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focus on

The lipid- and lipoprotein- [LDL-Lp(a)] apheresis techniques. Updating

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SUMMARY: **The lipid- and lipoprotein- [LDL-Lp(a)] apheresis techniques. Updating.**

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Therapeutic plasmapheresis allows the extracorporeal removal of plasmatic lipoproteins (Lipid-apheresis) (LA). It can be non selective (non specific), semi - selective or selective low density lipoprotein-lipoprotein(a) (specific [LDL- Lp(a)] apheresis) (Lipoprotein apheresis, LDLa). The LDL removal rate is a perfect parameter to assess the system efficiency. Plasma-Exchange (PEX) cannot be considered either specific nor, selective. In PEX the whole blood is separated into plasma and its corpuscular components usually through centrifugation or rather filtration. The corpuscular components mixed with albumin solution plus saline (NaCl 0.9%) solution at 20%-25%, are then reinfused to the patient, to substitute the plasma formerly removed. PEX eliminates atherogenic lipoproteins, but also other essential plasma proteins, such as albumin, immunoglobulins, and hemocoagulatory mediators. Cascade filtration (CF) is a method based on plasma separation and removal of plasma proteins through double filtration. During the CF two hollow–fiber filters with pores of different diameter are used to eliminate the plasma components of different weight and molecular diameter. A CF system uses a first polypropylene filter with 0.55 µm diameter pores and a second one of diacetate of cellulose with 0.02 µm pores. The first filter separates the whole blood, and the plasma is then perfused through a second filter which allows the recovery of molecules with a diameter lower than 0.02 µm, and the removal of molecules larger in diameter as apoB100–containing lipoproteins. Since both albumin and immunoglobulins are not removed, or to a negligible extent, plasma-expanders, substitution fluids, and in particular albumin, as occurs in PEX are not needed. CF however, is characterized by lower selectivity since removes also high density lipoprotein (HDL) particles which have an antiatherogenic activity. In the 80's, a variation of Lipid-apheresis has been developed which allows the LDL-cholesterol (LDLC) (-61%) and Lp(a) (-60%) removal from plasma through processing 3 liters of filtered plasma by means of lipid-specific thermofiltration, LDL immunoadsorption, heparin-induced LDL precipitation, LDL adsorption through dextran sulphate. More recently (90's) the DALI®, and the Liposorber D® hemoperfusion systems, effective for apoB100-containing lipoproteins removal have been developed. All the above mentioned systems are established LDL-apheresis techniques referable to the generic definition of LDLa. However, this last definition cannot describe in an appropriate manner the removal of another highly atherogenic lipoprotein particle: the Lp(a). Thus it would be better to refer the above mentioned techniques to the wider scientific and technical concept of lipoprotein apheresis.

KEY WORDS: Lipid apheresis - Lipoprotein apheresis - LDL-apheresis - Severe Dyslipidemia.

Lipoprotein [LDL- Lp(a)] apheresis

LDL-apheresis is an extracorporeal technique that allows selective and specific removal of LDL and of other apoB100 -containing lipoproteins, such as very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and Lp(a) (1-5). Some authors state that the term LDL-apheresis is to be better related to the apheresis per immunoadsorption, experimentally evaluated by Stoffel 26 years ago, and introduced by Borberg into the clinical practice (4). It represents a selective alternative to the conventional therapeutic plasmapheresis which can be identified with PEX, already used in in the seventies to treat severe hypercholesterolemia and often used to treat acutely hyperlipidemic pancreatitis, that remove practically all plasma proteins/components, including HDL-Cholesterol (HDLC) (Table 1) (5-9).

The major advantage of selective techniques is that they do not remove HDLC and other essential plasma proteins, and make possible an high removal rate of

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TABLE 1 - PLASMAPHERESIS TECHNOLOGICAL ADVANCES IN THE TREATMENT OF SEVERE HYPERCHOLESTEROLEMIA.

Year	Author	Technique
1967	De Gennes JL	Plasmaexchange dyscontinuous flow
1972	Turnberg LA	Plasmaexchange
1975	Thompson GL	Plasmaexchange continuous flow
1976	Lupien PJ	LDL-apheresis by affinity chromatography
1981	Hayashi R	Double Filtration
1981	Kikkewa T	Double Filtration
1981	Stoffel W	Immunoadsorption
1983	V.Baeyer H	Double Filtration
1984-5	Yokoyama S	Double Adsorption
1986	Seidel S	Double Precipitation with heparin
1987	Antwiter GD,	Double Precipitation with dextrane
1990	Malchesky PS	Thermofiltration
1993	Bosch T	Hemoperfusion (Whole Blood)
2009	Stefanutti C	Lipocollect
2010	Hequet O	Double-Column Whole Blood

