Recent developments in low-density lipoprotein apheresis

Thomas Demant and Dietrich Seidel

Institute of Clinical Chemistry at Klinikum Großhadern of the Ludwig Maximilians University, Munich, FRG

The three established methods for low-density lipoprotein (LDL) apheresis, LDL immunoabsorption, dextran sulfate cellulose-LDL apheresis and heparin-induced extracorporeal LDL precipitation (HELP)-LDL apheresis, are equally safe and effective. Hemorrheological parameters are also improved by these procedures, notably by HELP-LDL apheresis which also eliminates fibrinogen from plasma. Preliminary data suggest that LDL apheresis may be an important tool for primary and secondary prevention in selected patients with a particularly high risk for coronary heart disease.

Current Opinion in Lipidology 1992, **3**:43–48

Introduction

In the last decade several systems have been developed for the extracorporeal specific elimination of low-density lipoprotein (LDL) cholesterol from patient plasma. These procedures are collectively referred to as LDL apheresis. Today LDL apheresis has largely replaced plasma exchange therapy, as introduced by DeGennes *et al.* [1] and Thompson *et al.* [2], in the treatment of patients with otherwise refractory hyperlipidemia such as homozygous familial hypercholesterolemia. Now, with the experience gathered in the course of several years of clinical application, the efficacy, specificity and safety of different methods of LDL apheresis can be compared. Besides the marked reduction of LDL plasma concentrations it has become apparent that at least some of the LDL lowering procedures result in an equally significant change of hemorrheologically important parameters. This and the long-term clinical benefits of LDL apheresis treatment, in particular for the secondary prevention of coronary heart disease, are still under investigation by a number of multicenter clinical trials. The present review covers the issues of safety, efficacy and specificity as well as clinical results of LDL apheresis treatment based on papers published within the last 2 years.

Short-term effects and safety of low-density lipoprotein apheresis

Three methods of selective removal of LDL from plasma have been established and are now widely used for the treatment of hypercholesterolemic patients: LDL immunoabsorption, using immobilized anti-apolipoprotein (apo)B antibodies for LDL binding [3]; heparin-induced extracorporeal LDL precipitation (HELP)-LDL apheresis [4]; and LDL binding to dextran sulfate cellulose (DSC)-LDL apheresis [5]. Another method proposed is double plasma filtration which retains LDL by virtue of its molecular size rather than by specific affinity binding [6].

In a recent review Keller [7••] compared the different procedures for LDL apheresis with regard to efficacy in lowering LDL concentrations and safety in patient treatment. Immunoabsorption, heparin precipitation and dextran sulfate binding all achieve a 60–80% decrease of LDL in plasma in the course of a single LDL apheresis session (Table 1). The reduction in high-density lipoprotein (HDL) levels and immunoglobulins was usually less than 20% with no significant differences between the three LDL apheresis methods. These apparent losses are at least to some extent due to unspecific plasma dilution by the saline priming solution from the extracorporeal plasma circuit. However, a careful study of albumin losses induced by DSC-LDL apheresis which takes plasma dilution into account comes to the conclusion that 4–9% of the total plasma albumin reserve is lost by a single apheresis treatment [8•].

Double plasma filtration achieves the same reduction of LDL concentrations as the methods mentioned above but the selectivity of the procedure is much lower. Total plasma protein losses are significant and concomitant albumin substitution is regularly required. Therefore double plasma filtration holds an intermediate position between plasma exchange therapy and selective LDL apheresis. An interesting, although rare, application of double plasma filtration has been reported by Franceschini *et al.* [9•] who successfully treated a patient with primary sclerosing cholangitis and excessive debilitating

Abbreviations

apo—apolipoprotein; **DSC**—dextran sulfate cellulose; **HDL**—high-density lipoprotein; **HELP**—heparin-induced extracorporeal LDL precipitation; **HMG CoA**—β-hydroxy-β-methylglutaryl coenzyme A; **LDL**—low-density lipoprotein; **Lp**—lipoprotein; **Lp(a)**—lipoprotein (a); **VLDL**—very-low-density lipoprotein.

