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26 Years of LDL – Apheresis: A review of experience

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ABSTRACT

Since 1981, when LDL-Apheresis was introduced into the clinical routine at the University of Cologne as the first and so far only Apoprotein B specific LDL-cholesterol elimination technique, considerable experience has since then accumulated and has changed not only the operational technique but also extended the indications, the optimation of the target values, the introduction of supportive cholesterol lowering drug therapy, considerations of the potential pleiotropic mechanisms and the introduction of a quality control supported electronic data processing. Mild to moderate side effects range between 3% and 4.5%, whereas serious undesired reactions did not occur within 26 years with more than 80,000 treatments performed at Cologne and considerably more world wide. As cholesterol can nowadays be widely eliminated in patients with familial hypercholesterolaemia (FH), the focus of consideration should be more directed to the treatment of additional risk factors. Thus, centres of competence, providing for more than the ability to technically reduce cholesterol may be desirable. Whereas numerous diagnostic procedures exist to demonstrate the value of cholesterol lowering therapies, the prolongation of survival as demonstrated in 7 homozygous and 29 heterozygous FH patients and in 5 patients with end stage disease appears to be the most convincing evidence for the value of LDL-Apheresis. Due to the repetitive cycling and re-use LDL-Apheresis is furthermore not only the most efficient but also the most economic approach to extracorporeal LDL-elimination therapy.

1. Introduction

In 1981, when LDL (Low Density Lipoprotein)-Apheresis was introduced, it was already well established, that an eliminated LDL-cholesterol was a risk factor of the primary order for the development of atherosclerosis. It was thus obvious, that a decrease of the plasma cholesterol should also lead to a risk reduction for the corresponding patients. The efforts for a decrease of the eliminated plasma cholesterol and thus the reduction of risk developed into two directions, the decrease of LDL-cholesterol using diet and drugs and also the decrease using extracorporeal treatments. Both approaches were successful.

The first attempts to decrease plasma cholesterol applying extracorporeal procedures prior to the introduction of LDL-Apheresis were initiated from DeGennes in Paris [14] applying single plasma exchange therapies in 1996. Lupien was the first to use in 1976 therapeutic affinity chromatography applying heparin as ligand [24]. The first systematic investigation was applied from Thompson in England [36], who using regular plasma exchange therapy demonstrated, that the survival of the treated as compared to the untreated siblings with homozygous familiar hypercholesterolaemia (FH) was prolonged.

With the development of double filtration plasma differential filtration was also applied in Japan to demonstrate, that this treatment approach would lead to a semi-selective decrease of elevated LDL-cholesterol.

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This like other unspecific or semi-selective extracorporeal procedures had in common, that they could decrease the LDL-cholesterol, however, the efficacy was limited due to the removal of other plasma components. Thus the decrease of the elevated LDL-cholesterol remained limited after the treatment and still a reduced but present risk factor.

2. Methods

2.1. Original method

LDL-Apheresis is defined as the immune specific extracorporeal LDL-elimination using repetitive-cycling adsorption and desorption applying continuous blood flow (therapeutic affinity chromatography). The definition originated from Prof. Arens, Rockefeller University, New York, in 1982. The principle of therapeutic affinity chromatography as applied for immune apheresis for the virtually specific elimination of LDL-cholesterol [34,35] is shown in Fig. 1. Apolipoprotein B (Apo B) containing particles are independent from their size or consistency bound to polyclonal or later on monoclonal sheep antibody to an adsorber perfused from the separated plasma and subsequently eliminated. Repetitive-cycling adsorption and desorption permits to decrease at least 80% of the initial pre-treatment value and thus differs from other technologies, which also may eliminate LDL-cholesterol among other plasma proteins. The technique of LDL-Apheresis consists of a centrifugal continuous flow separation of blood cells from the plasma combined with a simultaneous continuous flow secondary separation of plasma using adsorption columns [8–10]. The systems are shown in Figs. 2 and 3.

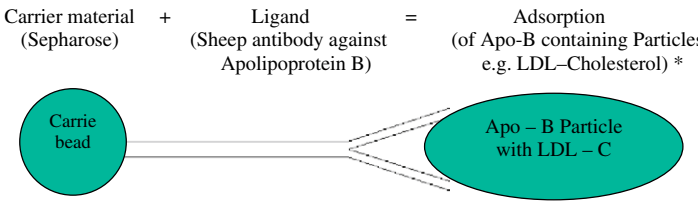
The technique of LDL-Apheresis was often copied, modified and claimed to be optimised. The name was and is frequently copied from so named "me-too-technologies", often to hide the disadvantages such "new" devices suffer from. Thus, frequently blood purification procedures, which together with other plasmatic substrates also eliminate cholesterol to some extent, are nowadays incorrectly named "LDL-Apheresis" for sales reasons. We left some of these procedures already in 1983–1984 during our own development; however, there are still sold as "modern" and "progressive". The misuse of terminology leads to confusion and misunderstanding.

