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What is the role of lipid lowering therapy in heart-allograft failure?

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What is the role of lipid lowering therapy in heart-allograft failure? Hypercholesterolemia is often the cause for the primary heart disease ultimately necessitating heart transplantation (HTx). After transplantation, persisting hypercholesterolemia results in an increased peroxidation of LDL retained by extracellular matrix of the intima. Oxidized LDL accumulates in monocyte derived macrophages, it leads to immobilization of tissue macrophages and provokes the expression of vascular adhesion molecules, growth factors and cytokines. In a prospective open controlled study, the impact of long-term cholesterol reduction by diet in combination with the HMG-CoA-reductase inhibitor Simvastatin on graft vessel disease (GVD) was evaluated. Patients of the control group received only a low fat diet. Simvastatin treatment decreased total and LDL-cholesterol significantly and was not associated with adverse effects. The one year angiographies revealed GVD in 24.1% of the control and 12.1% of the Simvastatin group (Study I). In high risk patients with LDL-cholesterol concentrations above 135 mg/dl, in spite of maximal Simvastatin treatment or plasma fibrinogen concentrations above 400 mg/dl, the heparin mediated extracorporeal low density lipoprotein precipitation (H.E.L.P.)-system was applied. H.E.L.P. was used either for prevention of GVD soon after HTx or for treatment of GVD after development of coronary lesions. Study II proved that the H.E.L.P.-system could significantly lower LDL-cholesterol, Lp(a) and fibrinogen in most high risk patients after HTx, resulting in successful prevention or even treatment of GVD.

After the first postoperative year, the major cause of heart allograft failure is graft vessel disease (GVD) [1]. Its pathogenesis is still not well understood, but elevated plasma low density lipoprotein (LDL)-cholesterol and fibrinogen levels seem to be a major factor. While high LDL-cholesterol induces the development of atheromas filled with monocyte derived foam cells [2], elevated plasma fibrinogen levels cause an increased blood and plasma viscosity as well as erythrocyte aggregation. There is a high prevalence of these risk factors in heart transplant patients [3–5].

In addition, approximately 30% of the heart transplant recipients show an increase of lipoprotein (a) [Lp(a)] levels, possibly due to the immunosuppressive therapy. Since Lp(a) is an independent risk factor for coronary heart disease, it could also enhance the risk for GVD, particularly in combination with high fibrinogen levels [6].

Based on these assumptions, we induced two clinical studies for the prevention and treatment of GVD after heart transplantation (HTx). Simvastatin, an HMG-CoA reductase inhibitor, was used to evaluate the effect of LDL-lowering therapy on GVD (Study I) [7]. Patients with an insufficiant LDL-lowering effect of Simvastatin (LDL-C > 135 mg/dl) were treated in addition with the heparin mediated extracorporeal low density lipoprotein precipitation (H.E.L.P.) in order to decrease LDL, Lp(a) as well as fibrinogen at the same time (Study II) [8].

Study I

In 1992, HTx patients on standard triple drug immunosuppression were prospectively randomized either into a treatment (N = 33) or a control group (N = 29) receiving diet only. Plasma LDL-cholesterol levels were aimed at below 110 mg/dl. To achieve this goal, Simvastatin was administered at a dose of 5 to 20 mg in addition to dietary measures.

The incidence of GVD was assessed by yearly coronary angiograms that were compared with baseline angiographies performed within the first four post-operative weeks after HTx. The post-operative angiographies were interpreted by two independent cardiologists in a blinded fashion using the quantitative analysis system for angiographically assessed data (QANSAD).

Demographic data of the recipients, indications for HTx and donor data were similiar in both groups. Factors which also might have an impact on the incidence of GVD were evenly distributed, as were the number of rejection episodes, the cyclosporine A plasma levels and the cytomegalovirus (CMV) infection rates.

Simvastatin treatment was well tolerated without any adverse effects. As a result, the plasma cholesterol levels dropped as depicted in Figure 1. The target of ≤ 110 mg/dl was reached in 31 patients (94%) of the treatment group, but only in 3 patients (10%) of the control group. HDL-cholesterol remained unchanged; however, the LDL/HDL ratio was again significantly better when Simvastatin was administered. Simvastatin had no effect on plasma Lp(a) and plasma fibrinogen levels (data not shown).

The incidence of GVD in both groups is depicted in Table 1. After a follow-up time of three years, 12.1% of the Simvastatin group (4 of 33) and 24.1% of control (7 of 29) had signs of moderate to severe GVD. These results were significantly different ($P < 0.01$) between the two groups.