 ISSN 0957-9672

Table 1. Short-term effects of different forms of LDL apheresis on LDL and Lp(a) plasma concentrations.

LDL	Number of patients	LDL	Lp(a)	Reference
Immunoabsorption	8	−68%	−58%	[15•]
DSC-LDL apheresis	54	−76%	−65%	[17]
	2	−63%	−80%	[13•]
HELP apheresis	5	−50%	−45%	[15•]
	7	−64%	−62%	[16]

Reductions induced by a single treatment are expressed as a percentage of the pre-treatment values.

xanthomatosis due to a massive increase of lipoprotein X in plasma. Since lipoprotein X lacks apoB selective LDL apheresis was ineffective whereas double-plasma filtration induced complete regression of xanthomas. Side effects like vagal reactions, fever, chills, flushing or angina pectoris occurred at a rate of less than 3% of treatments with no preference for one of the three LDL apheresis schemes [7••,10••]. A special concern with LDL immunoabsorption was the possibility of immunization of patients with sheep immunoglobulins which may be shed from the LDL-immunosorbent columns. Gordon *et al.* [11•] investigated this problem in detail. They demonstrated that antibody shedding does occur and that most patients on treatment develop antibodies against sheep immunoglobulin G. However, clinical reactions like flushing and diaphoresis, which were observed in about 1% of patients, were unrelated to this immunization. In contrast, a consistent correlation was found between clinical reactions and complement activation (*i.e.* generation of fragment C 5a), which was induced by plasma passage through the immunosorbent column. Complement activation was also found in the HELP-apheresis process [12•]. Activated complement factor C3, complement factor fragment C5a and terminal complement complex are generated at the plasma/blood cell filter but activated C3 and terminal complement complex are largely adsorbed to the following HELP-specific filter, resulting in patient plasma concentrations which were actually below those measured before treatment. C5a is not retained in the filter system but plasma levels at the end of treatment were within the normal range and leucocytopenia, a hallmark of complement activation, was never observed.

Specificity of extracorporeal low-density lipoprotein elimination and effects on hemorrheological parameters

Although LDL apheresis is designed for the selective removal of LDL from plasma, none of the three methods described above is absolutely specific for LDL only. Immunoabsorption and DSC apheresis are highly specific for apoB-containing lipoproteins which include very-low-density lipoprotein (VLDL), intermediate-density lipoprotein, LDL and lipoprotein (a) [Lp(a)]. A detailed study of the lipoproteins eliminated from the plasma by DSC apheresis has been published by Gairin *et al.* [13•]. Lipoproteins were analyzed by sandwich-type immunoenzymometric assays and characterized by their apolipoprotein composition rather than by the conventional density nomenclature. Plasma concentrations of apoB-containing lipoproteins, including those which also contain apoE, apoC-III and apo(a), were reduced by 65–88%. However, this does not necessarily mean that these lipoproteins were directly eliminated by affinity binding to dextran sulfate as evidenced by comparatively small amounts of lipoprotein (Lp)B : E and LpB : CIII particles recovered from the dextran sulfate columns. It is assumed that heparin, which is injected as an anticoagulant during apheresis, activates lipolytic enzymes. These in turn transfer *in vivo* LpB : CIII and LpB : E (*i.e.* VLDL and intermediate-density lipoprotein) into LDL which extracorporeally binds avidly to the dextran sulfate matrix. This view is supported by observations published by Richter *et al.* [14•] who found a marked increase of lipoprotein lipase and hepatic lipase activity after a single treatment with LDL immunoabsorption. Plasma VLDL was reduced by 50% but no VLDL eluted from the immunoabsorption column.