Fig. 2. Primary separation system.

Fig. 3. Secondary separation system.

2.2. Subsequent development of the treatment technique

The very first treatments were performed with single columns of a volume between 400 and 800 ml per column.



* Other Apoprotein B containing particles: VLDL = Very low density lipoprotein, IDL = Intermediate density lipoproteins, Lp(a) = Lipoprotein (a)

Fig. 1. Principle of LDL-Apheresis: secondary continuous flow plasma separation using therapeutic affinity chromatography.

The approach using a single column was not pleasing as the elimination capacity for LDL-cholesterol was unsatisfactory due to the limited column volume. It is not surprising if the currently promoted whole blood adsorbers with their limited volumes suffer from the same problem. Also due to the simultaneous volume challenge for the patient the column volume was then decreased to 200 ml and divided into four adsorbers, which were loaded subsequently. This decreased the volume burden for the patient, who quite frequently suffered from symptoms of a progressed coronary heart disease associated with cardiac insufficiency; however, the problem of the limited capacity remained. The currently promoted whole blood columns used as single column or combined in series are able to increase the elimination capacity, however, with the disadvantage of either increasing the costs or the volume problems. Especially if the LDL-cholesterol values prior to therapy are rather high, the capacity remains unsatisfactory. Thus, in analogy of the earlier promoted repetitive-cycling loading and desorption of granulocyte filters this principle was successfully transferred into LDL-Apheresis.

Further improvement of the adsorber capacity was reached in Moscow from Prof. Pokrovski with the application of monoclonal rather than the otherwise used polyclonal antibodies.

During the very early treatments the primary and the secondary separation systems had to be taken care of from one person each. Subsequently, the treatment procedure was developed towards automation and the most recent state of the technological development is represented in Fig. 4 and 5. Also it is essential for some patients that using centrifugal devices the single needle technique can be used if a patient presents with only one good cubital vein.

Fig. 4. Primary separation system.

Fig. 5. Secondary separation system

3. Results

The following review of our own experience applies the term LDL-Apheresis exclusively to the original definition.

3.1. Overview of performance and achievements during the period of 1981–2008

Up to 2009 more than 80,000 treatments were performed in Cologne, world-wide more by far more. The therapies were performed on an outpatient basis. So far no severe side effects were seen (at present approximately 4% of minor undesired reactions) mainly no anaphylactic shocks, no need to transfer any patient into a hospital as complication of any of the treatments and no necessity for an artificial access to the circulation, even under long term therapy (according to our experience in apheresis an artificial access to circulation is generally not necessary in apheresis, thus avoiding associated complications, e.g. due to shunts or arterial catheters which, under these circumstances, may well be considered as medical malpractice). The indication was extended from originally homozygous FH-patients to an increasing number of heterozygous patients without treatment alternative leading to an improvement or maintenance of the quality of life (e.g. decrease of the number or severity of angina pectoris attacks up to their complete elimination. Cardiological or cardiosurgical interventions (PTCA or bypass surgery) were prevented or delayed depending on the compliance of the patients or the existence of additional risk factors for instance $LP_{(a)}$, low HDL-cholesterol or others. The morphological – clinical parameters were positively influenced

leading generally to a complete regression of xanthomas, xanthelasmae, regression (as shown by radiological procedures) of coronary heart disease in young patients of high risk (up to at least 18 years of age, probably up to a higher age) and secondary prevention [17,26] (delay of progression and under optimal target values also a hold of progression) in the elderly. Primary prevention was observed, depending on the age of the patient and the beginning of the treatment respectively. Life expectancy was substantially prolonged in homozygous patients (so far no atherosclerosis related death in 28 years). According to the current data and experience a corresponding experience was observed also with heterozygous patients and finally we saw an unexpected impressive survival of patients with end-stage-disease [10–12]. The technological principle of therapeutic affinity chromatography was also transferred to other applications (e.g. Digoxin-, Ig-, $Lp_{(a)}$-Apheresis).

3.2. Survival as proof of efficacy

Imaging morphology of atherosclerotic alterations in the vessel walls is mainly used to prove the efficacy of LDL-cholesterol lowering treatments. However, these diagnostic procedures are either of qualitative or, if an appropriate standardisation is used, of semi-quantitative nature only. Also, such examinations must not be used if performed for scientific reasons only without clinical indication. Trials, mainly with cholesterol decreasing medications, which demonstrate the slow down of angiographicly demonstrated progression or the carotis intima-media-thickness may often support the value of cholesterol lowering therapies, but may also be of borderline value.

In contrast the prolongation of survival is the most efficient proof of the efficacy of LDL-Apheresis. Table 1 shows the total of the homozygous FH-patients treated in Cologne. It is obvious, that none of the patients died from premature atherosclerosis.

