The H.E.L.P.-Report 1994

10 Years of Clinical Experience

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1. Preface

In collaboration with B. Braun Melsungen AG, Germany, we were able to develop the **H**eparin-mediated **E**xtracorporeal **L**DL:fibrinogen **P**recipitation (H.E.L.P.) system and to introduce it into clinical use.

The H.E.L.P. apheresis system is the most potent technique to reduce at the same time LDL, Lp(a), and Fibrinogen plasma concentrations if the physiological clearing mechanisms are insufficient and if diet and drug fails to achieve target concentration of 100 mg/dl LDL-cholesterol or lower, required for secondary prevention of coronary heart disease.

The H.E.L.P.-LDL-apheresis system in addition efficiently improves plasma viscosity and microcirculation.

The clinical experience with the H.E.L.P. system has proved its clinical utility; regression of coronary heart disease occurs, a decrease in events of coronary heart disease takes place and acute as well as chronic impairment of microcirculation shows a remarkable improvement with the H.E.L.P. therapy.

For the future, the availability of this safe and efficient apheresis technique may provide a help for many patients who before could not be treated adequately.

2. Introduction

2.1 Rationale for the Treatment of Severe Hypercholesterolemia in Coronary Heart Disease (CHD)

Current management of coronary artery disease consists primarily of medical therapy designed to increase oxygen supply to the heart or to reduce myocardial oxygen consumption; treatment with vasoactive agents as well as angioplasty and bypass surgery have become routine techniques to increase myocardial oxygen delivery. Only the minority of coronary diseased patients received therapy to change the atherosclerotic process itself, although several recent studies have demonstrated that aggressive lipid management can accomplish the same treatment goals i.e. reduction of arteriographic stenosis, prevention of disease progression, reduction in anginal frequency, increase of exercise tolerance, decrease of cardiovascular events and mortality. Most comprehensive reports on this topic are the detailed meta-analysis of angiographically controlled intervention studies by Blankenhorn and Hodis [1994] and also a recent series of 'cholesterol papers' by Law et al. [1994].

It has been estimated that at plasma cholesterol concentrations above 200 mg/dl the risk for future coronary heart disease events is 5- to 10-fold higher in CHD-patients than that of the general population [Cremer et al., 1991; Castelli, 1984]. Results of secondary intervention trials indicate that cholesterol lowering by 10% will reduce recurrence of myocardial infarction by approximately 25%, also with a strong trend towards reduction in total mortality [Law et al., 1994].

To our knowledge the USA National Cholesterol Educational Program [1993] in accordance with recommendations by the German Society for Internal Medicine [Greten, 1994] has recently recommended that aggressive cholesterol lowering therapy should be carried out in patients with established coronary heart disease. This holds even more for heart-transplant patients with primary hypercholesterolemia as the basic metabolic defect. The recommendation is that LDL cholesterol level should then be reduced to **100 mg/dl or lower**.

In most patients this goal may be attained by maximal dietary and drug therapy in combination with reduction of overweight and increased physical activity. It is, however, a general experience that there exists a group of patients left with CHD on the basis of severe hypercholesterolemia who in addition will require LDL apheresis to achieve the **therapeutic goal of LDL <100 mg/dl**.

2.2 Pathogenesis of Coronary Heart Disease

Atherosclerosis is a proliferative process of vessel wall cells (endothelial cells and smooth muscle cells) and

blood cells (monocyte-derived macrophages, and T-lymphocytes) adhering to the vessel wall. The process may lead to the formation of foam cells and to the production of a specific matrix with the risk of chronic or acute thrombotic occlusion.

The initial identification of the most important risk factors for cardiovascular disease was primarily brought about by pathophysiological observations. Thus, more than 80 years ago, Windaus [1910] was first to show that an atherosclerotic plaque contains enormous amounts of cholesterol. 25 years later, the Norwegian clinician Carl Müller [1938] described a familial form of hypercholesterolemia which is characterized by the combination of xanthomatas, high blood cholesterol and premature coronary sclerosis. The unique cause of this serious condition is a defective LDL receptor activity leading to massive elevation of LDL cholesterol in the blood stream of these patients. The pathophysiology of this disease is now well understood, it is designated as familial hypercholesterolemia (FH) or Type II hyperlipoproteinemia [Fredrickson et al., 1967].

Today, there is no doubt that the cholesterol of an atherosclerotic plaque is derived from the LDL particles. Increased LDL cholesterol is the only risk factor that can lead by itself to premature coronary sclerosis. Hypertension, cigarette smoking, elevated blood glucose, and overweight in many patients potentiate the risk derived from LDL and also in itself have an impact on early cardiovascular events. More recently, Lp(a), fibrinogen, and a biological modification of lipoproteins have been added to the list of important risk factors for mechanisms of atherosclerosis [Seidel et al., 1991; Koenig and Ernst, 1992; Ernst et al., 1992; Smith, 1986, 1990; Kienast et al., 1990; Esterbauer et al., 1990; Steinberg and Witztum 1990; for review see Seidel 1993].

As to Lp(a), this particular lipoprotein has a lipid composition almost identical to LDL but it carries - besides Apo B-100 - a second protein compound with great homology to plasminogen. The proteins are linked to each other by a disulfide bridge. Lp(a) has been identified as an independent risk factor, especially in younger ages (less than 60 years) and if LDL cholesterol is also elevated [Armstrong et al., 1990; Seidel et al., 1992]. 40% of the plasma level of Lp(a) is determined by a genetically regulated size polymorphism. Isoforms affect the rate of synthesis but not the FCR of Lp(a). Synthetic rates also seem to be affected by the Apo-A-IV gene and by growth hormones. The Apo(a) protein inhibits the Apo B mediated LDL receptor uptake of this lipoprotein and leads to an inhibition of the function of plasminogen by binding competition to endothelium cell receptors and fibrin. The particles have been identified in atherosclerotic plaques and they bind with high affinity to the atherosclerotic matrix.

Fibrinogen and its degradation products have become very important as postulated risk factors both in clinical research and in clinical practice over the last 10 years [Smith, 1986; Ernst, 1990].

High plasma fibrinogen concentrations lead to an increase in blood and plasma viscosity and provoke adhesion of erythrocytes and platelets to the endothelium. Fibrinogen is involved in erythrocyte and platelet aggregation, it strongly increases the procoagulate activity of monocyte/macrophages and provokes thrombus formation. Increased fibrinogen concentrations cause disordered endothelial permeability and increases vascular tone as does LDL. Fibrinogen and its degradation products can be regarded as growth factors, they increase pinocytosis of DNA synthesis in the endothelium, they cause cellular growth and cell migration, promote angiogenesis and smooth muscle cell collagen synthesis.

In heart transplant recipients plasma fibrinogen levels are significantly increased and show a close relationship to accelerated coronary sclerosis. Although fibrinogen is understood as acute phase protein, there is no correlation of fibrinogen with the C-reactive protein in these patients [Hunt et al., 1993].

In hypercholesterolemic patients the fractional catabolic rate of LDL in plasma is delayed. The extended circulation time favours the oxidation process of LDL, followed by the activation of blood and vessel wall cells, causing the atherogenicity of the particle.

Low density lipoproteins (LDL) develop after biological modification (oxidation) cytotoxic effects on the endothelium through induction and inhibition of cell mediators [Hessler et al., 1983]. They activate platelets, monocytes, and smooth muscle cells [Ross, 1993]. Platelet activation is followed by an increased platelet aggregation, increased stimulation by thrombin and disordered prostaglandin balance. LDL effects the vascular tone by inhibition of the endothelium derived relaxing factor (EDRF) and at the same time stimulates endothelin production. LDL stimulates synthesis and release of PDGF in almost all cells tested. However, PDGF expression in endothelial cells is inhibited by oxidized LDL, possibly leading to endothelial defects [Fox et al., 1987]. Oxidized LDL is taken up increasingly by macrophages and smooth muscle cells and leads to cholesterol storage in these cells. It has procoagulant effects and is antigenic causing formation of antibodies, immuncomplexes are formed and taken up by Fc receptors of macrophages. Oxidized LDL has chemotactic properties for circulating monocytes and leads to immobilization of tissue macrophages in the vascular wall. It provokes the expression of vascular cell adhesion molecules such as VCAM-1 and many others on monocytes and endothelial cells, and in the latter it also effects the expression of IL-1, IL-4, TNF-α, interferon-γ, and colony stimulating factor [Ross, 1993]. LDL particles, no doubt, are the most atherogenic particles of the blood stream, if present in abnormally high concentrations.

Most forms of primary hypercholesterolemia result from a defect in the removal of LDL from plasma by the liver. The structure of Apo B-100 and/or the LDL receptor activity are now recognized as the crucial elements in the control of LDL choles-

terol homeostasis [Brown and Goldstein, 1986; Seidel et al., 1985].

If the physiological clearing mechanisms for LDL are insufficient dietary and drug therapy alone are often ineffective. This holds true also for Lp(a) and fibrinogen, either of which at present can hardly be lowered by diet or drugs at all.

2.3 Treatment of Severe Hypercholesterolemia

Various radical measures for the treatment of severe hypercholesterolemia such as partial ileal bypass [Buchwald, 1964], portocaval shunt [Starzl et al., 1983], liver transplantation [Starzl et al., 1984], and plasma exchange [De Gennes et al., 1976; Thompson et al., 1975] have been tested in patients in whom drug and diet failed or were insufficient. Although effective, most of these treatments have severe side effects and are not routinely used.

Since plasma exchange requires substitution of plasma fractions with its inherent danger the first attempt to be more selective for LDL removal in an extracorporeal system was undertaken by Lupien et al. [1976]. Since then several LDL apheresis procedures with varying degrees of selectivity and efficiency have subsequently been developed, some of which have gained clinical distribution. With the experience gathered in the course of several years of clinical application, efficiency, and also of safety, the different LDL apheresis methods have been compared [Keller, 1991; Demant and Seidel, 1992]. Besides the marked reduction of LDL concentrations by all techniques it has become apparent that only the H.E.L.P. system results in an equally significant change in hemorheology because of its simultaneous removal of LDL, Lp(a), and fibrinogen.

Two other basic techniques have been established: the use of LDL immunoadsorption, using immobilized mono- or policlonal antibodies to apoprotein B100 [Stoffel and Demant, 1981; Riesen et al., 1986] and LDL binding by dextran sulphate attached to cellulose [Yokoyama et al., 1985]. Plasma membrane filtration has also been proposed, but this technique retains other macromolecules apart from LDL, such as high density lipoproteins, immunoglobulins and albumin and therefore cannot be considered as being specific. This technique closely resembles plasma exchange with all its disadvantages for longterm therapy.

The H.E.L.P. system was introduced in 1984 and has now been widely used.

The combination of H.E.L.P.-LDL-apheresis together with diet and the appropriate drugs now allows a maximal lowering of LDL-cholesterol up to 80%. This holds true also for patients who only a few years ago were classified as resistant to the treatment of hypercholesterolemia.

It now appears that the abnormal physiology of vascular spasm, lipid accumulation, and lesion rupture with thrombosis is quite dependent on the plasma lipoproteins and fibrinogen not only in the long run but also over a relatively short period of time.

The H.E.L.P. therapy improves blood flow physiology more than does lipid management alone and its effect is not limited to the target vessel as it is with angioplasty. Coronary sclerosis, coronary and cerebral flow reserve as well as work capacity on exercise testing improves substantially after initiation of the H.E.L.P.-therapy and remains for a long period of time. A reduction of non fatal cardiovascular events and mortality although generally difficult to demonstrate is - on the basis of accumulated clinical data with the H.E.L.P.-system during the past ten years - now quite obvious.

This report focusses on the H.E.L.P. system as a new therapeutic tool.

3. The H.E.L.P.-System, a New Therapeutic Tool in the Treatment of Atherosclerosis

3.1 The H.E.L.P.-Apheresis System

The name H.E.L.P. stands for
Heparin-mediated
Extracorporeal
Low-density Lipoprotein
Precipitation.

The technique operates by an increase in the positive charges on LDL and Lp(a) particles at low pH (5.12), allowing them to specifically form a network with heparin and fibrinogen in the absence of divalent cations [Seidel and Wieland, 1982; Armstrong, 1987; Seidel, 1990]. Only a limited number of other heparin-binding plasma proteins are coprecipitated by heparin at low pH. Proteins such as apo A, albumin or immunoglobulins do not significantly bind to heparin at low pH and are not precipitated in the system [Eisenhauer et al., 1987; Armstrong, 1987]. Complement activation takes place in all extracorporeal therapy systems. However, as a specific feature of the H.E.L.P.-system, activated complement C 3, C 4 as well as the terminal complement complex are largely adsorbed to the precipitation filter, resulting in plasma concentrations which are actually below those measured before apheresis [Würzner et al., 1991]. Leucocytopenia, a hallmark of complement activation, has not been observed under H.E.L.P. therapy [Eisenhauer et al., 1987; Seidel and Thiery, 1993].

The H.E.L.P-System has Unique Features:

1. It removes LDL, Lp(a) and fibrinogen with high efficiency.
2. It does not remove HDL.
3. It does not alter or modify plasma lipoproteins.
4. It does not change plasma concentrations of cell mediators.
5. It avoids the use of compounds with immunogenic or immunostimulatory activity.
6. It uses only disposable material and avoids regeneration of any of the used elements.
7. It is a technically safe and well standardized procedure.
8. In short and long-term treatment, tolerance and benefit are excellent.
9. Its clinical utility has been established by the outcome of controlled clinical trials.

The major steps of the H.E.L.P. system to remove the atherogenic compounds are illustrated in the flow sheet (see Figure 1).