A second apoB-containing lipoprotein which is significantly correlated with the risk for coronary heart disease is Lp(a). Immunoabsorption, DSC-LDL apheresis and HELP-LDL apheresis all eliminate Lp(a) to about the same extent as LDL [15•,16,17]. Table 1 summarizes results for Lp(a) elimination by different methods of LDL apheresis published within the last 2 years. An interesting aspect of selective LDL binding procedures is the potential use of the vast amounts of LDL recovered from affinity columns or precipitation filters in biomedical or clinical research. LDL recovered from dextran sulfate columns, heparin LDL precipitates or plasma double filtration was found to have almost normal receptor binding affinity in hepatoma cell cultures, although binding to or desorption from dextran sulfate cellulose seems to induce proteolytic cleavage of apoB [18•]. Whether this finding is of clinical significance and whether LDL derived from LDL apheresis can be used as a drug targeting vehicle is presently under investigation.

In contrast with LDL immunoabsorption and DSC-LDL apheresis, HELP-LDL apheresis also eliminates fibrinogen, resulting specifically in a 50–60% reduction of plasma concentration through a single treatment [19,20]. Parallel measurements of plasma viscosity and erythrocyte aggregation before and after HELP-LDL apheresis revealed significant reductions of 15 and 40%. The muscle oxygen tension was found to be significantly higher directly after treatment when compared with pre-treatment values, probably as a result of improved microcirculation [20]. In another study of 12 patients, values for blood viscosity, plasma viscosity and erythrocyte aggregation were lower after treatment than before LDL immunoabsorption ($n = 8$) or HELP-LDL apheresis ($n = 4$), with no significant differences between the two methods [21•]. However, a specific reduction of fibrinogen was only observed in the group treated with HELP-LDL apheresis

(−51%). The hematocrit in this group was unchanged whereas it dropped by 10% in the LDL immunoabsorption group. DSC-LDL apheresis, on the other hand, induced no changes of plasma fibrinogen levels and plasma viscosity before and 7 days after treatment in 10 patients with familial hypercholesterolemia. However, blood viscosity was significantly reduced, which was probably also due to a concomitant decrease of the hematocrit [22•]. Hemostatic variables such as tissue plasminogen activator, plasminogen activator inhibitor, platelet aggregation and monocyte procoagulant activity were unaffected by DSC-LDL apheresis when measured before and 7 days after treatment [23].

Long-term effects and clinical results of low-density lipoprotein apheresis treatment

Results from two multicenter studies of LDL apheresis as a means of aggressive lipid-lowering therapy were published in 1991 (Table 2). The HELP-LDL apheresis study was designed to test the role of LDL apheresis in the secondary prevention of coronary heart disease [10••]. Fifty-one patients with coronary heart disease and LDL cholesterol concentrations ≥200 mg/dl despite diet and drug therapy were also treated with weekly HELP-LDL apheresis for 2 years. After 12 months LDL cholesterol had been lowered from 283(±86) mg/dl before treatment to pre- and post-apheresis levels of 203(±41) mg/dl and 76(±24) mg/dl, respectively. With 7-day treatment intervals the time-averaged LDL cholesterol concentration can be calculated as the mean of pre- and post-treatment levels, which is 140 mg/dl. Thus the application of HELP-LDL apheresis in this study resulted in a long-term reduction of LDL cholesterol concentrations of about 50%. At the same time pre-treatment HDL cholesterol increased significantly from 41(±11) to 48(±11) mg/dl. The LDL:HDL cholesterol ratio was reduced from 7.0 before treatment to approximately 3.5 after 12 months. The same reduction of the LDL:HDL ratio was achieved in the Familial Atherosclerosis Treatment Study [24] by drug treatment with a combination of either lovastatin and colestipol or niacin and colestipol. β-Hydroxy-β-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors were not available when the HELP study was started. In the meantime it has been shown that a combination of HMG CoA reductase inhibitor and LDL apheresis treatment results in an even more pronounced decrease of LDL concentrations [25]. Interestingly, this regimen is also effective in the treatment of homozygous familial hypercholesterolemia, as shown by one patient who on weekly HELP-LDL apheresis alone had pre/post-treatment LDL cholesterol levels of 100/400 mg/dl [26•]. Additional therapy with lovastatin (20 mg/day) resulted in a further 20% reduction of these values. Since LDL receptor activity was less than 10% of normal in this subject the effect of lovastatin was probably mediated through a mechanism independent of the LDL receptor.