The patient who died after surgery was the first homozygous FH-patient treated with LDL-Apheresis in 1981. The majority of surgeons rejected bypass-surgery in this patient due to his extremely progressed state of atherosclerosis. The subsequently performed bypass-surgery in another country led to the foreseeable death after surgery. The surgical procedure was justified according to the state of the art in 1981, however, according to

Table 1
26 years of LDL-Apheresis in *homozygous* patients with FH.

		Age of death	Period of apheresis	Result of apheresis
Total number of patients	10			
Cause of death				
After surgery	1	16 year	8 month	?
Suicide	1	30 year	18 years	Regression
Neoplasia	1	47 year	20 years	2 Prevention
Currently under treatment	7 (see Table 2)			

Note: No death due to coronary heart disease in 26 years.

Table 2
Results of long-term LDL-apheresis of homozygous patients with FH.

Patient	Date of birth	Years under therapy	Status of the coronary heart disease	Age (years)
1.	1968	28	Initial regression, now progression (due to additional risk factors)	42
2.	1963	25	Primary prevention[a]	47
3.	1970	25	Partial regression, now progress[c]	40
4.	1947	24	Secondary prevention[b]	63
5.	1971	16	Secondary prevention[c] (progress expected)	39
6.	1983	16	Complete regression	27
7.	1963	17[d]	Progression (additional risk factors)[c]	47
			Average age	43.6

Average age of death (according to Goldstein and Brown) for receptor negative 11, receptor defective 23 years.
[a] Though with aortic valve replacement.
[b] According to clinical criteria.
[c] Under unsatisfactory cholesterol depletion.
[d] Interruptions of 4 and 5 years each.

Table 3
Causes of treatment termination during 26 years of LDL – apheresis in heterozygous patients with familial hypercholesterolaemia.

		Average age of death	Period of Apheresis	Apheresis result
Total number of patients	16			
Deaths of unknown cause	3	40 year	21 months	?
Myocardial infarction	1	50 year	10 months	Negative
Death due to neoplasia	1	60 year	6 ½ years	2° prevention
Lack of compliance	7	?	22 months	?
Move to another location	4	?	75 months	?
(Currently under treatment 31)				

our current experience LDL-Apheresis would have led most likely to a complete regression of his cholesterol deposits.

Table 2 shows the survival of the 7 homozygous patients currently treated at Cologne. The average age is now more than 41 years (range 25–61), however, it appears that the survival is not only influenced from the extent of the cholesterol reduction but also or even more from additional risk factors.

Table 3 summarises the 16 heterozygous FH patients who terminated their treatment or could not be treated furthermore. 3 patients died of unknown reasons, one most likely from thrombo-embolism and 2 during undue exercise or physical challenge in between the treatments. 1 patient died from documented myocardial infarction after 10 moths of treatment, whereas a lack of compliance led to termination of 7 patients.

The prolongation of survival in heterozygous FH-patients under LDL-Apheresis therapy is more difficult to evaluate as the initial diagnosis, the severity of the disease and the need for indication of LDL-Apheresis are by far more heterogeneous as compared to homozygous FH-patients. Also in at least some of the heterozygous FH-patients cholesterol lowering drugs or drug combinations can be applied though in relatively low dosages after individual dosage testing. Table 4 summarises the survival of those patients recruited 1981–1983 as compared to 2008 and the average age of all patients currently under treatment.

The results of LDL-Apheresis for the treatment of patients with end-stage-disease may also be of considerable interest. According to the general cardiological and cardiosurgical criteria the assumption is justified that patients after exhaustive conventional therapy and without treatment alternatives have limited chances for a treatment success with LDL-Apheresis.

The experience with the 5 in Table 5 presented patients with an end stage disease of their atherosclerosis and coronary heart respectively teaches that using an aggressive lowering of the LDL-cholesterol can lead overtime to a respectable improvement of the quality of life and a prolongation of life expectancy over years.

3.3. Side effects

The total number of *side effects* of 4000 performed treatments is summarised in Table 6. Complement activation, bradykinin activation and the activation of cellular systems were extensively investigated and published in several theses [15,19,21]. The measurement of complement activation using standard diagnostic procedures shows no alteration. The application of more sensitive procedures showed a moderate activation of complement for some early treatments, when new adsorbers were applied, however, this was without clinical relevance and decreased overtime with the number of treatments [20,29,30]. This

Table 4
Average Age of heterozygous Patients under long-term LDL – (immune)-apheresis.

Period of time[a]	Age (years)	Number of patients
1981–1983[a]	**33.3** (11–50)	9
Same patients 2008	**68.8** (37–75)	9
Average age of all patients in 2008	**58.1** (37–75)	31

The earlier treatments 1981–1982 were performed with suboptimal technology as being still under development.
[a] At start of apheresis.

