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Safety and Tolerability of Long Lasting LDL-apheresis in Familial Hyperlipoproteinemia

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Abstract: The aim of this work is to arbitrate the incidence of side effects and tolerability of long lasting LDL-apheresis in familial hyperlipoproteinemia. 1200 procedures were performed and the last 463 of them were evaluated. An immunoadsorption method of LDL-apheresis was used (continuous blood cell separator Cobe Spectra; secondary device: automated adsorption-desorption ADA, Medicap; absorption columns: Lipopak). As a whole, 6.26% adverse events were found and subsequently resolved by standard symptomatic therapy. Vaso-vagal reactions (symptoms of neurovegetative lability) were the most common adverse effects, presented as malaise, weakness, slight and short-term drop in blood pressure or other general signs. They were all well controlled by symptomatic therapy. We conclude that LDL-apheresis in the hands of experienced personnel is a safe procedure. An acceptable procedure duration limit, balancing the possibility to achieve a targeted cholesterol level while still maintaining an acceptable patient tolerance, was confirmed to be 4 hours.
Key Words: Adverse events, Atherosclerosis, Familial hyperlipoproteinemia, LDL-apheresis, Side-effects.

Clinical consequences of atherosclerosis, i.e. ischemic heart disease, vascular cerebral strokes and incidence of the peripheral vascular diseases are the leading causes of mortality in industrial countries. Thus, a number of researchers (1–5), as well as our team, focus on pathophysiological mechanisms, which could be used in prevention but mainly in therapeutic practice. Familial hypercholesterolemia (FH) and familial combined hyperlipidemia (FCH) are genetic disorders, which in affected individuals lead to a high incidence of severe cardiovascular complications in young people. When the dietary measures and pharmacotherapy do not yield sufficient results (approximately 5% of patients), it is necessary to use extracorporeal lipoprotein elimination. Several methods for this purpose exist and have been described in published material (2,5,6). Our working group has been using low-density lipoprotein (LDL)-apheresis, which is an effective and life saving method in homozygous FH and can improve health status in heterozygous FH.

Immunoapheresis procedures are amongst the most technically complex of all hemapheresis procedures used for treatment. The duration of the procedure should not be neglected because prolonged procedures might not be well tolerated by patients. This is particularly because of the fact that the upper limbs are fastened securely while the sampling needle is in place. The aim of this is to arbitrate the incidence of side-effects or complications of therapy and their tolerability. This was done after standardization of the method at a workplace with sufficiently trained attending personnel.

METHODS AND PATIENTS

We used the method of immunoadsorption LDL-apheresis (centrifugal separator, separator columns). Plasma was obtained by centrifugation using a blood-cell separator (Cobe-Spectra, Denver, CO, USA). Blood flow: 50–70 mL/min—depending on the condition of the peripheral vein. Heparin was used as an anticoagulant, with an initial bolus of 2500 I.U.,

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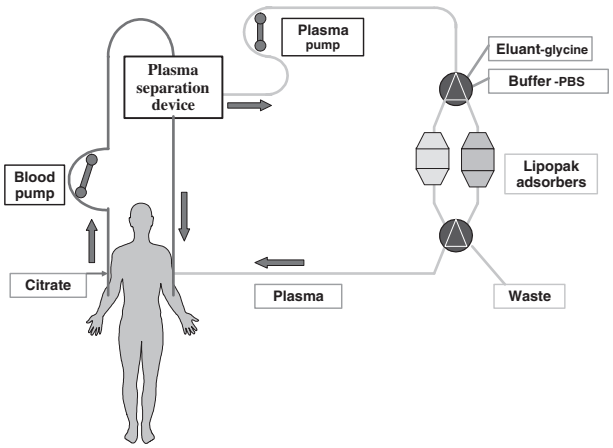

FIG. 1. Scheme of the procedure.

followed by 50 I.U./min, halved as each adsorber became saturated. Along with this, citrate was added 1:22 (ACD-A, Baxter, Deerfield, IL, USA). Plasma flowed through the adsorption capsules (Pocard, Moscow, Russia), controlled by adsorption-desorption equipment (ADA, Medicap, Ulrichstein, Germany). We used Lipopak 400 (Pocard) as adsorbers where the LDL-cholesterol and a part of lipoprotein (a) were adsorbed and then the plasma was returned to the patient. Once the capsule became saturated, the machine automatically switched over to a fresh capsule and the first one was rinsed and prepared for reuse. Washing solutions used included: saline; glycine; and pH correction with the phosphate puffer (PBS, Serag-Wiessner, Naila, Germany). The pair of columns thus alternatively functions until the cholesterol levels are substantially below normal levels (target level is below 2 mmol/L). A scheme of the procedure is shown on Fig. 1.