In the first step, plasma is obtained by filtration of whole blood through a plasma separator. This is then mixed continuously with a 0.3 M acetate buffer of pH 4.85 containing 100 IU heparin/ml. The sudden precipitation occurs at a pH of 5.12, and the suspension is circulated through a 0.4 µm polycarbonate filter to remove the precipitated LDL, Lp(a) and fibrinogen.

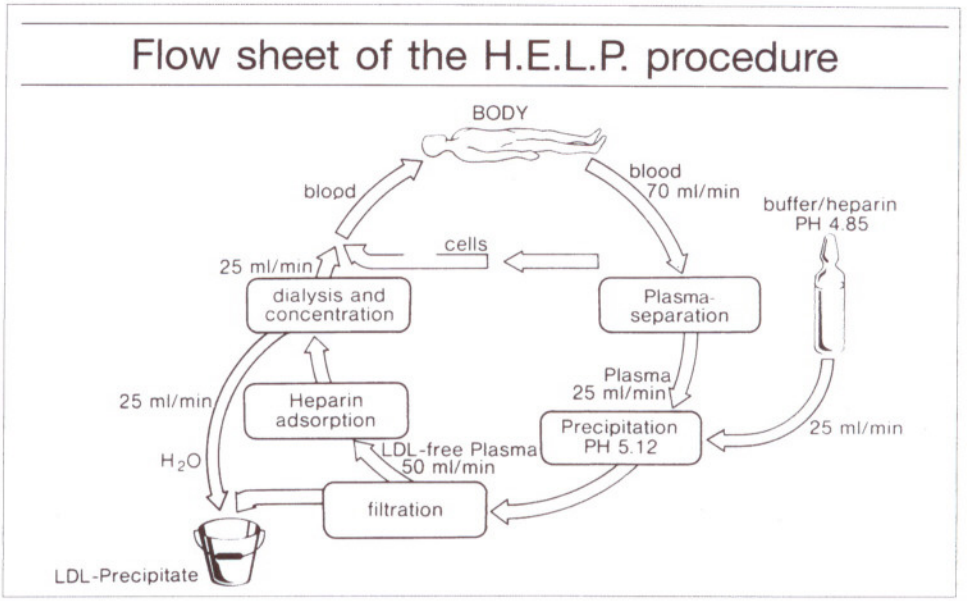

Fig. 1: Flow sheet of H.E.L.P. procedure. 2.8 to 3 l plasma are treated in one session, lasting about 2 hours.

Excess heparin is adsorbed by passage through an anion-exchange column which binds only heparin at the given pH. The plasma buffer mixture is finally subjected to a bicarbonate dialysis and ultrafiltration to remove excess fluid and to restore the physiological pH, before the plasma is mixed with the blood cells and returned to the patient. All filters and tubings required for the treatment are sterile, disposable and are intended for single use only. This makes it easy and reliable to work with the system and guarantees a steady quality for each treatment, independent of the clinic performing the procedure. Safety is assured by a visual display and two microprocessors operating in parallel (see Figure 2). Due to the excellent tolerance of the procedure the patients leave the hospital shortly after the end of the treatment session.

3.2 Clinical Experience With the H.E.L.P.-System

The clinical experience with the H.E.L.P. system goes back to 1984. Since then and up to 1994, approximately 380 patients were treated in over 40.000 single treatments. Some patients are treated for more than 8 years. Currently, the system operates in approximately 65 centers in Germany, Austria, Italy, Ireland and USA.

The efficiency of the system is 100 percent for the elimination of LDL, Lp(a) and fibrinogen. Per single treatment (lasting 1.5 to 2 hours), 2.8 to

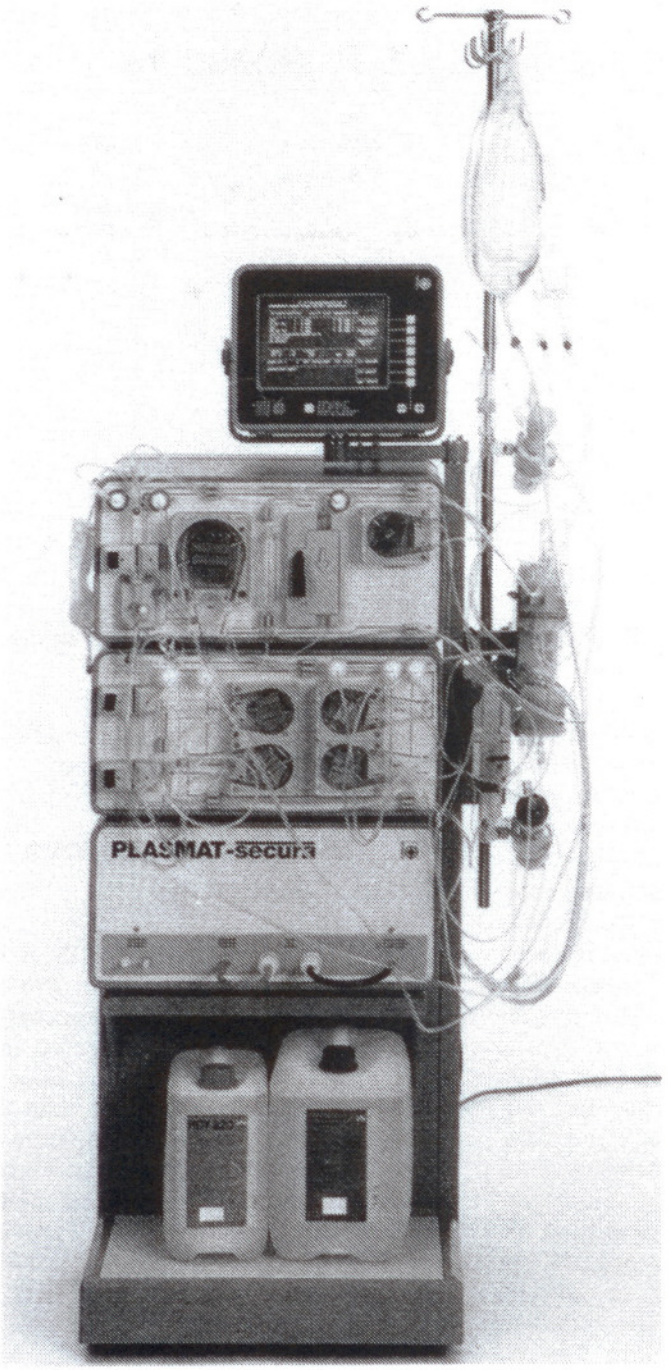

Fig. 2: The PLASMAT-SECURA® (Braun - Melsungen) for the performance of the H.E.L.P.-procedure.

Table 1: Long-term effects of the H.E.L.P.-treatment.

	Mean interval values of approximately 6000 treatments		
LDL cholesterol	- 51 %	±	14
Lp(a)	- 45 %	±	5
Fibrinogen	- 46 %	±	15
Apoprotein B-100	- 45 %	±	10
HDL cholesterol	+ 12 %	±	2
Apoprotein A-1	+ 9 %	±	2

three litres of plasma are treated, causing an actual reduction of approximately 65-70 percent of these three compounds in plasma of the treated patients.

The rates of return to pre-apheresis concentrations for LDL differ between normocholesterolemics and heterozygous as well as homozygous FH patients, while they are almost identical for Lp(a) [Armstrong et al., 1989; Thiery et al., 1990]. Normocholesterolemics return rather quickly towards the steady-state pretreatment levels. Heterozygous FH patients display a rate of return intermediate between normocholesterolemics and a homozygous FH patient, the latter being slowest in their rate of return to pretreatment LDL concentrations. In biweekly treatment intervals the pretreatment values usually reach a new steady state after four to eight treatments.

Long-term effects of the H.E.L.P. treatment based on interval concentrations between two treatments (c after H.E.L.P. + c before H.E.L.P. :2) and expressed as percentage of plasma levels at the start are shown in Table 1.

Of particular clinical relevance is the considerable effect that H.E.L.P. treatment has on blood rheological parameters, which are especially important in coronary heart disease. H.E.L.P. treatment reduces plasma viscosity by 15% and erythrocyte aggregation by 50%, while erythrocyte filtrability rises by 15% and tissue partial pressure of oxygen by 20 to 30%. It has been shown that the changes in plasma viscosity and erythrocyte aggregation are brought about by the reduction of both, plasma fibrinogen and LDL.

Changes in blood viscosity leads to an improvement equivalent to an 8% reduction of the haematocrit, of course without changing the latter. It seems likely that the rapid improvement in clinical symptoms associated with coronary heart disease in treated patients, shown by a decrease in angina attacks and improvement in myocardial stress ability, is primarily related to improved rheology and in addition, possibly to a positive influence on endothelium function.

3.3 Clinical Utility of the H.E.L.P. Treatment

The first coronary angiograms two years after H.E.L.P. treatment in over

50 patients of the H.E.L.P. multicenter study [Schuff-Werner et al., 1994] lend support to the hope that the regression of coronary heart disease is possible in humans.

In this study angiograms obtained before and after two years of regular treatment were evaluated blindly using the CAAS-system. The rate of regression was 1.8 times the rate of progression for the period of two years (Fig. 3). This factor is independent of the cut-off value used to define significance of changes.

In the H.E.L.P. multicenter study only 15% of the coronary lesions progressed on the basis of an 8% detection limit for the significance to estimate the change.

Another small study of seven patients with heterozygous familial hypercholesterolemia also revealed evidence that H.E.L.P.-LDL-apheresis administered once a week for 7 to 24 months induced regression of carotid atherosclerotic plaques [Hennerici et al., 1991]. In this study, plaques were evaluated by a three-dimensional reconstruction of ultrasound images. Out of 21 observed plaques only one progressed, 12 did not change and eight regressed within 6 to 12 months.

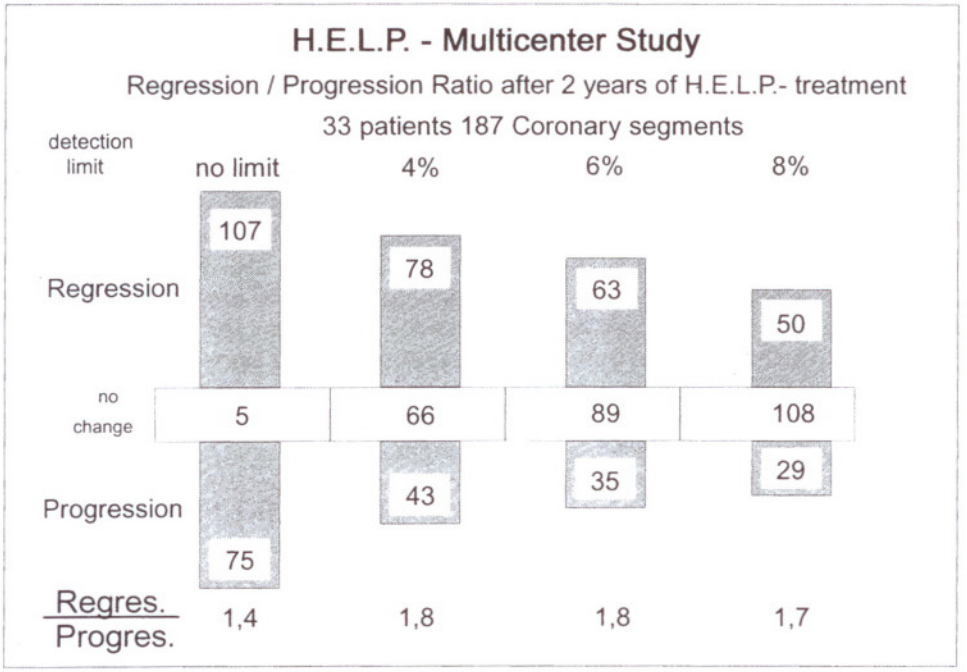

Fig. 3: Effect of H.E.L.P. treatment on coronary heart disease in the 2-year H.E.L.P. multicenter study.
There is a significant trend to regression over progression of coronary stenosis irrespective of the detection limit of coronary angiographical assessment.

Similar results as in these two clinical studies have not been achieved in any other intervention study monitored by coronary angiography, but are in agreement with trends of the reports by Hombach et al. [1986], Brensike et al. [1984], Brown et al. [1990], Kane et al. [1990], Gohlke [1991], Blankenhorn and Hodis [1994], and Law et al. [1994].

Figure 4 indicates the myocardial infarction incidence in a high risk coronary heart disease patient group (n=180) which was followed by history for 10 years before undergoing H.E.L.P. therapy. On an average, 4.5 myocardial infarctions (MI) per year and 16 in the preceding 2 years before the H.E.L.P. treatment were recorded. Immediately after the start of the H.E.L.P. treatment the MI-incidence fell to 3 per 2 years and to 1.5 for following 4 years after start of treatment.