Table 5
Survival of heterozygous patients with end-stage-disease and insufficient response or side effects of cholesterol lowering drug therapy under long-term LDL-Apheresis.

Gender	Apheresis time (years)	Age (years)	Current status[b]
1. ♀	23	67	At present normal quality of life
2. ♂	21	70	died 2008 after coronary angiography
3. ♂	17	52	Normal quality of life
4. ♀[a]	10	70	Quality of life still reduced
5. ♀	9	67	Quality of life still diminished

[a] Type III with extremely elevated Lp (a).
[b] 1.5.2008.

Table 6
Safety of LDL-Apheresis[a].

Total number of treatments from 2002 to 2006	4006	
Total number of side effects	189	(4.7%)
Serious (e.g. leading to hospitalisation)	0	
Moderate (e.g. prophylactic termination of treatment)	54	(1.3%)
Mild	135	(3.4%)

[a] Exclusive the "me-too" therapies.

demonstrates that the re-use in always the same patient is a safe procedure.

The formation of just demonstrable anti-sheep antibodies in approximately 50% of the patients at low titres is without significance, except if a pre-existing incompatibility against sheep protein is demonstrable. Within 26 years we could never observe such incompatibility using immune-LDL-Apheresis. Also, overtime a reduction of the antibodies, which are bound to the adsorbers during therapy without influencing their capacity, could be observed.

We repeatedly examined the particle release in the immune adsorbers applied. We used the limits as defined in the German and European pharmacopoeias for infusion solutions. The limits of 100 allowed for particles of up to 5 μm, 25 for particles of up to 10 μm and three for particles of up to 25 μm were never ever found to be exceeded. Analogous measurements with the same procedures in other systems, especially whole blood adsorbers, led at least in some instances to remarkable deviations from normal. Potential clinical consequences if considerable particle release occurs have to be discussed.

A special safety control program for the re-use of the adsorption columns was established from the very beginning before any legal regulation existed and since then refined furthermore. Based on our experience of 28 years and the established safety program we conclude that the reuse in the same patient is safe. Alternatively disposable systems may have a higher rate of side effects, e.g. due to Bradykinin activation.

4. Discussion

28 Years of LDL-Apheresis have led to modifications, alterations and change of paradigms of the treatment philosophy.

The *technological developments* have already been described.

Based on these optimations mainly on the increased technical capacity and the improved economy of LDL-Apheresis an *extension of indications* could be approached.

Since 1981 until today there is no satisfactory drug therapy for homozygous patients with familial hypercholesterolaemia. Thus, the indication for LDL-Apheresis was originally restricted for homozygous patients.

However, it became soon obvious that heterozygous patients with a severe expression of their disease should also be treated with apheresis therapy, mainly if side effects, drug intolerance and an insufficient response to the LDL-cholesterol lowering medication turned out to be obstacles for an optimal therapy, as these patients were then without treatment alternatives. Limited drug tolerance may be due to the medications used (e.g. severe constipation after applying bile acid binding drugs, so named "flush reactions" applying nicotinic acid) or may be due to an additional disease of the patient (e.g. chronic gastritis, oesophagitis with reflux).

Following the introduction of statins and ezetrol or the combination of both the frequency of drug induced incompatibilities is clearly reduced. It appears that the limitations of drug tolerance may sometimes be neglected from the pharmaceutical industry. Approximately, 5–8% of the heterozygous patients who need a cholesterol lowering therapy remain for extracorporeal elimination mainly if suffering from advanced coronary heart disease.

Patients with a late or end stage of their atherosclerotic disease turned out to be another group of patients who need extracorporeal LDL elimination therapy. The following criteria may be used to define end stage disease for patients with advanced coronary heart disease and without treatment alternative or progressed atherosclerosis respectively.

- Resuscitation after myocardial infarction due to progressed coronary sclerosis.
- No further therapeutic cardiological (e.g. stents) or cardio surgery (e.g. 3 or 4 bypass surgeries) or analogous angiological surgical procedures.
- Minimal working exercise (e.g. underneath 25 W).
- More than 3 angina pectoris attacks per day at rest without physical challenge in spite of maximal antianginal therapy.
- Optimal treatment or exclusion of other risk factors.
- Proof of far advanced pathological coronary morphology.
- Exhaustive application of all maximal possible cholesterol lowering diet and drug therapy especially applying different drug combinations.

This group thus also embraces patients without treatment alternative. Applying an especially aggressive diminution of the LDL-cholesterol they frequently respond not only with an improvement of their quality of life but also with an extension of their life expectancy.