In conclusion, the three year follow-up results of this ongoing study indicate that diet and additional treatment with Simvastatin significantly decreases the incidence of GVD. This effect may be due to lowering of plasma LDL-cholesterol, but a drug-mediated

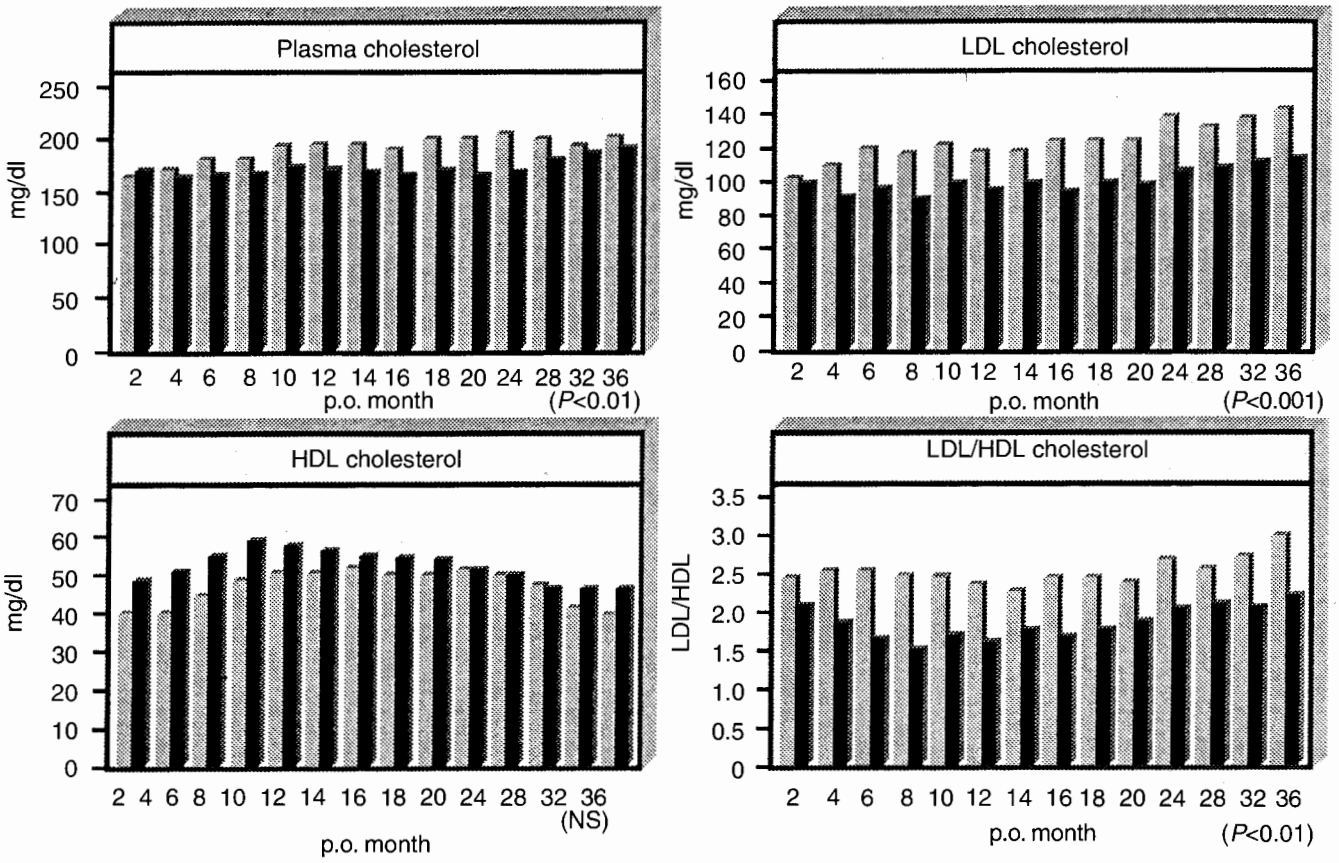

Fig. 1. *Total-cholesterol, LDL- and HDL-fraction of control group (diet only) and patients who had in addition Simvastatin.* Simvastatin treatment decreased total- and LDL-cholesterol significantly. HDL-cholesterol remained unchanged. As a result the LDL/HDL ratio improved.

Table 1. Coronary angiograms of control group (diet only) and simvastatin treated patients over of a follow-up period of three years

	Time after HTx			
Arteriosclerotic lesions %	Immediately p.o.	12 months	24 months	36 months
Control $N = 29$				
<50	—	—	—	—
50–75	—	2	3	4
75–99	—	1	2	3
100	—	—	—	—
Σ	0%	10.3%	17.2%	24.1%
Simvastatin $N = 33$				
<50	—	1	1	—
50–75	—	—	2	2
75–99	—	—	—	2
100	—	—	—	—
Σ	0%	3.1%	9.35%	12.1%

direct inhibition of intima and media cell proliferation may also play a role [7, 9].