Table 2. Long-term effects of LDL apheresis on plasma lipoproteins and fibrinogen concentrations as determined by two recent multicenter studies (see text for details) [10••,17].

	HELP-LDL apheresis	DSC-LDL apheresis	
Subjects treated	n = 51	n = 54	n = 10
Intervals between treatment	7 days	7–14 days	7–14 days
Duration of treatment	12 months	4 months	4 months
LDL (mg/dl)			
Before treatment	283	243	447
On LDL apheresis	76–203*	139†	210†
HDL (mg/dl)			
Before treatment	41	n.s.	n.s.
On LDL apheresis	41–48*		
Fibrinogen (mg/dl)			
Before treatment	308	n.d.	n.d.
On LDL apheresis	96–235*		

Concentrations before and on treatment are significantly different ($P < 0.001$ for HELP-LDL apheresis). *Plasma concentrations directly after treatment and before the next treatment session; †time-averaged concentrations.

Data on the second multicenter study [17], using DSC-LDL apheresis, are at present only available in preliminary form. Sixty-four patients with familial hypercholesterolemia (54 heterozygous and 10 homozygous) were treated at 7–14-day intervals for 18 weeks. Baseline LDL cholesterol concentrations were 243 mg/dl and 447 mg/dl, respectively. Time-averaged LDL cholesterol levels on treatment were 139 mg/dl in heterozygotes and 210 mg/dl in homozygotes. HDL cholesterol increased slightly but changes were not significant. Lp(a) levels were reduced markedly by the procedure but — as in the HELP study — long-term concentrations are not given. In the previously mentioned paper on Lp(a) reduction by HELP-LDL apheresis and LDL immunoabsorption long-term reductions of the initial Lp(a) concentration by 43% after 1 year and 30% after 2 years were observed [15•]. A multicenter study of LDL immunoabsorption supervised by Borberg *et al.* is still ongoing with even preliminary data unavailable at present (H Borberg, personal communication, 1992). Long-term observations in eight patients with severe heterozygous familial hypercholesterolemia treated at weekly intervals with LDL immunoadsorption showed a 30% increase in HDL pretreatment levels after 1 year of therapy [14•]. This rise was entirely due to an increase of HDL_3 whereas HDL_2 remained unchanged.

The average LDL cholesterol concentration obtained by repetitive LDL apheresis depends on the time interval between treatments, on the recovery curve for the LDL concentration following apheresis and on the volume of plasma treated. Franceschini *et al.* [27] have published formulae which, for LDL apheresis treatments of one plasma volume, allow an estimation of the LDL concentration time course which helps to define optimal treatment intervals. In practice, options for treatment intervals are

often confined by organizational needs to weekly and biweekly schedules which have to be tested pragmatically.

As mentioned previously, LDL apheresis, besides lowering lipoprotein concentrations, may also have an impact on hemorrheological parameters. In the HELP-LDL apheresis study a long-term decrease of the plasma fibrinogen concentrations from initially 308(±98) mg/dl to pre/post-treatment levels of 235(±78)/96(±42) mg/dl was observed. In a study of five heterozygous patients with familial hypercholesterolemia treated weekly with HELP-LDL apheresis for 12 weeks, a similar reduction in fibrinogen concentrations was accompanied by a 20–30% reduction of pre-apheresis values for plasma viscosity and a 10% reduction of erythrocyte aggregation. Yet another study of 10 patients with familial hypercholesterolemia (10 homozygotes, two heterozygotes) has also been mentioned previously [22•]. Here, arterial blood flow measurements by plethysmography revealed an increase of flow in the forearm and calf before and 3 weeks after a course of six DSC-LDL apheresis treatments applied at biweekly intervals.