Other risk factors not always sufficiently taken into consideration in earlier years may now play a more important role, e.g. a frequently elevated $LP_{(a)}$. It is elevated in approximately 60% of our patients with familial hypercholesterolaemia and may especially if considerably elevated (e.g. more than 100 mg/dl) reasonably decreased with repetitive cycling of loading and desorption of the columns. According to our experience a selectively elevated $LP_{(a)}$ without clinical symptoms is no indication for $LP_{(a)}$-Apheresis, however the clinical and angiological state should be annually controlled. Alternatively, $LP_{(a)}$-Apheresis is indicated if an objectively proven progress can be demonstrated, clinical symptoms are present and premature atherosclerosis exists even if no further risk factor is present.

The treatment of patients with type III or type IV–V according to Frederickson characterised from an elevation of the IDL- and VLDL-cholesterol and thus serum triglycerides, remain a rare exception. An extracorporeal elimination therapy can only be recommended if these patients cannot be controlled with an appropriate diet in combination with a corresponding lipid lowering therapy, however neither LDL-Apheresis nor plasma differential filtration can often not be applied for technical reasons. As sometimes the elevated triglycerides depending on particle size and serum concentration remain in the adsorber or filter and lead to clogging, plasma exchange has to be used. An analogous situation exists in patients with diabetes and hypertriglyceri-

demia. The treatment in such diseases is generally not indicated unless acute pancreatitis (a typical complication in patients with type IV–V, sometimes also including diabetes mellitus) is present. Only a few plasma exchange therapies often lead to dramatic improvement. As these complications are mainly due to metabolic derangements following a dietary excess it must be pointed out that the control of the life style mainly the maintenance of an appropriate diet is the therapy of choice. However, in rare occasions this does not apply to patients in a kind of end-stage-disease where a control of the diet does not suffice any more. These patients cannot be judged with conventional standard, but need special consideration.

During the early years of development the *clinical-chemical target values* were mainly determined from technical limitations. During the early 80th the unlimited efficacy of the repetitive-cyclic approach was basically known, however could not necessary always be applied [18]. However, over time and with increasing experience this technical potential was more precisely defined. In the mid 80th the application of our group to perform a controlled trial was rejected for "ethical reasons", however, an open multicenter trial was supported instead. When finally performed it was not as innovative as originally planned and possible, however the result of this trial demonstrated the value of LDL-Apheresis without any additional medication [39]. Based on this trial, our additional experience with LDL-Apheresis and the increasing extent of overall data on the value of cholesterol lowering drug therapy, we recommend already since many years the following clinical-chemical target values, which years later were also recommended for the cholesterol lowering drug therapy in patients with advanced coronary heart disease [1]. It is rational that a risk factor, if possible, should be completely eliminated or that one should come as close to this aim as possible. Such recommendation also includes the use of such optimal target values for primary prevention.

Thus, the *clinical-chemical target values after apheresis* therapy should be decreased to the lowest possible LDL-cholesterol (e.g. lower than 50 mg/dl for heterozygotes, whereas the rapid increase in homozygous FH-patients, and the associated higher values prior to and in between the treatments have to be taken into consideration). Generally this recommended value should be reached after each single therapy independent from the initial values prior to apheresis. Thus, it should be possible to obtain *values in between two treatments* (=pre-value + post-value/2) to be in the range of "normal" LDL-cholesterol (e.g. 100 mg/dl, in high risk patients accordingly lower). LDL-cholesterol values *prior to apheresis therapy* should also include the consideration of HDL-cholesterol and assure a ratio of total cholesterol/HDL-cholesterol of 1:4 or as close as possible.

Such consideration needs a correction of the following historical aspects.

1. The different procedures used to lower LDL-cholesterol should be evaluated and considered differently according to their specificity, their efficacy per single treatment and their economy. Thus, an LDL-elimination register pooling the data from very different technologies does not provide for useful informations.
2. Target values to achieve optimal clinical results should be introduced and replace the general recommendation of a decrease of 60%, as recommended in the German guidelines.
3. Quality control procedures are necessary to improve the safety and the clinically available aims, such as regression, decrease of progression or complete halt of progression. The establishment of individual risk profiles prior to the first therapy is a must according to our experience.
4. According to the opinion of our patients (and not only they) believe that a more precise definition of the qualification for the treating physician is pre-requisite for the permission to perform extracorporeal LDL-cholesterol decreasing therapies. The establishment and promotion of centres of competence may well contribute to the efficacy and improve the cost-efficacy relation.
5. The selection and the competence of so named "competent board", if established and deciding upon the indication for LDL-Apheresis should be transparent. A definition of the competence of the board members in terms of apheresis needs to be defined and appears to be obligatory.
6. In case physicians applying extracorporeal LDL-cholesterol lowering therapies are supported from the industry they should be obliged to reveal their relations to industrial sponsors.
7. An individual judgement for the treatment indication should in special cases be possible.

An individualised *supportive cholesterol lowering medication* eases such consideration.