The prompt reduction of MI incidence of high risk patients following the H.E.L.P.-therapy, substantially testifies to the clinical efficiency of this

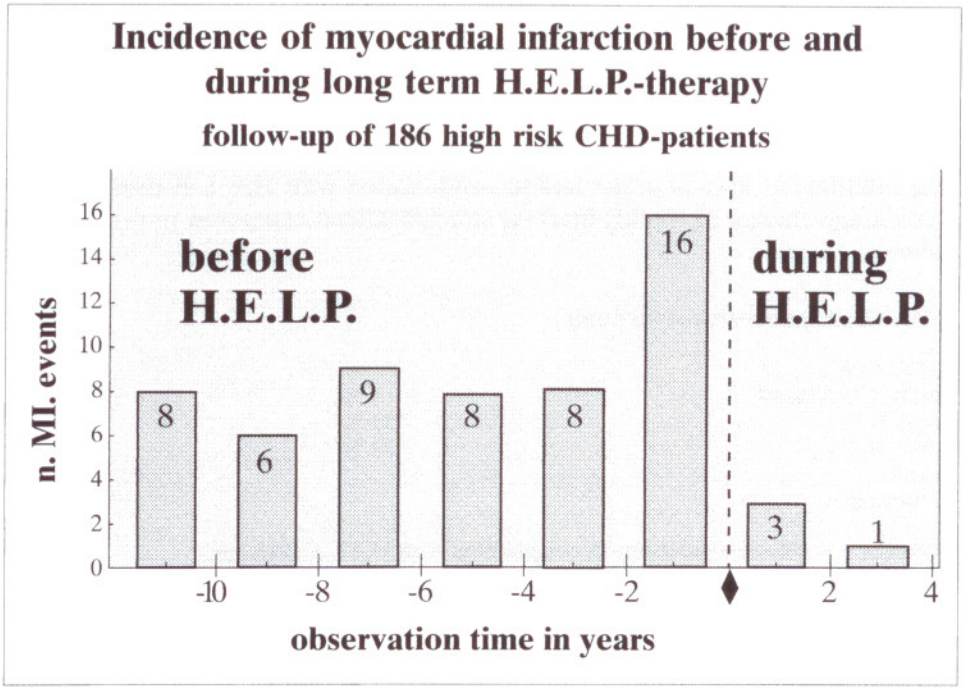

Fig. 4: Effect of long-term H.E.L.P. treatment on the incidence of myocardial infarction.
There is a significant reduction from 4.5 myocardial infarctions / year preceding the H.E.L.P.-therapy to 1.5 / year after two, and to 0.5 / year after four years of continuated H.E.L.P. therapy.

treatment. Its clinical utility and benefit to the patient is further substantiated by the number of deaths due to heart disease in the total group of patients treated with H.E.L.P. until 1993. Up to this date 350 high risk patients for coronary heart disease were treated over 9.3 months. During this period there were 15 deaths due to heart disease recorded, equivalent to 1 death for every 52 years of treatment. Comparable data from other intervention studies are not available.

Our results clearly demonstrate that regular H.E.L.P. treatment favorably influences the progression of coronary artery disease, decreases the incidence of coronary events, and prolongs survival time of CHD-patients.

3.4 Maximal Treatment of Hypercholesterolemia in CHD-Patients: Experience With Combined H.E.L.P. and HMG-CoA Reductase Inhibitor Therapy

J. Thiery

In cases with plasma cholesterol levels exceeding 300 mg/dl, the use of specific diets and drugs may not be sufficient if LDL concentrations <110 mg/dl and/or regression of CHD are aimed at as a means of secondary intervention.

HMG-CoA reductase inhibitors were not available when the H.E.L.P.

Table 2: Long-term effects of 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitor treatment alone and in combination with H.E.L.P.-therapy. Percentage change of weekly interval concentrations compared to the baseline values.

HMG-CoA reductase inhibitor only		
LDL Cholesterol	- 38 %	± 12
HDL Cholesterol	+ 10 %	± 9
Apo B	- 30 %	± 9
Apo A-1	+ 13 %	± 4
Lp(a)		no change
Fibrinogen		no change
HMG-CoA reductase inhibitor in combination with H.E.L.P. therapy		
		Mean interval values of approximately 1400 treatments
LDL Cholesterol	- 69 %	± 12
HDL Cholesterol	+ 14 %	± 6
Apo B	- 53 %	± 8
Apo A-1	+ 12 %	± 9
Lp(a)	- 43 %	± 7
Fibrinogen	- 44 %	± 10

multicenter study was started. In the meantime we and others have investigated the efficacy of a combined therapy, using HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin) together with H.E.L.P. apheresis [Thiery, 1988].

These compounds significantly decrease the rate of return after H.E.L.P. apheresis in both heterozygous and homozygous FH patients by 20 to 30 percent [Seidel, 1990; Armstrong et al., 1989; Thiery et al., 1990]. When the two treatments are combined, a reduction of the interval LDL-C level of 70 percent and more may be achieved while Lp(a) and fibrinogen are not further affected over the effect by the H.E.L.P. treatment alone (see Table 2). In the combined form, therapy intervals between two H.E.L.P. treatments may, in many cases, be extended from seven to 14 days, depending on the synthetic rates for LDL or the severity of CHD. The combination of both therapies is well tolerated.

3.4.1 Case 1: Premature Coronary Heart Disease, Strongly Elevated LDL and Lp(a) Plasma Concentrations

A typical follow-up kinetic for LDL and Lipoprotein(a) under H.E.L.P.-treatment of a patient with severe progressive coronary heart disease is shown in Figure 5 (see page 20).

At the start of our therapy the 33 year old MI patient had a history of coronary bypass and PTCA treatment. He showed LDL cholesterol levels of 350 mg/dl and a marked Lp(a) elevation of 165 mg/dl.

LDL cholesterol could be lowered with an HMG-CoA reductase inhibitor (simvastatin) by about 48 percent to 170 mg/dl, but no effect on lipoprotein(a) levels was observed.

In the combination with regular H.E.L.P. treatment we were able to maintain LDL-concentration at an interval value of about 100 mg/dl. In addition, H.E.L.P. treatment resulted in a marked decrease of post-apheresis lipoprotein(a) concentrations. The interval Lp(a) levels maintained about 60 mg/dl. Fibrinogen was lowered from a baseline value of 317 mg/dl to a H.E.L.P. interval value of 177 mg/dl, which is equivalent to a 44 % reduction. A control angiography after 3 years revealed that the combined treatment was able to stop the very progressive coronary heart disease, which was developing in the patient prior to the treatment. In addition, PTCA results before H.E.L.P. therapy were well maintained after 4 years of treatment.

3.4.2 Case 2: Homozygous Form of Hypercholesterolemia

Early death from cardiac consequences of premature coronary sclerosis and aortic stenoses is the usual outcome of homozygous familial hypercholesterolemia [Goldstein and Brown, 1983]. Inherited as an autosomal dominant defect of the LDL-receptor gene, this disease is character-

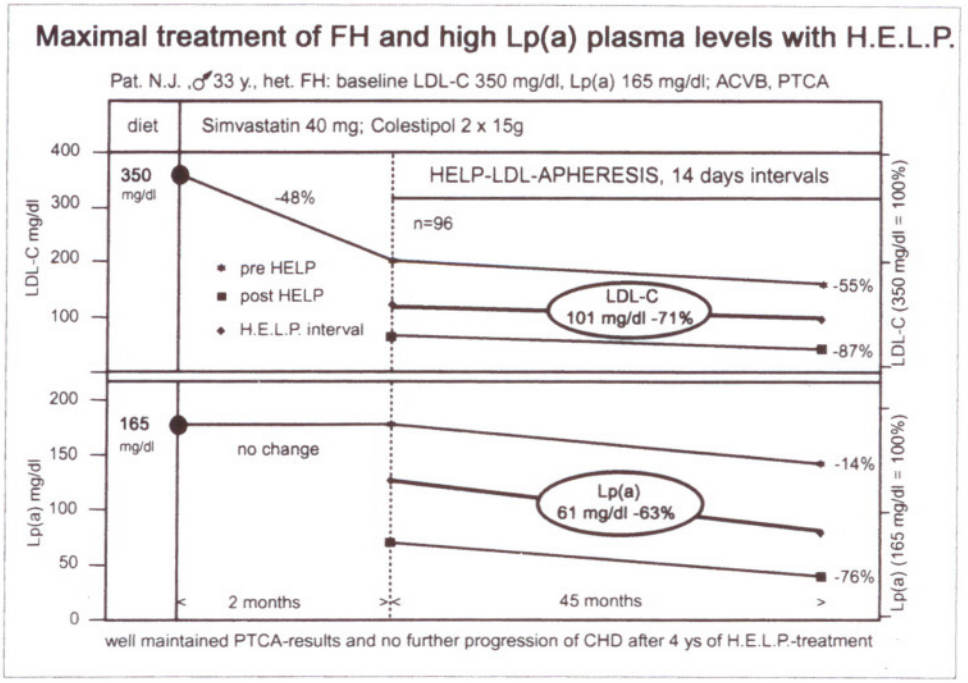

Fig. 5: Effects of H.E.L.P. treatment in combination with simvastatin and colestipol on plasma LDL-cholesterol and Lp(a) concentrations in a CHD patient with heterozygous familial hypercholesterolemia and high Lp(a) levels.
H.E.L.P. treatment started two months after conventional lipid lowering therapy.
Values represent the mean of pre-, post-, and interval-H.E.L.P. -LDL resp. Lp(a) concentrations of 45 months combined plasma therapy.

ized by very high plasma LDL-cholesterol concentrations (between 600 and 1000 mg/dl) and the development of severe cutaneous and tendon xanthomata in childhood. All conventional lipid lowering treatments with diet and medication are completely insufficient.

Since 1985 we have been following and treating an FHH patient, born in 1979, with the H.E.L.P.-apheresis procedure [Thiery et al., 1990]. LDL-cholesterol concentrations before the start of treatment exceeded 800 mg/dl. The follow-up of LDL concentrations under the H.E.L.P.-treatment alone and in combination with lovastatin and regular cholestyramine is shown in Figure 6.

The girl was treated for two years by a weekly H.E.L.P.-apheresis. Under this procedure the LDL-C interval levels were maintained below 280 mg/dl. At this time a rapid regression

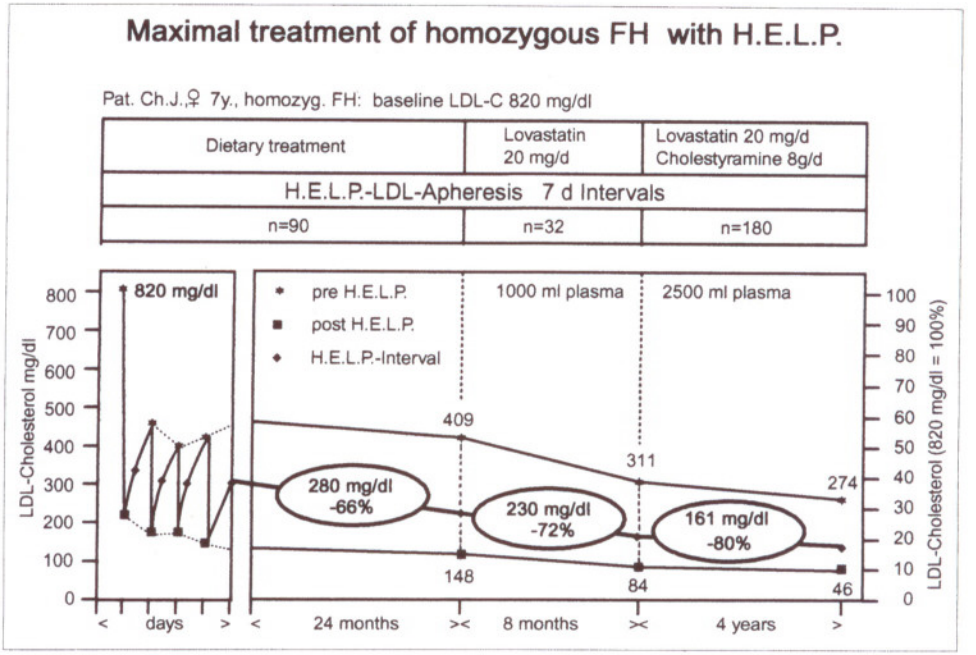

Fig. 6: Effect of H.E.L.P. treatment in a child with homozygous familial hypercholesterolemia. Values represent the mean of pre-, post- and weekly H.E.L.P. interval. LDL-concentrations of H.E.L.P. treatment alone and in combination with lovastatin and cholestyramine.

of multiple xanthomata could be observed. With additional medication of lovastatin and cholestyramine a further LDL decrease to 180 mg/dl could be achieved. The treated plasma volume could be recently enhanced from 1.5 to 2.5 liters. This has now resulted in a mean LDL-cholesterol level of 160 mg/dl, which is equivalent to a decrease of 80 percent as compared to pretreatment values. The therapy is excellently tolerated. The girl is well and shows normal growth and development (Fig. 7). No signs of cardiovascular symptoms have been noted as yet.

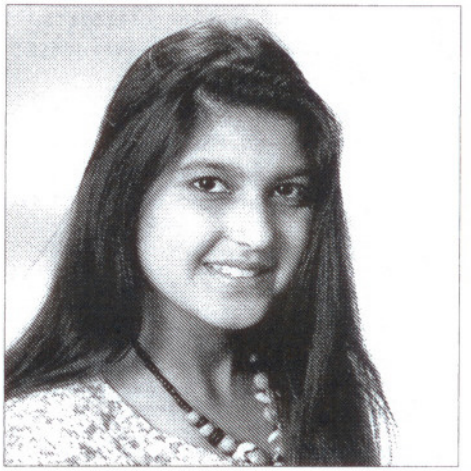

Fig. 7: The now 15 years old FHH patient, who is under regular H.E.L.P.-treatment for the last 8 years.

3.5 Maximal Treatment of Hypercholesterolemia in Coronary Bypass Patients: First Results From the Proceeding Munich Coronary Bypass Intervention Trial, The MCBIT-Study

J. Thiery

The Munich Coronary Bypass Intervention Trial is a controlled five year study to evaluate the effects of cholesterol lowering therapy with or without an antioxidative agent in patients after bypass operation. 600 bypass patients are recruited over two years and randomized into three treatment groups:

Group I: Lovastatin, dosage according to LDL-C levels; if required: H.E.L.P.-therapy

Group II: Treatment of LDL-C as in Group I plus Vitamin E, 800 I.U./day;

Group III: no recommendation for therapy, the decision is left to the family doctor (good general practice).

The LDL-C in groups I and II is adjusted to a level between 60-110 mg/dl. Patients with insufficient response to lovastatin are treated with extracorporeal LDL-apheresis (H.E.L.P.). Control angiographies and stress ECGs are performed 4 weeks and 2 and 5 years after surgery. Angiograms are evaluated using a computer based quantitative method. During the first 20 months of the study 440 patients were included. In four patients additional H.E.L.P.-apheresis is performed because LDL-cholesterol concentrations could not be lowered below 135 mg/dl by lovastatin treatment alone (Tab. 3).