The crucial question for the evaluation of LDL apheresis as a means of patient treatment is whether or not the development of atherosclerosis can be prevented or even reversed by this invasive therapeutic approach. For primary prevention of coronary heart disease in homozygous familial hypercholesterolemia, LDL apheresis is of proven benefit and now constitutes an established therapy. The role of LDL apheresis in the secondary prevention of coronary heart disease is less clearly defined. As mentioned before, the HELP-LDL apheresis study was designed to address this problem [10••]. All participants were examined by coronary angiography at start and after 2 years of treatment. As in the Familial Atherosclerosis Treatment Study, a comparison of angiograms in a subset of patients (n = 5) shows that more regression than progression occurred [28]. Another small study of seven patients with heterozygous familial hypercholesterolemia produced evidence that LDL apheresis administered once a week for 7–24 months induced regression of carotid atherosclerotic plaques [29•]. Plaques were evaluated by a three-dimensional reconstruction of ultrasound images. From 21 observed plaques one progressed, 12 did not change and eight regressed within 6–12 months. The complete evaluation of angiograms from the HELP study and from the ongoing LDL immunoabsorption study will soon provide results which will enable a rational determination of the role of LDL apheresis in the secondary prevention of coronary heart disease compared with combined drug treatment alone.

Based on present experience a German consensus panel has recently published guidelines as to when LDL apheresis treatment is indicated [30]. These are as follows:

> in the presence of homozygous familial hypercholesterolemia;
>
> in the primary prevention of coronary heart disease in young patients with severe hypercholesterolemia, mild coronary heart disease (stage I–II) and a family history of coronary heart disease provided LDL cholesterol cannot be decreased below 200 mg/dl by lipid-lowering diet and maximal drug therapy;
>
> in the secondary prevention of coronary heart disease in patients with severe coronary heart disease (stage III-IV) and severe hypercholesterolemia provided LDL cholesterol cannot be decreased below 135 mg/dl by maximal dietary and pharmacological treatment.

In any case diet and drug therapy should be continued while patients are on LDL apheresis treatment. Guidelines for secondary prevention will have to be reconsidered in the light of results from multicenter studies.

Conclusion

LDL immunoabsorption, DSC-LDL apheresis and HELP-LDL apheresis are all safe and equally potent methods of extracorporeal LDL elimination. Lp(a) can also specifically be removed from plasma by these procedures. In addition, HELP-LDL apheresis selectively reduces plasma fibrinogen which seems to have a beneficial effect on the microcirculation. Long-term observations show that besides the marked reduction in LDL cholesterol some increase of HDL cholesterol occurs which may add to the antiatherogenic effect of LDL apheresis treatment. Multicenter studies which will soon be published in full will help to define the role of LDL apheresis in the primary and secondary prevention of coronary heart disease.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. DE GENNES JL, TOURAINE R, MAUNAND B, TRUFFERT J, LAUDANT P: **Formes Homozygotes Cutaneotendineuses de Xanthomatose Hypercholesterolemique dans une Observation Familiale Exemplaire.** *Bull Mem Soc Hop Paris* 1967, 118:1377–1402.

2. THOMPSON GR, MYANT NB, KILPATRICK D, OAKLEY CM, RAPHAEL MJ, STEINER RE: **Assessment of Long-Term Plasma Exchange for Familial Hypercholesterolemia.** *Br Heart J* 1980, 43:680–688.

3. STOFFEL W, DEMANT T: **Selective Removal of Apolipoprotein B-Containing Serum Lipoproteins from Blood Plasma.** *Proc Natl Acad Sci U S A* 1981, 78:611–615.

4. ARMSTRONG VW, WINDISCH M, WIELAND H, FUCHS C, RIEGER J, KÖSTERING H, NEBENDAHL K, SCHELER F, SEIDEL D: **Selective Continuous Extracorporeal Elimination of Low-Density Lipoproteins with Heparin at Acidic pH.** *Trans Am Soc Artif Intern Organs* 1983, 29:323–327.

