M, Deckelbaum RJ (1984) Abnormalities in very low, low and high density lipoproteins in hypertriglyceridemia. Reversal toward normal with bezafibrate treatment. J Clin Invest 74:470–82

53. Deckelbaum RJ, Granot E, Oschry Y, Rose L, Eisenberg S (1984) Plasma triglyceride determines structure-composition in low and high density lipoproteins. Arteriosclerosis 4:225–31

54. Ly H, Francone OL, Fielding CJ, Shigenaga JK, Moser AH, Grunfeld C, Feingold KR (1995) Endotoxin and TNF lead to reduced plasma LCAT activity and decreased hepatic LCAT mRNA levels in Syrian hamsters. J Lipid Res 36:1254–63

55. Khovidhunkit W, Shigenaga JK, Moser AH, Feingold KR, Grunfeld C (2001) Cholesterol efflux by acute-phase high density lipoprotein: role of lecithin: cholesterol acyltransferase. J Lipid Res 42:967–75

56. Christen S, Finckh B, Lykkesfeldt J, Gessler P, Frese-Schaper M, Nielsen P, Schmid ER, Schmitt B (2005) Oxidative stress precedes peak systemic inflammatory response in pediatric patients undergoing cardiopulmonary bypass operation. Free Radic Biol Med 38:1323–32

57. Hacquebard M, Ducart A, Schmartz D, Tembo N, Carpentier YA (2004) Tocopherol in lipoproteins and blood cells after cardiac surgery. Ann N Y Acad Sci 1031:432–4