Table 3: MCBIT-Study: Plasma LDL-cholesterol, plasma α-tocopherol, and LDL-lag-phase at baseline and after 6 months of therapy (means and standard deviation).

	Baseline			6 months therapy		
	LDL-C mg/dl	Vit.E µg	lag-phase min	LDL-C mg/dl	Vit.E µg	lag-phase min
Group I	150 ± 37	6.5 ± 2	95 ± 32	111 ± 33	6.8 ± 3	113 ± 24
Group II	153 ± 41	6.6 ± 3	92 ± 32	112 ± 28	16.0 ± 7	202 ± 46
Group III	148 ± 39	6.3 ± 2	97 ± 27	149 ± 32	6.7 ± 2	116 ± 39

3.6 The Application of the H.E.L.P.-System in the Treatment of Heart Transplant Patients

J. Thiery, Brandl U, Meiser B, Wenke K, and B. Reichart

The major cause of morbidity and mortality in heart transplant recipients after their first post-operative year is accelerated coronary sclerosis [Schroeder and Hunt, 1987]. Graft atherosclerosis is a proliferative disease of the arterial intima with fast progression. The pathogenesis of the disease is uncertain, but three main factors involved are:

1) Multiple rejection episodes of the graft with infiltration of T-Lymphocytes into the intima,

2) plasma fibrinogen, which is chemotactic for smooth muscle cells and increases smooth muscle cell proliferation. High plasma fibrinogen levels also increase blood and plasma viscosity significantly as well as erythrocyte aggregation. This may have a significant impact on hemorheology and microcirculation in the graft tissue.

3) Plasma LDL-cholesterol, which induces the development of atheromas with accumulation of monocyte derived foam cells [Ross, 1993].

Both risk factors, hypercholesterolemia and hyperfibrinogenemia show a very high prevalence in heart transplant recipients [Barbir et al., 1991; Eich et al., 1991; Kubo et al., 1992; Hunt et al, 1993]. Also, approximately 30% of the heart transplant patients develop elevated lipoprotein(a), possibly caused by the immune-suppressive therapy. Lipoprotein(a) is known as an independent risk factor for coronary heart disease and could enhance the risk for graft vessel disease, particularly if plasma fibrinogen is also increased.

On the basis of our present knowledge we therefore started in 1992 a pilot 'intention to treat' study with heart transplanted patients and severe hypercholesterolemia and/or markedly elevated plasma fibrinogen concentrations.

The goals of this proceeding study in heart transplant recipients are the prevention of graft vessel disease at an early stage after transplantation and the regression of pre-existing coronary lesions by drastically lowering plasma fibrinogen, lipoprotein(a), and LDL-cholesterol levels.

The inclusion criteria for this study are elevated plasma LDL-cholesterol concentrations (>135 mg/dl under drug treatment) and/or plasma fibrinogen concentrations above 400 mg/dl.

In one group of patients treatment is started directly after heart transplantation, in a second group H.E.L.P. treatment is started only after graft vessel disease has already developed. Up to now, 11 patients are enrolled in the study, three patients are treated for more than two years. In all patients, treatment with simvastatin (5-20 mg/day) was not sufficient to lower hypercholesterolemia to the desired LDL-cholesterol level of less than 135 mg/dl. A higher dosage of HMG-CoA reductase inhibitors increases the risk of adverse events and interactions with the immune suppressive therapy and was therefore not applied to the patients.

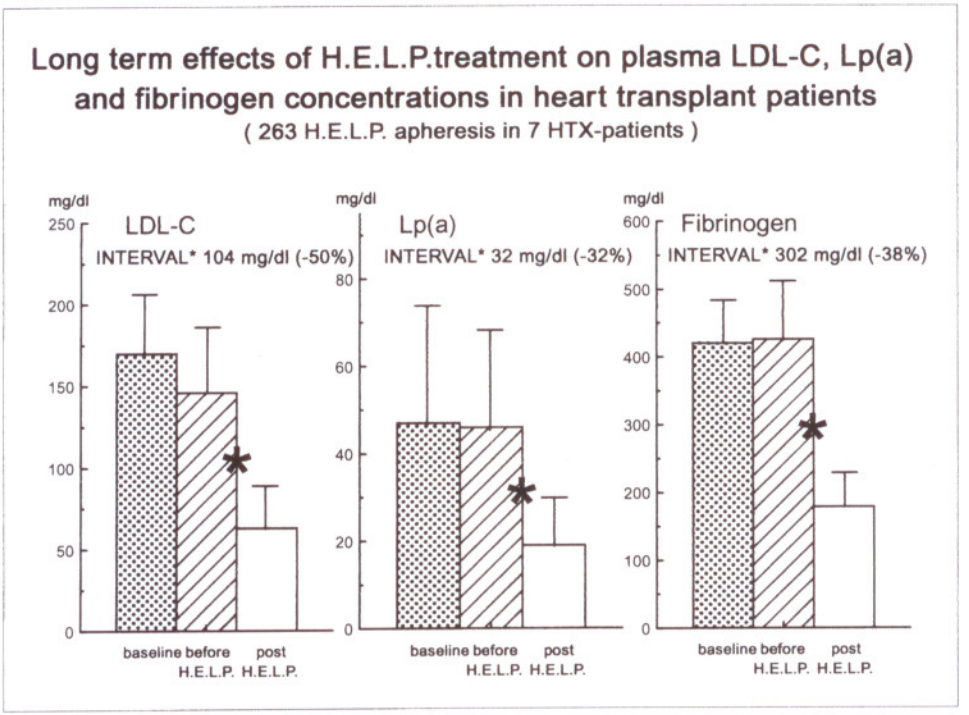

Fig. 8: Effects of H.E.L.P. treatment on LDL-cholesterol, Lp(a) and plasma fibrinogen concentrations.
The interval values between two treatments are indicated with stars. Values represent means ± SD concentrations at baseline, before and post H.E.L.P. apheresis.

So far, H.E.L.P. therapy (n=263 treatments) was excellently tolerated in all HTX-patients. In general the treatment was performed every one to two weeks. Mean LDL-concentrations could be lowered from 147 mg/dl before to 72 mg/dl directly after apheresis. Plasma fibrinogen was lowered from 426 mg/dl (mean) to 150 mg/dl (mean). As compared to the baseline value, the mean interval LDL-cholesterol was reduced by 50%, plasma fibrinogen by 38%, Lp(a) by 32% (Fig. 8).

In some, not all of the patients, multiple episodes lasting up to two months of high plasma fibrinogen levels before the H.E.L.P.-treatment were observed. This may enhance the risk for coronary sclerosis in these patients (Fig. 9).

H.E.L.P. treatment revealed no acute or chronic changes of the plasma levels of different cytokines and cytokine receptors: interleukin-6, interleukin-2 receptor, interferon-γ, TNF-α, and TNF-receptors (Tab. 4).

Special attention was given to the tolerance and pharmacokinetics on both, simvastatin and cyclosporine A

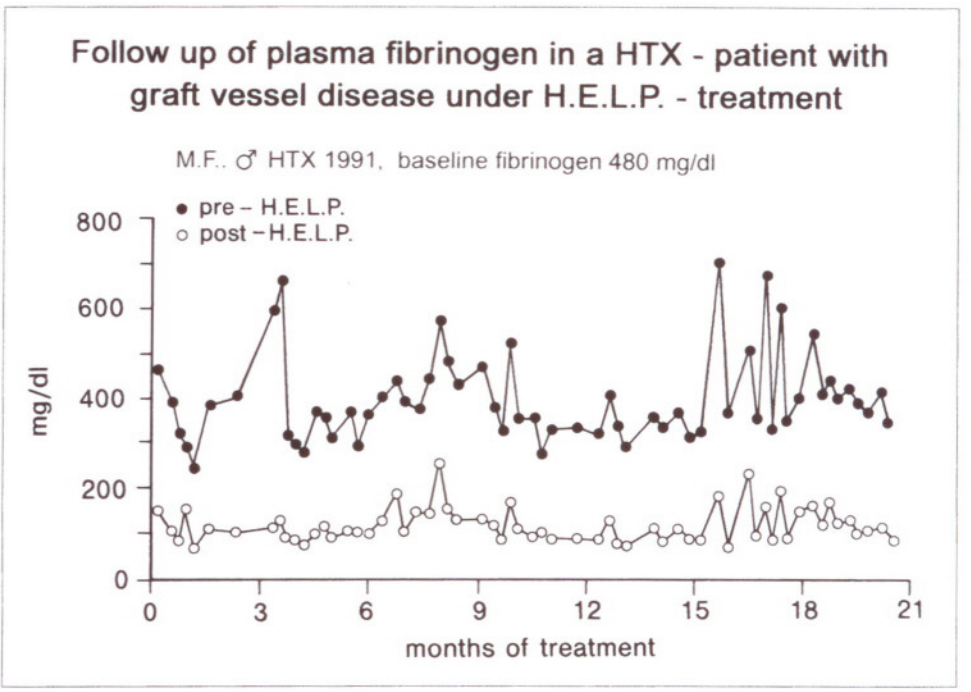

Fig. 9: Effect of H.E.L.P. treatment on plasma fibrinogen levels in an HTX patient with graft vessel disease and episodes of increased of plasma fibrinogen.

Table 4: H.E.L.P. treatment in heart transplant patients and effects on serum cytokine levels (n=45 H.E.L.P. treatments in 7 HTX-patients).

		pre-H.E.L.P. mean ± SD	post-H.E.L.P mean ± SD
Interleukin - 6	pg/ml	13 ± 7	14 ± 5
Interleukin-2-receptor	U/ml	354 ± 196	323 ± 192
TNF	pg/ml	13 ± 5	14 ± 6
TNF - receptor 55	ng/ml	4.1 ± 1.4	6 ± 1.7
TNF - receptor 75	ng/ml	6.4 ± 2.1	7.6 ± 3.2
Interferon gamma	U/ml	0.1 ± 0.01	0.1 ± 0.01

p=n.s.

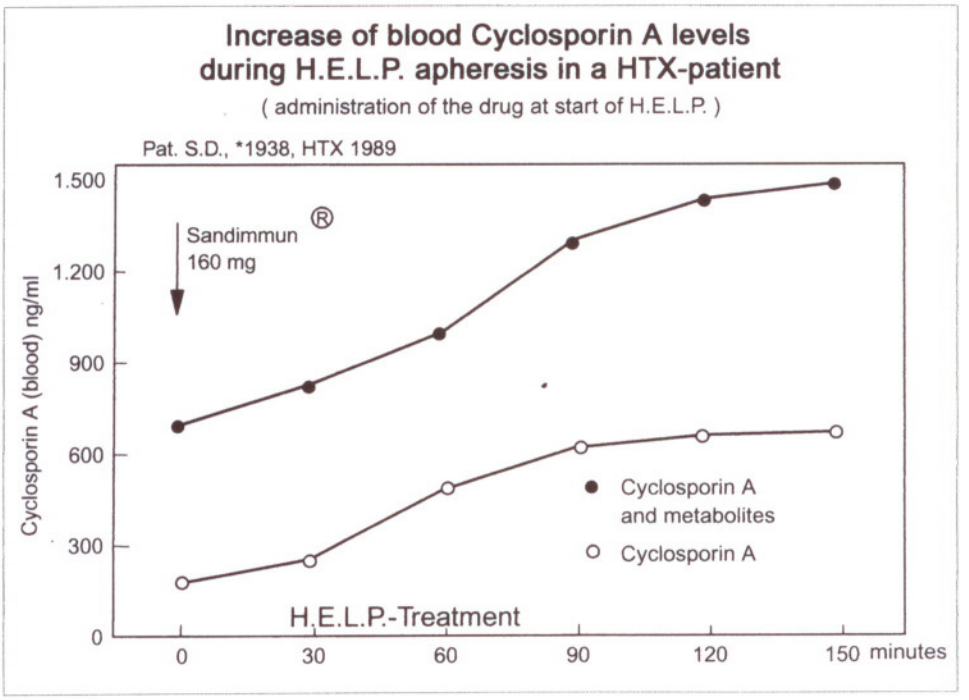

Fig. 10: Regular increase of blood cyclosporin A levels under H.E.L.P. treatment. The desired blood levels of the drug and their metabolites are not affected by H.E.L.P. apheresis.

in the transplant patients. Blood cyclosporine A levels (drug and metabolites) were not significantly affected by the H.E.L.P. procedure. Although a small amount of plasma cyclosporine A, binds to LDL (less than 5% of the plasma level), and is eliminated together with LDL. However, this did not effect the therapeutic blood levels, nor did it influence the adsorption kinetics of the drug (Fig. 10).

No signs of myopathias were observed, no accumulation of simvastatin blood levels were noted.

From our first clinical experiences with heart transplant recipients with severe hypercholesterolemia, the additional therapy with H.E.L.P.-LDL-apheresis seems to be a helpful tool to achieve long lasting benefit from the transplantation. The long-term effects of H.E.L.P.-treatment on the progression of graft vessel disease still remains to be elucidated. However, in only two of our 11 high risk patients, graft vessel disease developed under the H.E.L.P.-treatment. Six patients showed no progression of their preexisting coronary disease nor did a graft vessel disease develop. Three patients even showed regression of their coronary heart disease. The most impressive benefit of the treatment was achieved in one HTX patient (operat-

ed 1983) whose progressive graft vessel disease improved under the H.E.L.P.-treatment to an extent that re-transplantation could be avoided.

A similar observation was made by Park (see page below) who demonstrated regression of pre-existing atherosclerosis in a heart transplant recipient with graft vessel disease by regular H.E.L.P. treatment.