5. YOKOYAMA S, HAYASHI R, KIKKAWA T, TANI N, TAKADA S, HATANAKA K, YAMAMOTO A: **Specific Sorbent of Apolipoprotein B-Containing Lipoproteins for Plasmapheresis. Charac-**

terization and Experimental Use in Hypercholesterolemic Rabbits. *Arteriosclerosis* 1984, 4:276–282.

6. MABUCHI H, MICHISHITA I, SAKAI T, SAKAI Y, WATANABE A, WAKASUGI T, TAKEDA R: **Treatment of Homozygous Patients with Familial Hypercholesterolemia by Double-Filtration Plasmapheresis.** *Atherosclerosis* 1986, 61:135–140.

7. •• KELLER C: **LDL-Apheresis: Results of Longterm Treatment and Vascular Outcome.** *Atherosclerosis* 1991, 86:1–8.
A review article presenting comparative data on efficacy and safety of different methods of LDL apheresis as well as some clinical results achieved by long-term treatment.

8. • KOJIMA S, SHIBA M, NOMURA S, KIMURA G, TSUSHIMA M, KURAMOCHI M, YAMAMOTO A, OMAE T: **Evaluation of Albumin Loss During Low-Density Lipoprotein Apheresis.** *Trans Am Soc Artif Intern Organs* 1990, 36:830–833.
Albumin losses induced by DSC-LDL apheresis were assessed as between 4 and 9% of total plasma albumin by radioimmunoassay of the discarded fluid and by measurement of changes of the plasma albumin reserve.

9. • FRANCESCHINI G, BUSNACH G, CHIESA G, SIRTORI CR: **Management of Lipoprotein-X Accumulation in Severe Cholestasis by Semi-Selective LDL-Apheresis.** *Am J Med* 1991, 90:633–638.
A patient with primary sclerosing cholangitis, markedly elevated plasma levels of lipoprotein X and diffuse xanthomas was treated with DSC-LDL apheresis and double plasma filtration. Only the latter removed both LDL and lipoprotein X. The resulting reduction of plasma cholesterol levels was associated with a complete regression of xanthomas.

10. •• SEIDEL D, ARMSTRONG VW, SCHUFF-WERNER P FOR THE HELP STUDY GROUP: **The HELP-LDL-Apheresis Multicentre Study, an Angiographically Assessed Trial on the Role of LDL-Apheresis in the Secondary Prevention of Coronary Heart Disease. I. Evaluation of Safety and Cholesterol-Lowering Effects During the First 12 Months.** *Eur J Clin Invest* 1991, 21:375–383.
This is the first report from an LDL apheresis multicenter study. It describes the long-term effects on plasma lipoproteins and hemostaseological parameters in 51 patients treated with HELP-LDL apheresis for 12 months.

11. • GORDON BR, SLOAN BJ, PARKER TS, SAAL SD, LEVINE DM, RUBIN AL: **Humoral Immune Response Following Extracorporeal Immunoadsorption Therapy of Patients with Hypercholesterolemia.** *Transfusion* 1990, 30:327–332.
In this study patient immunization against detached sheep anti-apoB was investigated. Side effects of LDL immunoabsorption were found to be correlated with antibody titers.

12. • WURZNER R, SCHUFF-WERNER P, FRANZKE A, NITZE R, OPPERMANN M, ARMSTRONG VW, EISENHAUER T, SEIDEL D, GÖTZE O: **Complement Activation and Depletion During LDL-Apheresis by Heparin-Induced Extracorporeal LDL-Precipitation (HELP).** *Eur J Clin Invest* 1991, 21:288–294.
Complement activation was demonstrated to occur at the plasma filter of the extracorporeal circuit but most activated complement was retained subsequently by the HELP-specific filter. Plasma levels were never found to be elevated.