Adapted from: Borberg H. et al. (3).

apoB100-containing lipoproteins, the most atherogenic particles. On the contrary It has been suggested that the most effective LDLa technique is the adsorption through anti-LDL antibodies obtained immunizing sheep serum (immunoadsorption, IMA). LDLa per immunoadsorption implies plasma flow through columns where anti-LDLa antibodies adhere to a sepharose matrix, and are then removed (10). The adsorption is used also in other systems where apoB100 non covalent combinations interact with inert substrate with negative charge. This is also occurring in LDLa by means of dextran sulphate on cellulose where the plasma, obtained after separation of plasma from its cellular component in hollow-fiber filter of polysulphone, is perfused in two filters. The dextran sulphate (negatively charged: polyanion) embedded on cellulose (DSC) beads removes the apoB100-containing lipoproteins selectively (with positively charged: polycation). The interaction occurs by means of electrostatic bonds. The plasma after extraction of atherogenic proteins is retransferred to the patient together with its corpuscular components (11). Another method is based on apoB100-containing lipoproteins precipitation at low (acid) Ph induced by heparin solution. In this system (Heparin Extracorporeal LDL Precipitation – HELP®) the plasma, obtained after filtration of whole blood, is mixed in 1:1 proportion with a buffer solution at 4.85 Ph of acetate and heparin. Subsequently, it undergoes heparinization and Ph reduction in order to allow apoB100-containing lipoproteins and fibrinogen (F) precipitation, thus forming macroaggregates which are removed by a second filter. The atherogenic proteins depleted plasma is perfused through an additional filter which eliminates the excess of heparin following a dialysis process to take lower the Ph back to its physiological values. A more recent LDLa method is the D.A.LI® (Direct Adsorption of Lipids) hemoperfusion system (12). This technique does not imply the separation of the whole blood, but a selective removal of apoB100-containing lipoproteins directly from the whole blood. The blood runs through a filter made of polyacrylamide spheres with syalic acid molecules. These molecules bind selectively the apoB100-containing lipoprotein component through an electrostatic mechanism. It emerges quite clearly that the more selective the system is, the more specific and effective is the removal (Table 2).

Table 2 reports the average reduction of LDLC, HDLC, Apo B, AI, Lp(a) and F in plasma with different LDLa techniques. It is to be underlined that the D.A.LI® system allows atherogenic lipoprotein removal directly from the whole blood, whereas in other methods the same process is carried out with the plasma. Both DSC-LDLa- and IMA-LDLa allow the treatment of nearly unlimited plasma volumes while the LDLa-HELP method cannot exceed 3 L per treatment, limiting thus the application of the method. Recently, a variation of the system would allow the processing of larger plasma volumes. The s*et-up* of D.A.LI® system is very fast and easy. However, D.A.LI® like DSC-LDLa, and HELP-LDLa, is probably more expensive than IMA-LDL-a (reusable system). This latter permits the reuse anti-apoB100 columns in the same patient. However, as far as the cost of the above mentioned techniques are concerned, there are national and even regional differences also related to the local reimbursement policy. Another more recent LDLa technique is based on hemoperfusion, or the removal of apoB100-containing lipoproteins from the whole blood using dextran sulphate made filters: the Liposorber D® (8,13-15). Another new reusable LDLa method has been recently introduced: the Lipocollect 200®. This system allows the removal of apo B100-containing lipoproteins through plasmaperfusion in filters with polyanionic substrates (16). Like in the immunoadsorption apheresis technique, the filters are reused for the same patient. The Lipocollect 200® method consists of small volume filters which undergo repeated plasmaperfusion cycles and larger volume filters. The filters contain a porous surface of silica gel polyanion which removes apo B100-containing lipoproteins through adsorption. At present the system is in a testing phase and no significant side effects has emerged so far. As far the average reduction of atherogenic lipoproteins are con-

TABLE 2 - AVERAGE PERCENTAGE VARIATIONS OF LDLC, HDLC, APOLIPOPROTEIN AI, APOLIPOPROTEIN B100 (APO B100, APO AI), LP(A) AND F. DIFFERENCES OBSERVED AMONG SIX LDLA TECHNIQUES OF LDLA (1 PLASMA VOLUME TREATED).