We hope that further annual evaluations by angiography of the H.E.L.P. treated HTX-patients will provide a rationale for a drastic LDL, Lp(a), and fibrinogen lowering therapy in the prevention of graft atherosclerosis in heart transplant recipients.

3.6.1 Regression of Transplant Coronary Artery Disease During Chronic H.E.L.P.-Apheresis: A Case Report

Jai-Wun Park, M.D.

Despite the lack of understanding of the pathogenesis of transplant coronary artery disease, immune mechanisms may be primary and triggering stimuli in the early post-transplant phase [Hosenpud et al., 1992]. In the long-term phase, however, classical risk factors like hyperlipidemia and obesity may accelerate the progression of the disease [Winters et al., 1990].

This report concerns a heart-transplant patient with familial hypercholesterolemia who showed rapid development of a severe transplant coronary artery disease and in whom a significant regression occurred during chronic H.E.L.P.-apheresis.

The first coronary angiogram was performed six months after operation [1991]. Three serial angiograms followed on a yearly basis. To obtain reproducible QCA (Quantitative Coronary Angiography)- data, all angiograms were performed following exactly the same procedural protocol. The assessment of the 1992 and 1993 angiograms revealed so dramatic a progression of the transplant coronary artery disease that an additional treatment with H.E.L.P. on a weekly basis was given.

The lipid profile before introduction of chronic H.E.L.P.-apheresis was as follows: Cholesterol 258-397 mg/dl, LDL 174-286 mg/dl, HDL 45-59 mg/dl, Triglycerides 124-198 mg/dl, Lp(a) 138 mg/dl. The lipid lowering therapy consisted of an intensified diet and 10 mg pravastatine per day. During 12 months H.E.L.P.-therapy the mean LDL interval value (LDL before and following therapy divided by two) was 137 mg/dl, the mean Lp(a) interval value 53 mg/dl, and the mean fibrinogen interval value 192 mg/dl.

The QCA analyses of four serial angiograms (Fig. 11) clearly demonstrated that in the first 2.5 years following surgery there was a rapid simultaneous progression in both the transplant coronary artery disease, involving the entire coronary system, and the development of the segmental stenotic lesion. Drastic reduction of the serum LDL, Lp(a), and fibrinogen levels by means of a year's treatment of weekly H.E.L.P.-apheresis halted further progression in the decrease of coronary diameter throughout the whole of the coronary system and brought about the marked regression of segmental obstructive lesions.

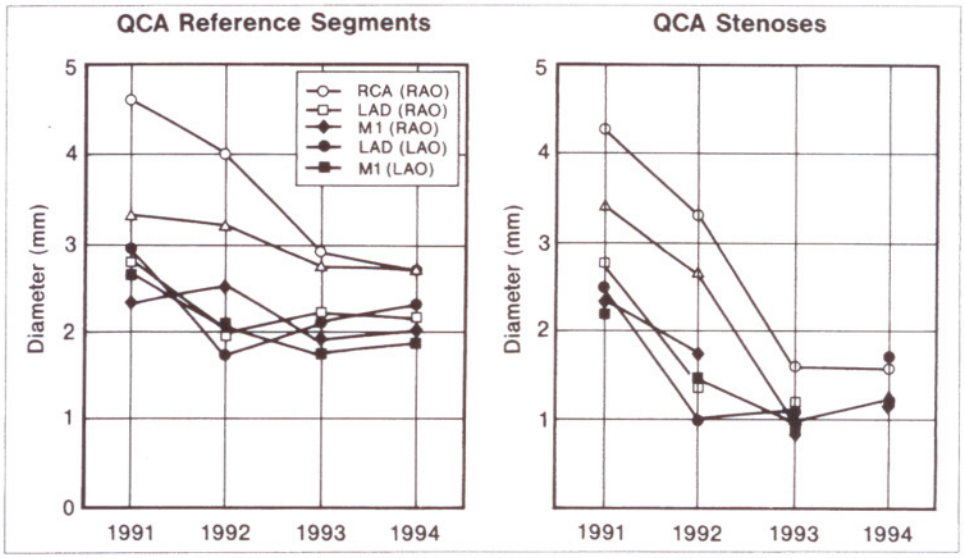

Fig. 11: Effects of H.E.L.P. treatment in an HTX-patient with graft vessel disease. After two years of treatment a significant increase of lumen diameter in stenosed coronary segments was to observe.

Thus, in transplant coronary artery disease patients with familial hypercholesterolemia, chronic H.E.L.P.-apheresis can prevent further progression of luminal narrowing within the whole coronary system and bring about marked regression in the stenotic lesions, even in advanced cases.

3.7 Heparin-Induced Extracorporeal Low-Density Lipoprotein Plasmapheresis in Hypercholesterolemic Dialysis Patients

Th. Bosch

Many patients with end-stage renal disease suffer from hyper- and dyslipidemia. This condition was correlated with the significantly increased cardiovascular mortality in dialysis patients as compared to the normal population. Moreover, as the fraction of geriatric and diabetic patients in the dialysis population increases, peripheral artery disease with claudication and gangrene becomes a serious problem in long-term maintenance dialysis. The predominant disturbance of lipoprotein metabolism in renal insufficiency is hypertriglyceridemia, but up to about 20% of patients are hypercholesterolemic. Moreover, a significant number of dialysis patients shows fibrinogen levels that are in the upper range of normal or elevated. However, conservative antilipidemic treatment with exercise, diet and drugs is impaired by dietary restrictions due to

renal failure, cumulation of drugs with renal metabolism and partly unsatisfactory effects.

Therefore, H.E.L.P. apheresis was applied to ESRD patients suffering from hypercholesterolemia [Bosch et al., 1990]. The treatment of about one patient plasma volume resulted in the following acute reductions: LDL-cholesterol 65%, VLDL-cholesterol 38%, total cholesterol 60%, triglycerides 32%, fibrinogen 61%, total protein 16%, albumin 22%, whole blood viscosity 22%. Hematocrit decreased by 8% due to hemodilution. Treating the patients at weekly intervals, long-term HDL-cholesterol increased by 15%. Thus, the efficacy of H.E.L.P. apheresis in dialysis patients was comparable to the results obtained in patients with normal renal function.

However, treating dialysis patients by apheresis is associated with two problems: first, patients that are treated by three hemodialysis sessions per week have to present for a fourth extracorporeal treatment in their center; second, due to the positive fluid balance associated with apheresis, this treatment can only be performed in the short dialysis interval and there is the potential risk of overhydration (cave pulmonary edema and hypertension!).

In order to overcome these problems, new hardware was developed (Plasmat U, Braun Melsungen, Germany) by means of which H.E.L.P. apheresis and hemodialysis can be performed synchronously. Blood is withdrawn from the av-fistula at a flow rate of 250 ml/min; while 200 ml/min are passed directly through the dialyzer, 50 ml/min are fed into the plasma separator and processed in the same way as in conventional H.E.L.P. apheresis. The LDL-depleted plasma is reunited with whole blood at the dialyzer inlet, dialyzed immediately and returned to the patient [Eisenhauer et al., 1991]. Using the fixed plasma flow rate of 15 ml/min, the apheresis of 3 l plasma takes 3.3h; during the residual time, dialysis is continued in order to provide the patients' full dialysis session. Thus, using the Plasmat U, no extra time is required for H.E.L.P. apheresis and overhydration is eliminated as ultrafiltration can be performed according to the patients' needs [Bosch et al., 1991].

Recently, a long-term study of combined H.E.L.P./hemodialysis was published with respect to its efficiency, biocompatibility and clinical safety in dialysis patients [Bosch et al., 1993]. Weekly sessions were performed for 65-104 weeks and one patient plasma volume was processed per treatment. Depending on the ultrafiltration volume, hemodialysis resulted in a reduction of plasma volume with concomitant increase of total cholesterol up to 30% after the session. This effect could be obviated by the combined procedure, resulting in moderate reductions of risk factors. In order to further improve efficacy, the so-called "reverse flux filtration" modification was introduced [Bosch et al., 1993]. If this modification was used and therapy-induced changes in plasma volume were taken into account mathematically, calculated risk factor reductions were in the same range as were achieved with H.E.L.P. in patients with normal renal function (-55% for LDL-cholesterol, Lp(a) and fibrinogen with good recovery of HDL-cho-

lesterol). Urea, creatinine and phosphate elimination was similar to normal hemodialysis.

Uncorrected mean interapheresis levels of risk factors after 1 and 2 years of treatment were critically dependent on ultrafiltration. In patients with ultrafiltration volumes of >3000 ml/session LDL-cholesterol was reduced from 185-220 mg/dl to 135 mg/dl, whereas in a patient with an ultrafiltration <2000 ml/session a decrease from 231 mg/dl down to 80 mg/dl was attained. Similarly, the atherogenic index (LDL/HDL-cholesterol) was reduced from 5.3-6.4 to 4.3 in the first group, while a decrease from 6.1 down to 3.3 was observed in the patient with low ultrafiltration. Fibrinogen and Lp(a) were normalized in all patients. Bicarbonate dialysis integrated in the H.E.L.P./hemodialysis circuit reversed the buffer-induced plus uremic acidosis completely (systemic base excess pre/post -6.4/+3.0 mmol/l). Ultrafiltration-induced hemoconcentration was blunted by the combined system (-acute whole blood viscosity change +5%); plasma viscosity was even reduced after the sessions on the average by 9%. Clinical side effects were few and mainly related to ultrafiltration, i.e. indirectly to the patient compliance of fluid restriction in the dialysis interval. Thus, in 242 sessions, 14 episodes of hypotension and 6 of hypertension were registered. Heat sensation (3), and vertigo (2), nausea (1), and arrhythmia (1) were further complaints. No session had to be stopped prematurely. The biocompatibility of the procedure was good. Blood cell losses, leukocyte and thrombocyte as well as complement activation were minimal. No signs of hemolysis could be detected. Moreover, most of the C3a generated in the extracorporeal H.E.L.P. circuit was immediately removed by the precipitate filter.

In summary, the combined H.E.L.P./HD treatment in hypercholesterolemic dialysis patients proved to be a safe, effective and selective procedure for lipoprotein and fibrinogen normalization with excellent biocompatibility and good clinical patient tolerance. Clinically, both angina in coronary artery disease patients and esp. the walking distance in patients suffering from peripheral artery disease could be improved.

4. Acute Application of the H.E.L.P. System in Patients With Hemorheological Disorders

4.1 The Effect of H.E.L.P.-Therapy in Cerebrovascular Disease

H. Lechner, W. Walzl, B. Walzl

Abstract

Cerebrovascular disease (CVD) is associated with elevated fibrinogen and plasma lipoprotein concentration leading to an increase of both plasma and whole blood viscosity as well as raised aggregability of blood cells. One important goal in the treatment of CVD therefore should be to reduce fibrinogen and lipoproteins and thereby to improve the hemorheological state.

The effect of H.E.L.P. was investigated in 55 patients with cerebrovascular disease. 30 of them suffered from acute ischemic stroke, 25 had cerebral multiinfarct dementia. All patients underwent 2 H.E.L.P. applications within 8 days. The impact of H.E.L.P. on CVD was studied by changes of laboratory data and by evaluation of clinical symptoms before and after treatment. Each H.E.L.P. session caused an immediate, safe and significant reduction of important rheological parameters such as fibrinogen ($p<0.001$), low-density lipoprotein ($p<0.0001$), lipoprotein(a) ($p<0.003$), triglycerides ($p<0.0001$), whole blood viscosity at high shear rates, plasma viscosity and red cell transit time ($p<0.01$ each).

The results in laboratory measurement were followed in both groups by a statistically significant improved neurologic recovery, represented in the values of the Mathew Scale, the Mini Mental Examination and the Activities-of-Daily-Living Test. These results can indicate the importance and influence of hemorheology on clinical symptoms in CVD.

Introduction and Methodology

Apart from being an acute phase reactant, plasma fibrinogen appears to play an important role in atherogenesis. High levels of fibrinogen have been investigated as an independent risk factor in the development of ischemic stroke, cerebrovascular multiinfarct disease (MID), carotid stenosis and myocardial infarction [Ernst, 1989; Wilhelmsen et al., 1984]. A relationship between plasma fibrinogen level, whole blood and plasma viscosity, and cerebral blood flow, has been reported [Ernst, 1990; Grotta et al., 1985]. Hence fibrinogen holds a key position in hemorheology and therefore in the treatment of cerebrovascular disease.

Several agents to lower plasma fibrinogen levels and to improve hemorheology and/or anticoagulant therapy are currently in clinical trials but most of these substances suffer from weakness in either efficiency and/or safety. In contrast, the H.E.L.P.-ther-

apy is rapid, well controlled and safe to improve the hemorheological pattern in patients with cerebrovascular problems [Walzl et al., 1994].

Our study, therefore, was designed to determine whether reduction of fibrinogen and apo B-carrying plasma lipoproteins can in fact improve the rheological pattern as well as the clinical symptoms in acute ischemic stroke and MID. The trial was performed in 165 patients of the Department of Neurology, Karl-Franzens-University of Graz. Besides meeting the diagnostic criteria of acute stroke and MID, detected by CAT-scan, only patients with fibrinogen levels of 500 mg/dl or above were taken into consideration for taking part in the study. The diagnosis of MID was additionally based on DMS-3, NINCDS-ADRDA criteria and on the Hachinski Scale. Finally 30 patients with single acute thromboembolic stroke and 25 patients with multi-infarct dementia (MID) were prospectively selected for H.E.L.P. by computer-randomization.

Thirty patients from the remaining cohort which were not considered by computer decision to be part of the H.E.L.P. group served as controls.