Study II

The heparin mediated extracorporeal low density lipoprotein precipitation (H.E.L.P.) is an effective and safe therapy which removes LDL, Lp(a) and fibrinogen (Fig. 2) [10]. It does not influence HDL, nor does it affect normal plasma concentrations of cell mediators such as interleukin-6, interleukin-2-receptor, tumor necrosis factor or interferon gamma.

Indications for the H.E.L.P.-treatment were LDL-cholesterol concentrations above 135 mg/dl in spite of the maximal Simvastatin dosage of 20 mg/d and/or plasma fibrinogen levels of above 400 mg/dl.

From August 1991 to January 1995, 767 treatments were performed in 13 patients. H.E.L.P. was applied once every one to two weeks. While group 1 ($N = 10$) had normal coronary angiographies at the time of induction of H.E.L.P. (prevention group), group 2 ($N = 3$) already revealed signs of severe ongoing graft vasculopathy (treatment group).

In all cases in which H.E.L.P. was successfuly applied, blood levels of LDL-cholesterol, Lp(a) and fibrinogen were effectively lowered (Fig. 3) and remained at a low level between two consecutive therapies (which were given every or every other week, as mentioned). Over the entire treatment period, the mean values of the three parameters decreased slowly in patients with good results. In cases in which GVD was proven or even progressed, however, an effective and lasting decrease of LDL-cholesterol, Lp(a) and of fibrinogen was not achieved. There were no obvious reasons why H.E.L.P. treatment was successful in most patients but not effective in all.

The results of the coronary angiographies are summarized in Table 2. In group 1, eight out of the 10 high risk patients had no signs of GVD after a mean follow-up of three years. The two