	PE	FC	DSC	HELP	IMA	DALI	Lipocollect
LDLC	72	65	73	69	65	67	61
HDLC	65	40	10	14	22	11	22
Apo B	69	59	62	53	56	55	51
Apo AI	68	45	16	12	20	25	25
Lp(a)	68	52	72	50	53	50	61
Fibrinogen	58	36	16	44	23	25	39

Adapted from: Stefanutti C. e Coll. (2).

cerned, the method appears to be efficient also in terms of selectivity. The same applies to small and larger volume filters. Given the same plasma volume, the reutilization of filters represents a cost-effective treatment for the patient. All LDLa techniques are effective in lowering the LDLC average post-apheresis concentration to a level below the threshold value of 70 mg/dL, which is the primary goal of the lipid-lowering therapy in patients at high cardiovascular risk (17). Clinical trials have demonstrated that all LDLa techniques can reduce significantly small dense LDL subfractions, inducing a quantitative and qualitative antiatherogenic effect, as well (18,19).

Pros and cons of Lipid and Lipoprotein apheresis techniques

Low cost, high efficacy, the removal of triglyceride-rich lipoproteins, F reduction and the use of a non-dedicated cell separator certainly represent the pros of PEX (Lipid Apheresis). The disadvantages, on the contrary, are the lack of selectivity (significant HDLC reduction) and the fact that the removed plasma must be replaced with human albumin (high cost) (2). CF is quite cost-effective, able at reducing F of approximately 41%, and the method has a firm *background* as it was used in the treatment of several diseases. Unfortunately, the method is semiselective and induces an undesirable statistically significant reduction of HDLC. Few studies of this technique in the treatment of severe dyslipidemia have been so far reported (20). The advantages of DSC-LDLa are the following: high efficacy and selectivity, long lasting use in clinical practice. The supposed disadvantages are: the need for a specific cell separator, quite high costs for the single use kit, potential activation of bradykinin during the treatment, and side effects if used in combination with ACE inhibitors (2,21). HELP-LDLa shows high efficacy, good selectivity, significant F reduction, and the procedure can be carried out very quickly. Disadvantages are: the need for a specific device, quite high costs for the single use kit, every treatment session is limited to 3 L plasma volume processing and the minimum *inlet* flow is relatively high: >40 ml/min (low or no indications for paediatric patients) (22-24). Theoretically, IMA-LDLa has low operating high efficacy and selectivity, and the possibility of reusing columns (30 to 35 times have been indicated). Disadvantages are the high cost of the single reusable column, the progressive reduction of the column's performance in terms of LDLC and Lp(a) removal, and the need of a device at present not exactly easily manageable. Other crucial points are the columns sterility control and their cooling procedure (2,3,25-27). D.A.LI system shows high selectivity and efficacy in the LDL hemoperfusional adsorption without plasma separation into its components. The system most appreciated characteristic is represented by the quick set up and relatively faster processing time. The disadvantages can be compared with those of other LDLa filtration methods: quite high cost, a specific device must be available, and side effects can occur when used in patients on ACE inhibitor therapy (28-31). A recent study on Lipocollect 200® reusable system reported high selectivity and efficacy. Disadvantages of this pioneering technique are the need of two integrated devices; one is specific, the second is usually a Cobe Spectra®. This association implies a rather complex management of the system. The columns must be refrigerated and frequently checked for sterility. Moreover, a simultaneous ACE inhibitor therapy is not recommended (16).

Lipid apheresis and Lipoprotein apheresis side effects

Hypotension and nausea are the most common side effects observed in the treatment with LDLa. Despite a definitely low incidence of side effects, we have to mention also the rare possibility of insurgence of chest pain in patients with ischemic heart disease due to transitory variations of circulating blood volume and modified

hemodynamic and hemorheologic conditions. Despite the changes occurring in the hemocoagulatory system, within and after apheresis hemorrhagic events are rare. Anafylactoid reactions in patients undergoing DSC-LDLa o DALI-LDLa or Lipocollect-LDLa may occur if ACE inhibitors are associated to apheresis. The above mentioned reactions are to be connected to the bradykinin release as its catabolism is blocked by ACE inhibitors. In 1997 Stefanutti et al. observed a low frequency of side effects in paediatric patients treated with DSC LDLa (32,33). Taking into account more than 300 sessions, in 93,5% of subjects no side effects have been observed. Only in 2% a mild hypotension was recorded, while 1% of the young patients had a severe hypotension. In 2% of the procedures venous access malfunction leading to further venipuncture, have occurred. Table 3 shows the occurrence of side effects and their frequency in a sample including patients of all ages and gender, observed within the frame of the Italian Multicenter Study on LDL-apheresis Working Group (IMSLDLa_WG), the most extensive multicenter study ever performed in Italy based on a *network* made up of 23 centers (2012) which use LA and LDLa techniques (Table 3) (31,35).