13. • GAIRIN D, MONARD F, CACHERA C, BARD JM, AMOUYEL P, DURIEZ P, TACQUET A, FRUCHART JC: **Lipoprotein Particles in Homozygous Familial Hypercholesterolemic Patients Treated with Portacaval Shunt and LDL Apheresis.** *Clin Chim Acta* 1990, 193:165–180.
This is careful study of changes in lipoprotein plasma concentrations during DSC-LDL apheresis and of the lipoproteins desorbed from the LDL affinity column.

14. • RICHTER WO, SÜHLER K, SCHWANDT P: **Extracorporeal LDL Elimination by Immunoabsorption: Side Effects and Influences on Other Serum Lipoproteins and Serum Parameters.** In *Treatment of Severe Hypercholesterolemia in the Prevention of Coronary Heart Disease 2* edited by Gotto AM Jr, Mancini M, Richter WO. Basel: Karger, 1990, pp 183–187.
In eight patients treated for 12–32 months a 40% increase of HDL_3 pre-treatment concentrations and a marked reduction of plasma ferritin were observed.

15. • RITTER MM, SUHLER K, RICHTER W, SCHWANDT P: **Short- and Long-Term Effects of LDL-Apheresis on Lipoprotein(a) Serum Levels.** *Clin Chim Acta* 1990, 195:9–16.
LDL immunoabsorption and HELP-LDL apheresis were compared with regard to their effect on Lp(a) levels.

16. ARMSTRONG VW, SCHLEEF J, THIERY J, MUCHE R, SCHUFF-WERNER P, EISENHAUER T, SEIDEL D: **Effect of HELP-LDL-Apheresis on Serum Concentrations of Human Lipoprotein(a): Kinetic Analysis of the Post-Treatment Return to Baseline Levels.** *Eur J Clin Invest* 1989, 19:235–240.

17. GORDON BR, BILHEIMER DW, BROWN DC, DAU PC, GOTTO AM, ILLINGWORTH DR, JONES PH, KELSEY SF, LEITMAN SF, STEIN EA, STERN TN, ZAVORAL JH, ZWIENER J, FOR LIPOSORBER STUDY GROUP: **Multicenter Study of the Treatment of Familial Hypercholesterolemia (FH) by LDL-Apheresis Using the Liposorber^R LA-15 System [abstract].** *Arterio Thromb* 1991, 11:1409.

18. • SCHULTIS H-W, V. BAYER H, NEITZEL H, RIEDEL E: **Functional Characteristics of LDL Particles Derived from Various LDL-Apheresis Techniques Regarding LDL-Drug-Complex Preparation.** *J Lipid Res* 1990, 31:2277–2284.
The *in vitro* metabolism of LDL recovered from DSC columns, HELP precipitates or double filtration was studied in hepatoma and macrophage cell cultures.

19. SCHUFF-WERNER P, SCHÜTZ E, SEYDE WC, EISENHAUER TH, JANNING G, ARMSTRONG VW, SEIDEL D: **Improved Haemorheology Associated with a Reduction in Plasma Fibrinogen and LDL in Patients Being Treated by Heparin-Induced Extracorporeal LDL Precipitation (HELP).** *Eur J Clin Invest* 1989, 19:30–37.

20. KLEOPHAS W, LESCHKE M, TSCHOPE D, MARTIN J, SCHAUSEIL S, SCHOTTENFELD Y, STRAUER BE, GRIES FA: **Acute Effects of Extracorporeal Elimination of LDL-Cholesterol and Fibrinogen on Blood Rheology and Microcirculation.** *Dtsch Med Wochenschr* 1990, 115:3–7.

21. • SUHLER K, VIERNEISEL K, MOHRLE W, RICHTER WO, SCHWANDT P: **Hemorheological Parameters during Extracorporeal LDL Elimination by Immunoadsorption and HELP.** In *Treatment of Severe Hypercholesterolemia in the Prevention of Coronary Heart Disease 2* edited by Gotto AM Jr, Mancini M, Richter WO, Schwandt P. Basel: Karger, 1990, pp 268–274.
Blood viscosity, plasma viscosity and erythrocyte aggregation were found to be reduced by LDL immunoadsorption and by HELP-LDL apheresis.