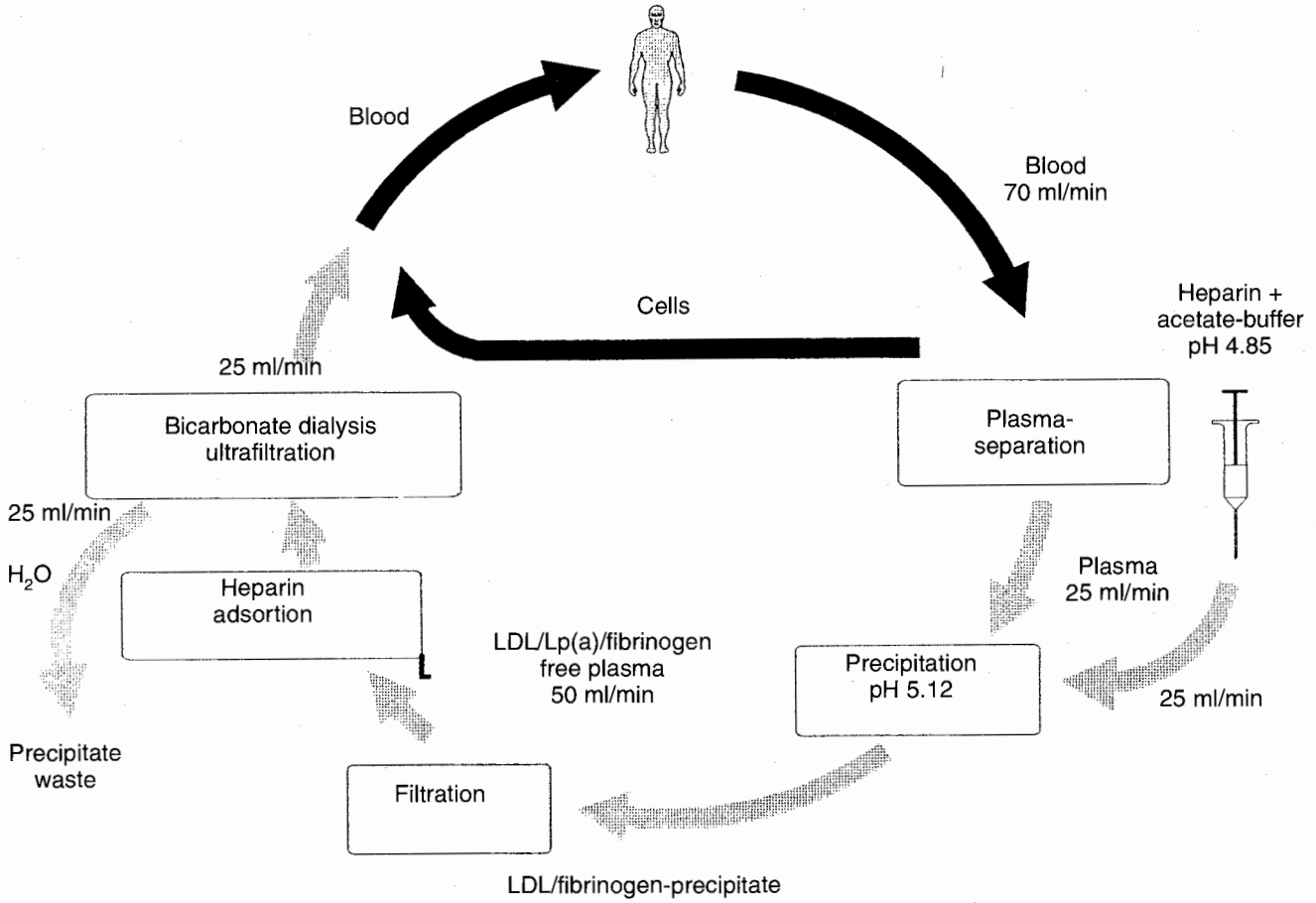

Fig. 2. *Flow sheet of the heparin mediated extracorporeal low density lipoprotein precipitation (H.E.L.P.).* In one session, LDL, lipoprotein (a) and fibrinogen are lowered in 2.8 to 3 liters of plasma. The procedure lasts two hours.

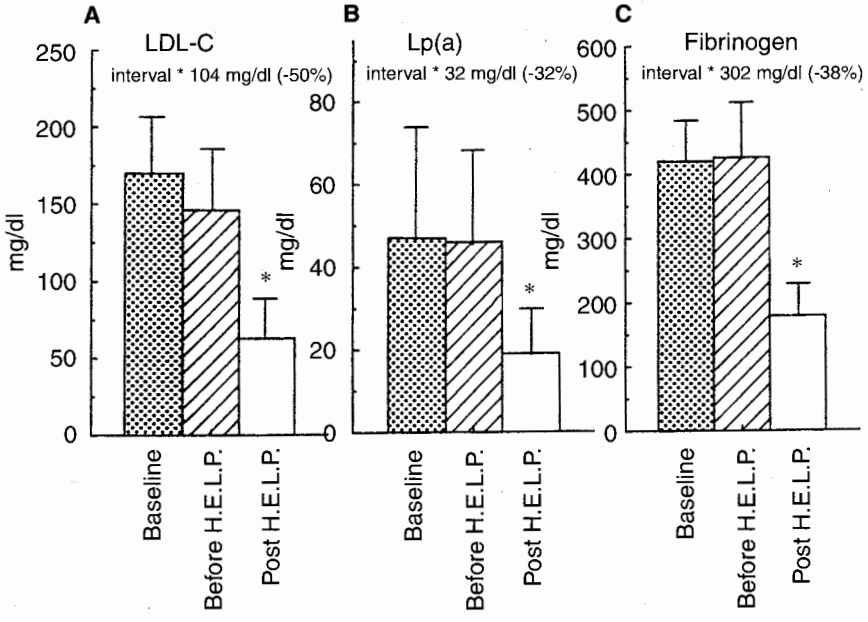

Fig. 3. *Effect of H.E.L.P. treatment on LDL-C, Lp(a) and fibrinogen mean plasma concentrations (+ SD) of 7 heart transplant patients and 263 H.E.L.P. treatments.* Baseline (dotted column) depicts levels just before the onset of the H.E.L.P. treatment. Cross-hatched and empty colums show LDL, Lp(a) and fibrinogen levels before and immediately after H.E.L.P. The interval values, that is, the levels between two consecutive treatments, are indicated by stars.

Table 2. Coronary angiograms of patients treated with the heparin mediated extracorporeal low density lipoprotein precipitation (H.E.L.P.) for prevention (group 1) or treatment (group 2) of graft vessel disease

	Results of coronary angiograms			
	At start of H.E.L.P.	After 1 year	2 years	3 years
Group 1 prevention (N = 10)				
No GVD	10	8	8	8
Progression	—	2	2	1
Further progression	—	—	—	1[a]
Group 2 treatment (N = 3)				
Regression	—	1	—	—
No change	—	1	2	2
Progression	3	1	1	1[b]

[a] Successful bypass operation
[b] Listed for retransplantation

remaining patients revealed signs of graft vasculopathy one year after H.E.L.P. was started. While further progression was withheld by continuing H.E.L.P. therapy in one, the condition of the second patient deteriorated and coronary artery bypass surgery became necessary.

In group 2 patients, angiographies over a time period of three years showed no further progression of the pre-existing GVD in two out of the three cases. One patient revealed signs of deterioration and has been listed for retransplantation. We believe that more frequent H.E.L.P.-therapy–at least once per week–may be beneficial in cases of further progression.

In conclusion, the H.E.L.P. study proves that in high risk HTx patients, drastic lowering of LDL-cholersterol may result in successful prevention or treatment of GVD. The Lp(a) and plasma fibrinogen reduction by the H.E.L.P. procedure has to be considered as an additional clinical benefit.

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