Test Battery

For clinical evaluation and grading all the patients were administered a test battery, consisting of the Mathew Scale (MS, range from 0-100), the Mini Mental State Examination (MMSE, range 0 to 30) and the Activities-of-Daily Living (ADL, range 0 to 100). Tests were performed before and 8 hours after 1st and 2nd H.E.L.P. as well as on day 3 after 2nd H.E.L.P. (=day 11). The team to carry out the testing was different from the team administering H.E.L.P.

Results

Laboratory Data

No statistically significant difference was found in fibrinogen, whole blood and plasma viscosity, RCTT, total cholesterol, LDL and triglycerides

Table 5: Influence of H.E.L.P. on plasma fibrinogen, whole blood and plasma viscosity and RCTT in CVD-patients.

H.E.L.P. (55 patients)	before 1st*	after 1st*	before 2nd*	after 2nd*	reduction %**
Fibrinogen	541.3 ± 109.5	361.3 ± 93.6^{++}	449.6 ± 97.2	294.1 ± 79.8^{+}	33.9
Whole blood viscosity					
High shear (94 sec^{-1})	5.49 ± 0.51	4.62 ± 0.58^{+}	5.19 ± 0.58	4.21 ± 0.80^{+}	17.4
Low shear (11 sec^{-1})	11.01 ± 1.32	8.99 ± 1.28^{+}	9.64 ± 1.81	8.27 ± 1.31^{+}	16.5
Plasma viscosity	1.53 ± 0.16	1.22 ± 0.12^{+}	1.41 ± 0.10	1.20 ± 0.09^{+}	17.7
RCTT	14.64 ± 2.58	11.80 ± 1.84^{+}	12.67 ± 2.09	10.48 ± 1.27^{+}	18.5

* = mean ± SD; ** = mean reduction between 1st and 2nd HELP / $^{++}$ = p<0.001, $^{+}$ = p<0.01.

Table 6: Influence of H.E.L.P.-apharesis on plasma total cholesterol, LDL-cholesterol and triglycerides in CVD-patients.

H.E.L.P. (55 patients)	before 1st*	after 1st*	before 2nd*	after 2nd*	reduction %**
Total cholesterol (mg/dl)	251.3 ± 47.6	128.9 ± 34.1§	209.0 ± 32.5	108.5 ± 30.6§	49.5
LDL (mg/dl)	168.3 ± 40.4	78.6 ± 27.8§	143.1 ± 19.4	72.4 ± 27.6§	51.6
Triglycerides (mg/dl)	241.7 ± 93.9	121.0 ± 69.9§	201.3 ± 84.2	97.1 ± 68.8§	50.8

mean ± SD; ** = mean reduction between 1st and 2nd HELP / + = p<0.01, # = p<0.003, § = p<0.0001

level in pretreatment values of the acute stroke group compared to the MID group. The two groups were therefore statistically combined.

By two H.E.L.P. sessions it was possible to reduce the measures relevant to hemorheology to between 16.5 and 51.6 percent. The reduction of these substances was statistically significant after each H.E.L.P.-treatment. Within the controls no significant changes were found (Table 5 and 6).

As expected, at day 11 (3 days after 2nd H.E.L.P.) an increase of the cited laboratory data occurred which was not statistically significant - except whole-blood viscosity at low shear rate ($p<0.05$).

Clinical Rating

MS improved after the first H.E.L.P. treatment $p<0.05$ and further after the second treatment $p<0.05$. At day 11 the difference between the H.E.L.P. group and the controls became statistically significant $p<0.05$. MMSE and ADL also showed an improvement after first H.E.L.P. $p<0.05$. At that time a significant difference to the controls was observed $p<0.05$. Similar to the laboratory data no significant changes could be seen within the control group (Table 7).

Table 7: The impact of H.E.L.P.-therapy on rating scales in relation to controls.

Type of test	before 1st HELP#/Cont.##	after 1st HELP/Cont.	after 2nd HELP/Cont.	day 11 HELP/Cont.
Mathew	85.4 / 85.1	90.8* / 84.3	93.6$+ / 86.0	94.5 / 86.6◆
Mini Mental	26.1 / 26.2	27.8* / 25.9**	29.4$ / 26.1§§	29.5 / 26.4◆
ADL	85.4 / 85.2	89.7* / 85.9**	93.1$ / 86.1§	93.3 / 86.5◆

* = $p < 0.05$ before and after 1st HELP; ** = $p < 0.05$ between HELP and control group; $ = $p < 0.01$ related to before 1st HELP; + = $p < 0.05$ re-lated to after 1st; §§ = $p < 0.01$ and § = $p < 0.05$ between HELP and Controls after 2nd HELP; ◆ = $p < 0.05$ between HELP and Controls at day 11; # = HELP group (n = 48), ## = Controls (n = 30)

Discussion

The aim of the trial was to explore if the H.E.L.P. treatment is able to change clinical symptoms due to an alteration of the hemorheologic pattern in cases of CVD. The importance and effect of fibrinogen in connection with CVD was clearly confirmed by cross-sectional and longitudinal studies [Ernst, 1989; Lechner et al., 1986; 1987; Wilhelmsen et al., 1984]. As high fibrinogen levels limit perfusion to the brain via their effects on blood rheology, which also reduces cerebral blood flow [Walzl et al., 1994], it was of interest to examine the relations between plasma fibrinogen level, whole-blood and plasma viscosity. Even high levels of total cholesterol, LDL, and the triglycerides seem to jeopardize the regular blood flow [Ernst, 1989; 1990; Lechner et al., 1986; 1987]. Therefore these factors were also taken in observation.

In contrast to other selective procedures for extracorporeal LDL elimination, H.E.L.P. does not only reduce plasma lipoproteins but also fibrinogen at the same time [Walzl et al., 1993]. This offers an explanation for the clinical improvement after H.E.L.P. and supports the importance of improving the microcirculation as a potential basis for recovery of brain function [Lechner et al., 1986; 1987; Walzl et al., 1993; 1994]. From this point of view the vicious cycle consisting of reduced blood flow, aggregation of blood cells, and finally complete stasis, may be interrupted by the fibrinogen and lipoprotein lowering power by the H.E.L.P. treatment. The main effect in the improved microcirculation [Kleophas et al., 1990]. Therefore the augmented oxygen delivery to brain cells may be one of the most important benefits of a treatment by H.E.L.P. in cerebrovascular disease, leading to salvation of borderline-damaged cells which still have a potential for recovery.

4.2 H.E.L.P.-Apheresis in the Treatment of Critical Limb Ischemia

B. Walzl, P. Lechner, M. Walzl, H. Lechner, H. Cesnik

Abstract

There is no doubt that an immediate, safe and significant elimination of excess fibrinogen and lipoproteins, caused by H.E.L.P. treatment, leads to a markedly improved microcirculation. The restoration of the latter obviously enabled us to perform limb-saving surgical procedures instead of mutilating amputations. 12 patients suffering from peripheral arterial disease were submitted to 18 H.E.L.P.-treatments in each case instead of having their critically ischemic legs removed. Surgery could be limited to necrosectomy only and the wounds were either primarily sutured or covered with skin-grafts. We were able to avoid 13 amputations in these 12 patients who could finally walk out of the hospital.

Introduction, Methodology and Clinical Experience

Several trials provide strong evidence that fibrinogen may hold a key-

position in the development of obstructive vascular diseases [Burr et al., 1992; Taylor et al., 1991]. Numerous studies suggest that not only hyperlipidemia, but also elevated fibrinogen levels may bring patients to a markedly increased risk for coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral atherosclerotic occlusive disease (PAOD). These findings have also been confirmed by experimental trials [Walzl et al., 1994].

As in other vascular beds, the hyperfibrinogenemia is thought to jeopardize blood flow owing to its effects on blood rheology, thus potentiating the hemodynamic effects of the vascular lesions that usually represent the obvious cause of ischemia [Ernst, 1990; Walzl et al., 1993]. Low-density lipoprotein (LDL) and fibrinogen severely influence most hemorheological parameters such as whole-blood and plasma viscosity or aggregation of blood cells. Red cell deformability - and therefore red cell transit time (RCTT) as a measure for it - is particularly influenced by high levels of total cholesterol and LDL. A decrease in LDL and fibrinogen should therefore lead to an improvement in at least some of these parameters and to the restoration of microcirculation, too. Hence, in some studies a conservative - hemorheologically active - drug treatment in patients with PAOD was proved to obtain good results in clinical symptoms [Ernst, 1989; 1990; Lechner, 1992; Walzl et al., 1992; 1993; 1994].

As a new possibility for a considerable intervention in situations where a quick and drastic fluidification of the blood is required, the H.E.L.P. system has been successfully used in the treatment of CAD and CVD [Lechner et al., 1992; Seidel, 1990; Walzl et al., 1992; 1993; 1994]. From these findings we concluded that a treatment modality which has proved to be useful in CAD and CVD should very well be applicable in PAOD, too.

The first patient to test this hypothesis was a 74 years old woman who was referred to the Department of Neurology, Graz University, for H.E.L.P.-treatment of stroke. At the time of admission she also suffered from a critically ischemic right leg with gangrenous toes and a deep and infected ulcer on the heel. There were no pulses palpable on the foot and Doppler-Duplex sonography showed only a weak signal in the knee. Detailed high-resolution angiography did not reveal any graftable vessels. Though she met all the criteria for primary limb amputation, the neurologically impaired patient was in a septic and critically ill state which forbade general or even spinal anesthesia. Therefore surgery, performed in order to prevent sepsis, was done under local anesthesia and it had to be limited to necrosectomy only. The wounds were left open and the patient was given antibiotics intravenously.

As soon as the signs of systemic infection were regressing, the woman was submitted to five consecutive H.E.L.P.-sessions, one every three days. She fully recovered from stroke, as we had expected. But as a surprising side effect we found rapid granulation of tissue in the wounds of the foot indicating an improved microcirculation. Another two weeks later, dur-

ing which the patient had undergone six more H.E.L.P.-sessions, we could re-operate on the leg and cover the wound with a meshed skin graft. Wound healing was uncompromized and so was the mobilization of the patient. After seven more H.E.L.P. applications she walked out of the hospital wearing an orthopedic shoe with a filler instead of having had amputation.

Encouraged by the unexpected outcome in this first case, we submitted another 11 patients - 4 women and 7 men, aged between 44 and 79 years - to the H.E.L.P. treatment. They all had been referred to surgery in order to have limb amputation for advanced PAOD, one of them was even considered to have both legs removed. The patients were either bedridden (7 pts.) or had a walking distance of less than 50 meters. They presented with gangrenous toes and/or ischemic ulcers. The ankle-brachial systolic pressure index (ABSPI) was - if ever measurable - below 0.4. The ankle systolic blood-pressure was less than 40 mm Hg in 10 and 55 mm Hg and 70 mm Hg, respectively, in the remaining 2 patients, both suffering from arterial hypertension. So the pedal pulses were not or only poorly palpable.

Tissue oxygen saturation, percutaneously measured at the toes, was below 60 p.c. in all of them, and it could not even be measured in 2 - diabetic - women. These data represent a most critical ischemic condition, usually going along with irreversible damage to the tissue.

In addition to their resting pain, the patients complained - because of vascular neuropathy - about dysesthesia, hypesthesia, hypalgesia and hypthermesthesia as well as about numbness and burning in both legs. Angiography did not reveal any vessels suitable for revascularization-surgery in any of them. All of the patients had had unsuccessful vascular surgery at least once before, also previously conventional treatment with prostaglandines had not led to sufficient effects. So - according to the state of the art - they met all the criteria for primary limb amputation. In those 5 patients, who had insulin-dependent diabetes, too, tissue necrosis went along with bacterial infection, the latter requiring immediate surgery.

In the expert-opinion of at least two independent vascular surgeons there was no other treatment option left then bi-femoral amputation in one patient, femoral amputation of one leg in another six and at least crural amputation in the remaining patients.

As a first step of treatment, the patients were operated on: Surgery was strictly limited to necro-sectomy, amputation of gangrenous toes or sparing excision of ischemic ulcers. All wounds were left open only covered with an antiseptic ointment. All resected tissue was submitted to a microscopic work-up: Pathology confirmed peripheral atherosclerotic occlusive disease to be the underlying condition. There were no signs of thrombangiitis obliterans in any of them.

Prior to surgery the patients were submitted to 4 H.E.L.P.-sessions (twice per week) followed by 14 apheresis-sessions (one per week) after surgical intervention.

Results

Each single H.E.L.P.-session led to a significant decrease in plasma fibrinogen, whole-blood- and plasma viscosity and RCTT, respectively. We also observed a marked, even statistically significant reduction in total cholesterol, LDL and triglycerides. After 18 H.E.L.P. applications these parameters were all within the normal range in our patients.

Skin temperature and rosy granulation tissue suggested that microcirculation had been restored. When we subsequently re-operated on the patients' leg, we could either obtain primary closure of the wounds (7 cases) or we covered the wounds with mesh-grafts (5 cases). There were no disturbances in wound healing and all patients left the hospital walking with the help of orthopedic devices.

None of them had limb amputation which previously had seemed to be inevitable. Their painless walking distances are now 800 to 1100 meters and they are free of resting pain. Neurological examinations which are performed every three months did reveal none or only none to little sensorical disturbances to date. With regard to their PAOD, the patients are in a stable clinical state, too. To maintain this state, they receive bezafibrate (sustained-release 400 mg/day), which is known for its positive impact on rheology [Walzl, 1993] and pentoxifylline (600 mg/day) because of its efficacy in PAOD.

After a mean follow-up of seven months (range 4 to 12 months) all laboratory parameters are still within the normal ranges.