As compared to the nowadays available statins the LDL-cholesterol lowering medications available in 1981 mainly fibrates, nicotinic acid, bile acid binding, drugs and sitosterol were frequently difficult to tolerate for the patient (e.g. constipation after treatment with bile acid binding drugs for the so named "flush syndrome" of nicotine acid). Statins are not only more efficient, but are accompanied with a lower rate of side effects, which allows to lower the LDL-cholesterol in patients with familial hypercholesterolaemia in more than 90% of the patients excluding the homozygous. Whereas the target values even under cholesterol lowering drug therapy are now much lower as compared to earlier years a considerable number of heterozygous patients tend to suffer from incompatibilities or a limited response to their medication. However it has to be stated, that side effects even for these drugs may exist thus extending the indication for LDL-Apheresis. The limited tolerance of applied cholesterol lowering drugs in our patients is summarised in Table 7.

Additional positive effects of such supportive cholesterol lowering medication may be observed if the available single drugs or their combinations and their minimal tolerated dosage are tested for each individual patient along with LDL-Apheresis. Such individual testing appears to be necessary due to their limited tolerance (mainly of statins) in FH-patients under LDL-Apheresis. The following additional effects of an additive cholesterol lowering therapy can be expected [11]:

Table 7
Side effects of statins in 29 patients with familial hypercholesterolaemia.

	N	(%)
Muscle pain, weakness	14	48
Hair loss	4	14
Gastrointestinal discomfort	3	10
Arthralgies, bone pain	3	10
CPK increase	2	7
Increase of transaminases	1	3
Pseudo allergic reactions	1	3
Severe sleeping problems	1	3
Total	29	98

1. Reduction of the LDL-cholesterol increase after therapy.
2. Optimation of the post-treatment values and values in between therapy.
3. Abbreviation of the LDL-Apheresis procedure.
4. Additional pleiotropic effects, though under debate.

The rather limited additional effect (maximal additional decrease under apheresis up to 30% of the initial value in patients in a metabolic equilibrium) should not be used to prolong the treatment intervals, as such procedure would automatically lead to a deterioration of the basic treatment approach and keep the total pool of cholesterol in the organism extended.

It may be assumed that apheresis therapies being semi-selective allow generally only for a slow down of the progression of the coronary heart disease. Applying a more potent decrease of the LDL-cholesterol by 70 to more than 80% of the initial value and taking the above mentioned more stringent target values into account the complete elimination of an elevated cholesterol as risk factor appears to be possible and lead especially in the elderly heterozygous FH-patients to a hold rather than slowing the progression down. Thus an optimation of the *clinical* targets can be anticipated aside from a regression or primary prevention in young especially homozygous patients.

The following aspects speak in favour of a more aggressive decrease as compared to the earlier considerations which limited the decreased to 60% of the pre-treatment value during extracorporeal therapies:

1. A diminution of 60% of the initial cholesterol does not represent the nowadays technical possibilities of a repetitive-cycling treatment procedure.
2. The increase of the LDL-cholesterol after apheresis should be taken more into consideration and related to the technical procedure.
3. End-stage-disease-patients can, if an aggressive lowering of the LDL-cholesterol is applied, experience an unexpected improvement of the quality of life and a remarkable prolongation.
4. According to newer insights drug therapy alone already favours a more intensive treatment [1,3,16,22].

Progression free survival or overall survival may be debatable as endpoints, unless they are influenced from additional risk factors. Thus, an optimation of the clinical aims must also include the treatment of additional risk factors and an intense consideration of the individual life style to obtain an optimal treatment strategy.

The positive effects of LDL-Apheresis were mainly attributed in the past to the diminution of the LDL-cholesterol. However, favoured from the discussion about the efficacy of statins additional *pleiotropic mechanisms* are taken into consideration. This includes among others:

- The removal of modified LDL-cholesterol.
- The influence on the rheology.
- The influence on the membranes of blood cells mainly of erythrocytes and platelets
- The influence on the endothelium (induction of blood vessel dilating factors and cytokines).
- The anti-inflammatory effect.

The importance of modified LDL-cholesterol is for many years under debate as an additional factor for atherogenesis. According to the oxidation hypothesis oxidised LDL-cholesterol develops under the influence of free radicals mainly in the vessel wall, was shown to be present in the atherosclerotic plaques, is considered to alter the composition of LDL-particles and promotes under experimental conditions the foam cell formation due to an increased uptake via the "scavenger" receptor, inhibits the mobility of macrophages in the tissues, inhibits the endothelial mediated vessel dilatation, increases the expression of molecules on the endothelial surface and may lead to antibody formation. The LDL-cholesterol lowering effect of statins reduces the formation of modified LDL-cholesterol, thus permitting the assumption that potential atherogenic effects of the modified LDL-cholesterol in the plasma are increased binding the Apolipoprotein B of the modified LDL-cholesterol to the adsorber. It is debatable whether the favourable influences on the cell surface and on the mediators, already seen after a single apheresis treatment, leading to an improved myocardial perfusion are due to a decrease of the oxidative stress or an improvement of the equilibrium between atherogenic and atherogenesis inhibiting factors. This holds especially true for long-term apheresis applications.