TABLE 3 - THE ITALIAN MULTICENTER STUDY ON LDL-APHERESIS WORKING GROUP: SIDE EFFECTS.

IMS-LDLa_WG Centers: No. 19	
Side effects	**# of events**
Symptomatic hypocalcemia	8
Venipuncture hematoma	230
Low outlet flow	125
Tubings coagulation	44
Allergic reactions	19
Gastrointestinal pain / Vomiting	6
Fever and shivers	--
Arterial hypotension / collapse	11
Vagal reaction	13
Hemodialysis	6
Cardiac arrhythmia	--

Treatment volume

An effective LA aims at obtaining LDLC and/or Lp (a) levels matching international standard targets without adverse effects. The rate of removal of a specific molecule from plasma or from the whole blood can be expressed in the following equation:

$$C = Ci \exp (- Vt/Vp);$$

where *C* is the concentration after apheresis expressed in gr/L, *Ci* is the initial concentration, *Vt* is the treated volume, *Vp* is the plasma volume, both expressed in liter, whereas *exp* means "e" raised to - *Vt/Vp*, where "e" is the irrational number of Nepero, equals to 2,718281.

The plasma volume is calculated with one of the following formula:

Vp (L) = 0.065 per body weight (Kg) per (L– hematocrit),

Vp (ml) = body weight (gr) per 0.042;

or simply expressed in ml by multiplying by 40 – 50 the body weight. The expected reduction of lipoprotein concentration is usually achieved through the effect of intravascular and extravascular redistribution and resynthesis, even though high molecular weight substances, like proteins, tend towards a gradual balance between intravascular and interstitial spaces. It is clear, therefore, that the post-apheresis concentration depends on the quality and quantity of the treated plasma, even though the efficacy of the removal process decreases on a continued plasma processing. One plasma volume apheresis, with a removal kinetic of 1, will reduce the circulating concentration of a given molecule of 55-60%, 75%, after processing 1,4 plasma volume, and more than 80% treating 2 plasma volumes (36). According the available evidence the data on plasma/blood volume to be treated are referred in general to a treatment of 1- 1,5 plasma volumes (37,38). However, the most significant goal is the so-called desirable *target* between consecutive apheresis procedures, relying also on the synergistic effect of the combined drug therapy. As far as the direct lipoprotein adsorption on whole blood is concerned, the total blood volume is to be taken into account. According to the formula first introduced by Otto C et al, the blood volume can be calculated in liters, like 1/13 of the body weight expressed in Kilograms (39). This method is used to establish individual total blood volume to be treated. In fact, it has been reported a lower lipoprotein particles removal rate using the whole blood apheresis methods, if compared to the plasma treatment techniques, at least for equal volumes (16,40).

Treatment frequency

LDLC or Lp (a) levels should be reduced between consecutive apheresis sessions to levels close to the *target* values recommended by the international guidelines for the prevention of cardiovascular (CV) complications in high CV risk individuals (17,38,41). Homozygous familial hypercholesterolemia (FH) form deserves a weekly treatment, while heterozygous form can be treated every 10-15 days. Since Lp (a) has probably a faster kinetic rebound than LDL, apheresis should be carried out every 7-10 days. The effects of treatment are also related to the patient's response. Accordingly, volumes

and treatment frequency can be established only after an initial accurate evaluation of the patient and *follow-up*. As a matter of fact, lipoproteins tend to decrease in the first 6-8 months of treatment, before reaching a constant *plateau* (level).

Conclusion

During the last three decades, lipid and lipoprotein apheresis were established as valuable extracorporeal treatment options for patients with severe heterozygous or homozygous FH non responding to usual medical therapeutic approach, such as diet and drugs given in combination, at maximum tolerated doses. The treatment of severe dyslipidemia by means of apheresis was progressively improved by technical processes and obtained wide documentation of beneficial clinical effects (15,37). Even more significantly, LA and LDLa various techniques have ensured survival to subjects at extremely high cardiovascular risk. Other favourable effects have been correlated to apheresis such as: the reduced susceptibility to the oxidation of LDL, the improvement of endothelial and hemorrhagic functions and of the procoagulatory pattern, the plasma reductions of Lp(a), and the reduction of the adhesion molecules and inflammatory peptides (cytokines) involved in the inflammation and, ultimately, to the development of atherosclerosis (42-50). Recently, new potent lipid-lowering drugs - MTP, PSCK9, CETP and Apo B synthesis inhibitors - have been developed and are currently under investigation. It would be of worthy scientific and clinical interest to evaluate these novel compounds in association to LA and LDLa to assess the impact and potential change of combined treatment on current procedure of administration of lipid, and in particular lipoprotein apheresis.

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