Discussion

According to the standards established by the Society for Vascular Surgery/North American Chapter and by the International Society for Cardiovascular Surgery, resting pain, gangrene, ischemic ulcers and an ABSPI below 0.4 represent a critical ischemic condition which usually requires primary limb amputation. Patients in that state, especially when neurologically impaired or nonambulatory, are not to be considered for revascularization procedures. Following these guidelines we should have performed 13 amputations in our 12 patients [Lechner et al., 1994; Walzl et al., 1993].

Amputation often means - especially in the elderly - immobilization, institutionalization and early death. Therefore the very utmost goal of treatment is to avoid amputation whenever possible.

However, Hagen-Poisuille's law offers two different approaches to obstructive arterial disease, which represents an inadequacy between the lumen of a vessel and its contents: When the treatment modalities concerning the vessel (bypass-surgery, angioplasty) are exploited, the only remaining option is to improve hemorheology.

Increased fibrinogen levels have repeatedly been demonstrated to occur in PAOD. Owing to its adverse effect on blood rheology, hyperfibrinogene-

mia has to be considered to jeopardize microcirculation [Ernst, 1989]. One might object that an increase in fibrinogen, which is an acute phase reactant, too, might eventually result from the inflammatory reaction that usually goes along with gangrene. But in our opinion it does not at all matter why fibrinogen levels are increased as long as they are increased, thus affecting whole-blood and plasma viscosity and aggregation of blood cells. In addition, we did not find a significant difference in fibrinogen levels in patients with and those without signs of infection. From this observation we conclude that fibrinogen is increased in all cases of far-advanced PAOD. If so, the lowering of excess fibrinogen should therefore lead to an improved blood rheology. Hence, the hemorheological effect of H.E.L.P. was even used in cases of PAOD.

In the face of previous observations that a simultaneous elimination of fibrinogen and lipoproteins by means of H.E.L.P. treatment led to a reduction of atherosclerotic plaques and might - especially since fibrinogen, LDL, and Lp(a) are accumulating in atherosclerotic plaques - have a therapeutical impact on the regression of atherosclerotic plaques and on the reopening of completely occluded carotid arteries, we do not think that the immediate improvement in our patients can be explained by a regression of atherosclerosis. Improved quality of pulses (Doppler-Duplex signals) therefore seem rather to be a result of hemorheological mechanisms as well as of endothelium function [Hennerici et al., 1991; Walzl et al., 1993; 1994].

4.3 The Application of the H.E.L.P. System in Acute Pancreatitis (A Case Report)

J. Thiery

This report concerns a female patient, age 44, suffering from severe angina abdominalis and hypertriglyceridemia with elevated serum amylase (380 U/l) and lipase activity (3100 U/l).

Massive hypertriglyceridemia and hyperfibrinogenemia are common signs of acute pancreatitis. We performed H.E.L.P.-Apheresis in our patient to remove plasma lipids and fibrinogen with the aim to improve blood viscosity and microcirculation. The hypertriglyceridemia (3050 mg/dl) and hypercholesterolemia (760 mg/dl) was caused by an accumulation of triglyceride-rich lipoproteins in the density fraction <1,006 g/ml (chylomicrons and very-low density lipoproteins). Plasma fibrinogen was also elevated to 420 mg/dl and blood viscosity to 5,06 mPa/s (normal: <1.8 mPa/s).

By a single H.E.L.P.-treatment plasma triglycerides could be lowered –38%, cholesterol decreased from 760 mg/dl to 510 mg/dl, apolipoprotein B from 157 mg/dl to 95 mg/dl and fibrinogen was lowered -60%. In addition, blood viscosity decreased from 5,06 mPa/s to 2,2 mPa/s (-56%), plasma viscosity from 1,48 mPa/s to 1,16 mPa/s (-22%). The angina abdominalis disappeared already during the H.E.L.P.-treatment. In the following

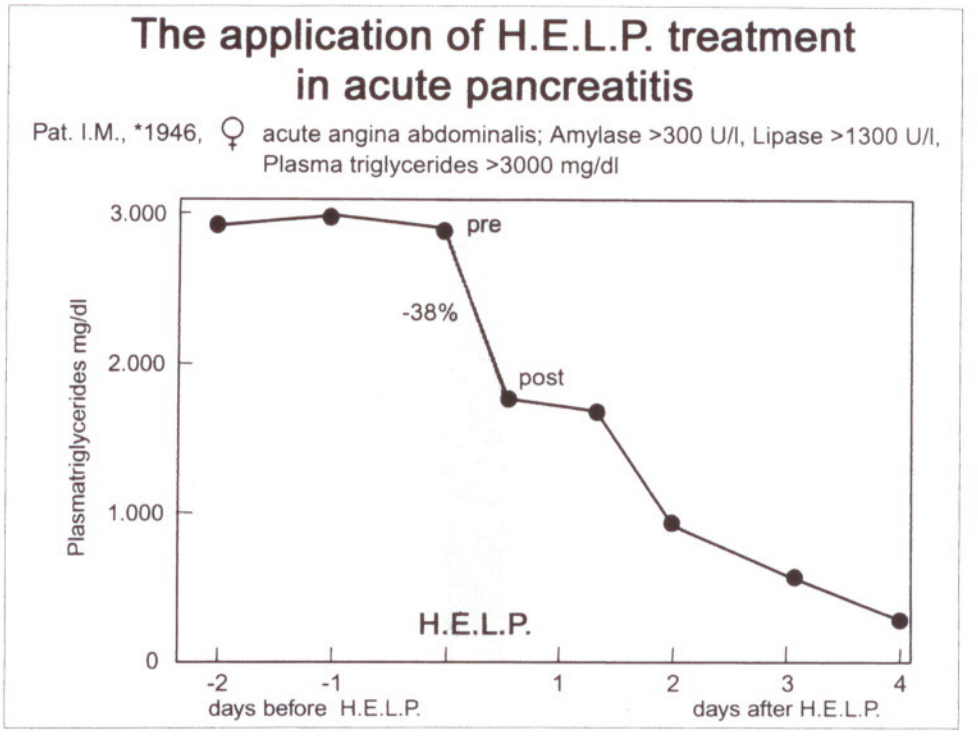

Fig. 12: Effect of the H.E.L.P. treatment in a patient with acute pancreatitis. A single H.E.L.P. treatment decreased significantly the massive hypertriglyceridemia and did support normalization of hyperlipidemia and clinical symptoms.

days the hyperlipemia and enzyme activities almost normalized (total cholesterol 182 mg/dl, plasma triglycerides 289 mg/dl, four days after H.E.L.P.), plasma fibrinogen, however, showed an increase after the H.E.L.P.-apheresis (Fig. 12).

The fast improvement in clinical symptoms after a single H.E.L.P.-treatment in this patient may be closely associated with the drastic hemorheological changes brought about by the drastic reduction of fibrinogen, cholesterol, and triglycerides.

4.4 Retinal Vessel Occlusion and H.E.L.P.-Therapy

M. Walzl, A. Haas, B. Walzl, J. Faulborn, H. Lechner

Abstract

As a treatment modality utilizing the H.E.L.P. system was proved to be successful in cases of cardiac and cerebrovascular disease as well as in peripheral arterial disease where the hemorheologic state and clinical symp-

toms were improved after H.E.L.P. series, this treatment was also used in 25 patients with ocular microcirculatory diseases (branch retinal vein occlusions, central retinal vein occlusion, central artery occlusion, non-arteritic anterior ischemic optic neuropathy). H.E.L.P. was applied 6 times in each case. Fibrinogen, total cholesterol, LDL, and triglycerides $p<0.001$ were significantly reduced, even whole blood and plasma viscosity $p<0.002$ each and red cell transit time $p<0.003$ had been ameliorated. At the end of the treatment session the patients showed an increase of their visual acuity by three or more lines as well as an improvement of the visual field. These very first results in ocular application of H.E.L.P. could open a new discussion about the hypothesis that improved hemorheologic property of blood is an important factor in clinical recovery as well as basic ophthalmological function.

Introduction, Methodology and Case Reports

Among the major causes for atherosclerosis high levels of plasma fibrinogen gather a raising number of evidence for its pathological function: Elevated fibrinogen has been assessed in cerebrovascular disease (CVD) as well as in coronary heart disease and peripheral arterial disease (PAD), whereby the hemorheological state is deteriorated [Ernst, 1990; Walzl et al., 1994].

Whole blood and plasma viscosity and red cell transit time as important factors for blood property are additionally influenced by the levels of total cholesterol, low density lipoprotein (LDL), or the triglycerides [Ernst, 1989; Kowal et al., 1993].

Although differences in the pathogenesis of atherosclerosis may exist and the exact underlying process remains uncertain, common risk factors - such as hypertension, diabetes mellitus or elevated levels of fibrinogen and lipoproteins - have been evaluated. Observations in cardiac and cerebrovascular disease but even in patients with PAD report a rapid and safe amelioration of the hemorheologic pattern followed by an improvement in clinical symptoms after a treatment by H.E.L.P., obviously caused by increases of blood flow and microcirculation [Lechner et al., 1992; 1993; Seidel, 1990; Walzl et al., 1992; 1993; 1994]. As there is some evidence that oculary microcirculatory disturbances could be related to a deterioration of the hemorheologic pattern [Dodson et al., 1993, Wick et al., 1992; Wolf et al., 1992] it was of interest to apply H.E.L.P.-treatment also in cases of oculary microcirculatory diseases. While the pathogenesis of anterior ischemic optic neuropathy (AION) and central artery or vein occlusion is still in discussion, disturbances in microcirculation, caused either by systemic or focal factors, are the most presumed primary source. In the absence of other justified treatment modalities H.E.L.P. was applied in five patients to achieve an improved hemorheological situation and so to ameliorate microcirculation.

Clinical Outcome and Case Reports

To date 25 patients suffering from oculary microcirculatory disturbances had been subjected to H.E.L.P. series [Walzl et al., 1994] leading to a significant improved visual acuity and visual field.

All the patients received six H.E.L.P. sessions, one per week.

Five typical cases will be reported:

Case 1: A 76-year old woman with one week history of decreased vision on her left eye. Her best corrected visual acuity (VA) was 0.8 in the right eye and 0.16 in the left eye. Results of ophthalmoscopic examination showed a supertemporal branch vein occlusion on the left eye. The left visual field revealed an inferonasal scotoma. She had a seven-year history of hypertension.

Clinical outcome:

After H.E.L.P. treatment VA increased from 0.16 to 0.6 in the left eye and the visual field was improved too.

Case 2: A 66-year old woman had been diabetic for 8 years. She was examined because of blurred vision on her right eye for two weeks. Examinations revealed VA of 1/9 in the right eye and 1.0 in the left eye. There was a relative afferent pupil defect on the right side, and the right visual field had a nasal superior and inferior arcuate nerve fibre defect (Fig. 13). The right disc was diffusely swollen and elevated. There was no diabetic background retinopathy in either eye. The diagnosis of AION was made at the right eye.

Clinical outcome:

VA on the right eye had improved from 1/9 to 0.3 and the right visual field was nearly doubled (Fig. 13) by the H.E.L.P.-treatment.

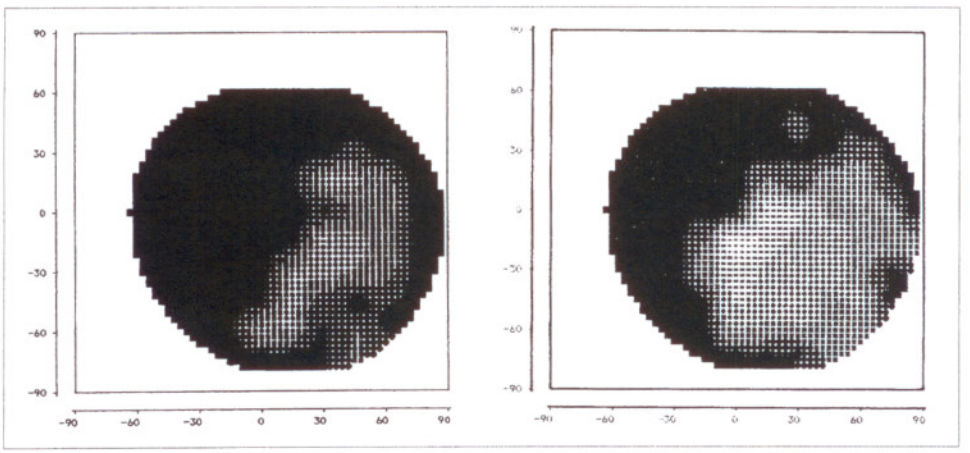

Fig. 13: Visual field (Octopus 2000™, program 24) of the right eye of case no. 2. Before H.E.L.P. treatment (left) with a nasal superior and inferior arcuate nerve fibre defect. After H.E.L.P.-treatment (right) an improved visual field appeared, which was nearly doubled.

Case 3: A 45-year old male patient reported a decrease of VA in his left eye since one week. He was otherwise well and his medical history was unremarkable. VA was 1.0 in his right and 0.2 in his left eye. The ophthalmoscopic examination showed a central retinal vein occlusion of the left eye with an edema of the optic nerve head with hemorrhages, increased venous diameter, paravenous intraretinal hemorrhages in the middle peripheral area and with a macular edema. The fluorescin angiography showed an increased arm retina time (ART) of 25.6 sec. (normal range 10 to 20 sec.) and arteriovenous time (AVT) of 5.6 sec. (normal range 1 to 2 sec.).

Clinical outcome:

After six weeks an increase of VA from 0.2 to 0.5, and an improvement of the funduscopic appearance with a reduction of the macular edema was seen.

Case 4: A 60-year old man reported the sudden loss of vision in his right eye since 14 hours. His vision was only light perception. The typical feature of a central retinal artery occlusion with narrowed arterioles and pale ophthalmoscopic appearance was found on the right fundus. Fluorescin angiography showed a delayed filling of fluorescin (ART: 48,9 sec.). The Doppler/Duplex sonography revealed an occlusion of the right internal carotid artery.