Rheological alterations advantageous for the patients were first described from a procedure using heparin precipitation [32]. However, it remains uncertain whether this is due to the decrease of the LDL-cholesterol and/or other plasma proteins such as fibrinogen. Subsequently analogous effects were also described for the specific decrease of LDL-cholesterol using LDL-Apheresis [31] from the plasma, but also for the reduction of the erythrocyte elevation [31] and the platelet aggregation [4,27].

Vasodilatation is due to the stimulated release of NO. An improvement of the endothelial function could also be described following cholesterol lowering therapy with statins [2,25,37] in an analogous system of selective LDL-decrease [38] and after LDL-Apheresis [5]. The induction of other factors and cytokine types as well as adhesion molecules (e.g. E-Selectin, P-Selectin, MCP 1, Il-1, ICAM 1, VCAM 1 and Endoglin) were [6] described.

An anti-inflammatory effect can be recognised due to the diminution of the C-reactive protein concentration among other factors [28]. In our patients we could not

observe impressive alterations; however this may be due to the already earlier applied treatment prolongation prior to the introduction of the high sensitive CRP-tests. The inhibition of pro-inflammatory cytokines, partially proven, partially speculative, may also especially refer to the behaviour of pro-inflammatory cells, the smooth vessel cells, and the maintenance or the recovery of plaque stability.

The question remains under debate which effects of LDL-Apheresis, accordingly to LDL-cholesterol lowering pharmaceutical treatments and other extracorporeal procedures, depend directly on the lowering of the LDL-cholesterol or the additional pleiotropic effects.

An electronic data supported *quality and safety control system of LDL-Apheresis* is not only able to control parameters of the treatment efficiency, safety and economy, but also supports numerous otherwise rather complex functions, which are indirectly related to LDL-Apheresis. This includes:

1. The control of the target values (laboratory data prior to and after each treatment).
2. The documentation of the type and frequency of side effects as well as due to the apheresis as to the additional cholesterol lowering medication as to the reuse of the adsorbers.
3. The technical documentation for instance of the
   - ♦ treatment technique (separation system, adsorbers, operators) and
   - ♦ processed blood- /plasma-volume,
   - ♦ flow rates, alarms, etc.
4. The detailed pre-treatment history and the documentations of the responsible operator.
5. The control of the patient data, interim history and all necessary forms.
6. Print outs of protocols and graphics of the treatment data.
7. Administration of safety certificates, validations and charges.
8. Statistical evaluations.
9. Support of the treatment reports.
10. Control of storage materials and purchasing.
11. Control of economy and accounting.

Another essential advantage of our quality control system is, that it enables us to develop an individual, predictive decrease of the total-LDL-cholesterol. This is available prior to the treatment and thus enables the responsible physician and the operator to determine the variables of the treatments especially of the target values [7,33].

The clinical efficacy of the LDL-decrease may be restricted from several *limiting factors*.

According to our experience the clinical efficacy is diminished if the desirable target values are not obtained. This refers mainly to disposable techniques which also decrease LDL-cholesterol but within the limits of a simultaneous removal of other plasma components.

So far quality control systems are not considered to be mandatory for extracorporeal LDL-elimination procedures and are often unsatisfactory as the appropriate decrease of the LDL-cholesterol is not sufficiently taken into consideration. The quality control system we developed overtime does not only permit a retrospective data analysis but also the prospective determination of the efficiency criteria [7,33].

Finally additional risk factors have to be taken into consideration. They may be of clinical–chemical nature (Table 8), but also imply additional atherosclerosis-inducing or other factors (Table 9).

The importance of a treatment of all risk factors beyond the elimination of the LDL-cholesterol does not represent a new information, however, as shown in the reduction of the rate of myocardial infarction as demonstrated in Finland [22] and the USA it is of considerable importance [13,23].

4.1. Economy of the repetitive-cycling technique and the reuse

After we could demonstrate that the safety of LDL-Apheresis is no issue for further discussions the question of the economy of the LDL-Apheresis arose. One major topic is the variety of the applications of the primary centrifugal separation systems, e.g. in transfusion medicine, haematology, oncology etc., which can be used for several different indications per day and enables a more economical approach as compared to specialised technologies, applicable for one purpose only. The assumed high platelet content of the separated plasma is a fairy tale (unless one refers to unsuitable centrifugal cytapheresis systems), if the separation systems are properly used.