22. • RUBBA P, IANNUZZI A, POSTIGLIONE A, SCARPATO N, MONTEFUSCO S, GNASSO A, NAPPI G, CORTESE C, MANCINI M: **Hemodynamic Changes in the Peripheral Circulation after Repeat Low Density Lipoprotein Apheresis in Familial Hypercholesterolemia.** *Circulation* 1990, 81:610–616.
Six treatments with DSC-LDL apheresis resulted in a decreased blood viscosity and a subsequent improvement of arterial blood flow in arms and legs.

23. DI MINNO G, CERBONE AM, CIRILLO F, POSTIGLIONE A, COLUCCI M, SEMERARO N, SCARPATO N, GNASSO A, MARGAGLIONE M, GALLOTTA G, MANCINI M: **Hemostatic Variables in Homozygous Familial Hypercholesterolemia. Effect of Regular Plasma Cholesterol Removal by Low Density Lipoprotein Apheresis.** *Arteriosclerosis* 1990, 10:1119–1126.

24. BROWN G, ALBERS JJ, FISHER LD, SCHAEFER SM, LIN JT, KAPLAN C, ZHAO XQ, BISSON BD, FITZPATRICK VF, DODGE HT: **Regression of Coronary Artery Disease as a Result of Intensive Lipid Lowering Therapy in Men with High Levels of Apolipoprotein B.** *N Engl J Med* 1990, 323:1289–98.

25. MABUCHI H: **Use of LDL-Apheresis in the Management of Familial Hypercholesterolemia.** *Curr Opin Lipidol* 1990, 1:43–47.

26. THIERY J, WALLI AK, JANNING G, SEIDEL D: **Low-Density Lipoprotein Plasmapheresis With and Without Lovastatin in the Treatment of the Homozygous Form of Familial Hypercholesterolemia.** *Eur J Pediatr* 1990, 149:716–721.
In a homozygous girl with familial hypercholesterolemia the effect of HELP-LDL apheresis was improved by concomitant drug treatment with lovastatin.

27. FRANCESCHINI G, BUSNACH G, CALABRESI L, CHIESA G, GIANFRANCESCHI G, ZOPPI F, MINETTI L, SIRTORI CR: **Predictability of Low-Density Lipoprotein Levels During Apheretic Treatment of Hypercholesterolemia.** *Eur J Clin Invest* 1991, 21:209–214.

28. GOHLKE H, BRAUNAGEL K, BESTEHORN HP, KETTNER U, BURGGRAF E, BAUER M, BETZ P, ROSKAMM H: **Heparin-Induced Extracorporeal LDL-Precipitation (HELP) Promotes Regression in Patients with Familial Hypercholesterolemia II (FH) [abstract].** *J Am Coll Cardiol* 1991, 17:47A.

29. HENNERICI M, KLEOPHAS W, GRIES FA: **Regression of Carotid Plaques During Low Density Lipoprotein Cholesterol Elimination.** *Stroke* 1991, 22:989–992.
In seven patients with a total of 21 carotid atherosclerotic lesions 38% showed regression in serial ultrasound examinations after an average of 17 months of HELP-LDL apheresis.

30. GRETEN H, BLEIFELD W, BEIL FU, DÄRR W, STRAUER E, KLEOPHAS W, GRIES FA, SCHUFF-WERNER P, THIERY J, SEIDEL D: **LDL-Apherese: Ein Therapeutisches Verfahren bei Schwerer Hypercholesterinämie. [LDL-Apheresis: A Therapeutic Principle in Severe Hypercholesterolemia.]** *Deutsches Ärzteblatt* 1992, 89:48–49.

T. Demant and D. Seidel, Institute of Clinical Chemistry, University Hospital Großhadern, Marchionministraße 15, 8000 München 70, FRG.