Clinical outcome:

After H.E.L.P. treatment the angiographic circulation times returned to normal and the VA improved to 1/60.

Case 5: A 59-year old man was referred with a two weeks history of decreased vision on his left eye. His best corrected VA was 1.0 in the right and 0.16 in the left eye. Results of ophthalmoscopic examination showed unremarkable findings on his right eye, but a supertemporal branch retinal vein occlusion of the left eye. Corresponding to the occlusion the left visual field showed an inferonasal scotoma. General examination showed hyperlipidaemia and an onset of renal insufficiency.

Clinical outcome:

After treatment VA increased from 0.16 to 0.3 in the left eye with improvement of the visual field.

Discussion

There is little doubt that elevated plasma fibrinogen and lipoprotein levels lead to disturbances of the hemorheologic pattern, whereby whole blood and plasma viscosity are influenced negatively [Ernst, 1989; 1990; Grotta et al., 1985; Wilhelmsen et al., 1985]. In spite of the fact that the pathogenesis of AION and papillophlebitis may differ in detail from other atherosclerotic occurences most disturbances in hemorheology are thought to be a major cause for this disease [Dodson et al., 1983; Wick et al., 1992; Wolf et al., 1992]. The occlusion of the posterior cilliar artery is supposed to be caused by atherosclerotic lesions, the cause of papillophlebitis is focused on an ignition of the stam vein and/or of one of the branch veins, respectively. However, risk factors like hypertension, diabetes, hyperfibrinogenaemia seem to have the greatest impact as these factors are influencing both the atherosclerotic changes and the hemorheologic pattern.

As plasmapheretic procedures were proved to be successful in cases of cardiac disease, CVD and PAD [Lechner et al., 1993; 1994; Seidel 1990; Walzl et al., 1992; 1993; 1994] it seemed logically to apply a treatment modality by means of H.E.L.P. also in cases of oculary microcirculatory disturbances.

Although measurable systemic rheological changes are not whole-hearted for clinical relevance in most cases, it seems logical that a compensation of the blood property by a normal hemorheological situation has its limits, as it was even demonstrated by cerebral blood flow [Brown et al., 1985]. A further development of the oculary disease mentioned above must therefore lead to a situation where the normal rheology (similar to the cases described in this paper) is unable to equalize demand and offer of blood in microcirculation.

However - for to obtain sufficient functional results the onset of treatment gathers great interest because of limitations in the neuroretina's survival time. From this point of view and in contrast to other treatment modalities the H.E.L.P. system seems to have undisputable advantages.

4.4.1 H.E.L.P. Application in a Case With Retinal Ischemia

J. Thiery

Amaurosis fugax is a clinical symptom indicative of transient retinal ischemia, which can be associated with ipsilateral internal carotid artery stenosis or to embolism of the retinal arteries. In most cases the occlusion of central retinal artery is recurrent in a few seconds or minutes. However, in some patients an irreversible loss of vision can appear.

We report on the successful application of H.E.L.P. treatment in one patient with long-lasting mono-ocular obliteration of the visual field caused by micro-embolism of the retinal artery.

The patient, a 64 year old surgeon, was referred to our clinic after he had observed unformed flashes of light and shadows falling over the visual field with a loss of peripheral vision of his right eye. The painless clinical symptoms were persisting for over 14 days. Treatment with anticoagulants and prednison remained without any effect. Ophthalmological investigations revealed a light papilledema and a bowlike narrowing of the upper segments of the visual field. He had normal cholesterol concentrations (LDL-C 129 mg/dl), but slightly increased plasma fibrinogen levels (384 mg/dl). All hematological, immunological and other clinical chemical indices were in a normal range. After informed consent we performed two H.E.L.P.-aphereses in a three day interval to remove plasma fibrinogen and to improve hemorheology and microcirculation of the retina. The patient did tolerate the H.E.L.P.-treatment very well. The plasma fibrinogen was lowered from 384 mg/dl to 105 mg/dl (-70%), plasma viscosity was diminished from 1,28 to 1,04 mPa/s. Repeated ophthalmological investigations one week and six months after H.E.L.P.-treatment showed a remark-

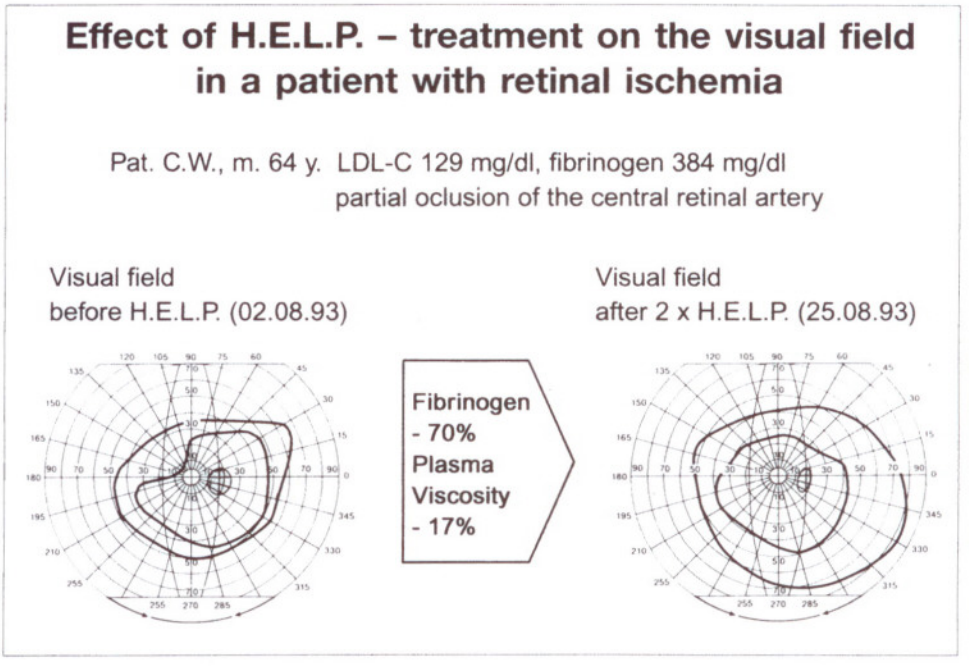

Fig. 14: Effect of H.E.L.P. treatment on the visual field in a patient with retinal ischemia. After two H.E.L.P. treatments with reduction of plasma fibrinogen a significant improvement of the visual field was achieved.

able improvement and recurrence of the peripheral vision (Fig. 14).

The clinical follow-up of the patient gives enough support that the application of H.E.L.P.-treatment may be a useful adjunct in sudden impairment of vision and central retinal artery occlusion.

5. Treatment Tolerance and Safety of the H.E.L.P.-System

Overall treatment tolerance has been very good, and no major complications have been observed after 45 000 treatments in approximately 400 patients. The treatment effects have been maintained on long-term treatment for over 8 years.

At the end of the H.E.L.P. therapy, plasma concentrations of proteins that are not selectively precipitated by heparin at low pH were generally in the range of 80 to 90 percent of the initial values and returned to their original level no later than 24 hours after the end of the treatment [Eisenhauer et al., 1987; Seidel, 1990; Seidel et al., 1991]. Substitution of any kind has not been necessary in the years of clinical experience with the H.E.L.P.-system. In contrast to some other LDL apheresis systems the H.E.L.P. procedure does not alter the physicochemical characteristics of LDL, nor does it alter the ligand quality of LDL for lipoprotein receptors as described for some of the other systems [Schultis et al., 1990].

No such problems as described for dextransulphate-adsorption-LDL-apheresis when combined with ACE-inhibitor-drug treatment (Keller et al.,1993; Olbricht et al.,1992) have ever been observed with the H.E.L.P. therapy.

Special attention has been focussed in all clinical trials on the effect of H.E.L.P. on hemostasis. All post-treatment controls were typical for extracorporeal procedures, and no critical bleeding complications have been observed. Complement activation is found in all extracorporeal procedures. However, as a specific feature of the H.E.L.P.-system activated complement C3, C4 and the terminal complement complex are largely adsorbed to the filter system of H.E.L.P., resulting in plasma concentrations which are actually below those measured before LDL-apheresis. C5a is not retained in the filter system but plasma levels at the end of the treatment were within the normal range and leucocytopenia, a hallmark of complement activation, was never observed under H.E.L.P. treatment [Würzner et al., 1991]. Plasma electrolytes, hormones, vitamins, enzymes, and immunoglobulin concentrations as well as hematological parameters remained virtually unchanged at the end of each treatment and on long-term application of H.E.L.P. alone and in combination with HMG-CoA reductase inhibitors [Seidel, 1990; Thiery 1988; Seidel et al., 1991] (see Table 8).

Long-term observations show that besides the marked reduction of LDL-cholesterol, fibrinogen, and Lp(a) some increase (10%) of HDL-cholesterol occurs which may add to the anti-atherogenic effect of LDL-apheresis treatment with the H.E.L.P.-system. The reason and the metabolic basis of this change is yet unknown. Similar effects, however, have been found with some lipid lowering drugs.

Table 8: Safety parameters under the H.E.L.P.-therapy.

Parameter		Baseline		24 months of therapy	
Substrates		x± SEM n.s.		x	± SEM
Sodium	mmol/l[133-150]	140.0	0.7	141.0	0.3
Potassium	mmol/l[3,5-5,5]	3.9	0.12	4.0	0.05
Calcium	mg/dl[8,6-11]	9.2	0.11	8.9	0.1
Phosphate	mg/dl[4-7]	3.7	0.16	3.3	0.03
Iron	µg/dl[53-167]	88.2	9.3	95.5	3.9
Creatinine	mg/dl[0,6-1,2]	0.85	0.04	0.9	0.02
BUN	mg/dl[5-25]	15.2	1.7	14.5	0.4
Uric acid	mg/dl[2.0-6.8]	5.3	0.4	5.3	0.4
Glucose	mg/dl[60-100]	94.0	0.9	100.0	6.4
Total bilirubin	mg/dl[<1.2]	0.43	0.03	0.56	0.4
Total protein	g/dl[6.2-8.6]	7.0	0.1	6.9	0.1
Albumin %	[55-70]	61.6	1.73	61.4	0.42
a1-Protein %	[2-4]	3.6	0.3	3.6	0.1
a-Protein %	[5-10]	8.0	0.42	8.3	0.14
β2-Protein %	[7-14]	13.0	0.56	12.0	0.03
γ-Protein %	[11-20]	13.7	0.99	14.8	0.14
Enzymes	U/l				
ALAT (GOT)	[<18]	10.0	0.4	13.5	0.4
ASAT (GPT)	[<22]	11.0	2.0	19.0	1.0
Gamma-GT	[<28]	21.0	5.8	25.0	2.1
CK	[<60]	45.0	7.0	45.0	2.0
LDH	[<200]	143.0	10.8	151.0	4.6
Amylase	[<34]	16.0	2.7	16.0	0.3
CHS	[>2000]	5151.0	525.0	5455.0	530.0
ALP	[<200]	101.0	6.6	110.0	2.8
Hematological indices					
Hemoglobin	g/dl[12-16]	14.0	0.44	14.3	0.07
Hematokrit	%[37-47]	41.8	1.1	42.0	0.73
Erythrocytes	10^6/µl[4,2-5,6]	4.4	0.14	4.6	0.1
Thrombocytes	10^3/µl[150-400]	226.0	10.2	220.0	9.5
Leukocytes	10^3/µl[4,0-8,5]	5.18	0.39	5.22	0.48
Lymphocytes	%[22-48]	37.4	2.76	33.3	2.1
Monocytes	%[0,6-9,4]	7.2	1.02	6.2	2.45
Neutrophils	%[41-70]	51.3	3.16	57.4	3.12
Eosinophils	%[0.7-6.3]	2.6	0.43	1.8	0.61
Basophils	%[0.1-1.4]	0.7	0.18	0.7	0.1
Hemostasis					
Quick test (PT) %	[70-100]	98.0	1.25	99.0	0.91
TT (s)	[15-19.5]	14.0	0.12	14.0	0.21
Endocrinological indices					
Cortisol	µ/dl	12.6	1.05	13.3	1.15
Testosterone	µ/dl	6.7	1.07	6.4	0.26
ACTH	µ/dl	40.3	3.78	40.4	6.18
LH[a]	ng/ml	15.9	8.36	11.1	5.91
FSH[a]	ng/ml	16.0	0.22	28.0	10.3
T3	ng/ml	133.5	7.35	123.5	12.4
T4	µg/dl	7.0	0.61	7.3	0.1

[a] In men and premenopausal women.

Adverse effects of the H.E.L.P. treatment were documented in less than 3% of all treatments and could be managed without any major problem [Eisenhauer et al., 1987; Seidel et al., 1991; Schuff-Werner et al., 1994].

6. Indication for the H.E.L.P.-Therapy

Based on the experience of many centers a German consensus panel has recently published differentiated guide lines as to when LDL-Apheresis should be used [Greten et al., 1992].

LDL-Apheresis treatment is indicated according to this as follows:

* in the presence of **homozygous FH**

* **for primary prevention of CHD** in young patients with severe hypercholesterolemia and a strong family history of CHD, provided LDL-C cannot be decreased below 200 mg/dl by a hyperlipidemic diet and maximal drug therapy;

* **for secondary prevention of CHD** in patients with severe CHD (stage III-IV) and marked hypercholesterolemia, provided LDL-cholesterol cannot be decreased below 135 mg/dl by maximal dietary and drug therapy. Diet and drug therapy should be continued while the patients are on H.E.L.P.-LDL-apheresis.

The therapeutic goal in secondary prevention for LDL is 100 mg/dl.

* Further indications for the H.E.L.P. therapy may be renal insufficiency, and after heart transplantation, acute or chronic circulatory problems, both of which will have to be considered in the lights of results from proceeding trials.

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