The adsorption columns can be reused between 50 and 200 times. Even if one takes the additional costs of the post-treatment handling, e.g. the control of the sterility

Table 8
Additional clinical-chemical risk factors in patients under long-term LDL-immuneapheresis.

	Homozygotes	Heterozygotes
Low HDL-C	4/6	18/31 = 58%
Elevated $Lp_{(a)}$ > 40 mg/dl	3/6	18/31 = 58%
Elevated fibrinogen	4/6	19/31 = 61%
Elevated homocystein[a]	1/6	19/31 = 61%

[a] As atherogenic substrate under debate.

Table 9
Additional atherosclerosis inducing and further accompanying risk factors in patients under long-term LDL-Apheresis.

	Homozygotes	Heterozygotes
Irregular treatments (compliance) or abbreviated treatment	2/7	5/29 = 17%
Dietary problems	1/7	5/29 = 17%
Overweight	1/7	8/29 = 28%
Smoking	1/7	1/29 = 3%
Lack of training	1/7	6/29 = 21%
Additional diseases		
Hypertonia	1/6	
Diabetes mellitus		5/29 = 17%
Small vessel disease		1/25 = 3%
Neoplasia[a]	1/7	(1/29)

[a] Patient deceased from neoplastic disease.

and other additional material costs into account, the total treatment costs decrease continuously after the 50th treatment. In contrast the treatment costs of disposable systems remain constant (Fig. 6).

An extended automation of the treatment process also decreases the number of operators, increases the versatility of the secondary system leading to a more intensive use of the whole versatile technical system.

4.2. Subsequent developments of the principle of therapeutic affinity chromatography

The principle of therapeutic affinity chromatography as suggested from W. Stoffel in 1981 was subsequently extended to the elimination of other undesired or pathological components of the plasma. At a time when intoxications with digoxin could only be treated with plasma exchange our group showed, that digoxin-apheresis using adsorption columns was by far more effective. This treatment is nowadays replaced from the direct injection of the ligands coupled earlier to the adsorber. The development of a C1q-adsorber initiated from our group could not be finished due to a lack of financial support though the clinical results were extraordinary. The major problem was the costly preparation of the C1q. We could demonstrate that the replacement of the sheep antibody using a peptide construct for the specific elimination of LDL-cholesterol was basically possible, however, clinically less effective.

Immunoglobulin (Ig) – Apheresis was developed from our group at Cologne in analogy to LDL-Apheresis. In 1992 our group (C. Jimenez-Klingberg) was rewarded for his work "Selective Adsorption of Immunoglobulin G" with the young investigators research award on the WAA Congress in Sapporo. The procedure was successfully applied for several autoimmune diseases and subsequently copied from the Baxter Company, which supported the therapy of dilatative cardiomyopathy. The result of this development is presented in several theses of the University of Cologne and was subsequently improved from the Russian National Academy of the Medical Sciences in Moscow.

$LP_{(a)}$-Apheresis as developed from Prokovski is based on the same principle and permitting a decrease of up to 85% of the initial value represents the most efficient procedure for the treatment of isolated atherogenic $LP_{(a)}$ –elevation.

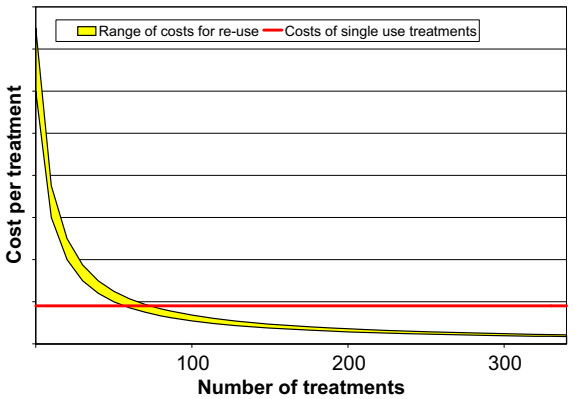


Fig. 6. Re-use cost development of repetitive-cyclic adsorption columns: exponential decrease of material cost during re-use (yellow line) as compared to constant costs of disposable, single use systems (red line) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

5. Summary

1. The prolongation of survival mainly of patients without treatment alternative for example homozygous FH patients is among other earlier published proof of efficacy the strongest argument in favour of the importance of LDL-Apheresis.
2. Further optimations are possible such as the update of guidelines, definition of target values, acquisition of sufficient competence for treating physicians and examination boards, quality control, further exploration of the pathophysiological mechanisms, development of competence centres etc. These improvements may lead to a depreciation of hypercholesterolaemia as risk factor, an increase of the quality of life, further prolongation of life expectancy and draw more attention to the consideration and treatment of other, simultaneously present risk factors.
3. Further economical improvements are possible due to the use of optimal technical devices and the reuse of suitable absorbers and new technical development.

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