The adsorbers used in the present study are made of a glass container containing sheep antibodies against apoprotein B bonded to sepharose 4B after activation with bromocyanide. The principle of adsorber action is immunoadsorption, or therapeutic affinity chromatography—a specific extracorporeal on-line LDL-elimination therapy. The biochemistry of the adsorber system led with increasing purification and improvement to a loading capacity (in our opinion this is 5 g of LDL cholesterol per column and sometimes more). The objective is to stabilize the patient with an average level of cholesterol only slightly exceeding normal values in homozygotes and in heterozygotes we try to reach normal levels. The number of days spent with a cholesterol level below normal represents a period where a regression in atherosclerotic changes can occur.

Patient group

The patients with familial hypercholesterolemia (FH) were chosen based on the set of criteria presented by Gordon et al. 1994 (6), but they were slightly modified. All homozygotes were included but in cases of heterozygous FH there was secondary prevention (active heart coronary disease and LDL cholesterol more than 5.9 mmol/L) and primary prevention (LDL cholesterol more than 6.4 mmol/L + positive familial history +1 or more other risk factors).

The research was carried out on patients undergoing long-term therapy at the second internal clinic at the Faculty Hospital in Hradec Králové (7,8), Department of Hematology, Hemapheresis Center, where immunoadsorption LDL-apheresis has been carried out for the past 10 years. Over the course of this time, more than 1200 procedures have been carried out. At present eight patients are being treated on a long-term basis (observation period 6.3 ± 2.0 years, range 2.9–8.5, median 6.7 years, treatment interval 17.5 ± 1.6 days), in whom a total of 463 procedures were carried out and consequently evaluated over the past 3 years (2001–2003), thus providing for a standardized method and relatively experienced personnel. Information on these patients is presented on Table 1: six of them suffered from severe FH (two homozygotes, five heterozygotes), one from combined FH. Increased Lp (a) was found in five patients. The body mass index was 26.4 ± 5.5 (range 18.3–32.4, median 28.4). Four patients suffered with ischemic heart disease (coronarographically confirmed, two were after bypass).

RESULTS

We based the present study on the fact that the adsorption procedure is most similar to exchange plasmapheresis. Most of the technical and clinical details are fully identical. This is why we mainly followed adverse effects that we noticed during the study or others, which are commonly known to occur during large volume plasma exchange or hemapheresis (9–13). In the plasmapheresis group we had found 6% of side-effects (10), the absolute majority were not serious.

Experienced personnel actively monitored the side-effects over the whole course of the procedure. Eventual delayed side-effects were uncovered later during consequent outpatient's examinations. Out of the 463 LDL-apheresis treatments carried out over the years 2001–03, 6.26% of side-effects were cased. These are summarized on Table 2. This table depicts

TABLE 1. *Patients*

Number	Gender	Age	Hyperlipidemia	AS	IHD	VCE	ILE
1	F	16	HFH	+	v.s.+	0	0
2	F	23	HFH	+	0	0	0
3	M	35	FH	+	+	0	0
4	M	53	FH	+	+	0	0
5	M	54	FCH	+	+	0	0
6	F	55	FH	+	+	0	0
7	F	57	FH	+	0	+	+
8	M	58	FH	+	0	+	+

AS, proven incidence of aterosclerosis; F, female; FCH, familial combined hypercholesterolemia; FH, familial hypercholesterolemia; HFH, homozygote familial hypercholesterolemia; IHD, ischemic heart disease; ILE, ischemic disease of the lower extremities; M, male; VCE, vascular cerebral event.

the side-effects, which were observed, but also those that might happen according to published material and from our own experience with more than 8000 other hemapheresis procedures.

Vasovagal events (symptoms of neurovegetative lability) were the most common adverse effect, and presented as malaise, weakness, slight and short-term drop in blood pressure or other general signs (see Table 2). They were also usually characterized by bradycardia (40–60/min). They were all well controlled by symptomatic therapy (Trendelenburgs position, stop of procedure, eventually quick dropping of the saline). These reactions were controlled in some tens of seconds or in some minutes maximally, EKG showed sinus bradycardia in two cases under 50/min (46 and 48/min).

TABLE 2. *Side-effects*

Type of side-effect	No	Rep
Early reactions		
Vascular origin		
1. Necessity for great vein catheterization	0	0
2. Hematoma at the access site	1	0
3. Totally unsuccessful blood sampling	3	0
4. Gangrene	0	0
5. Central nervous system event (embolism)	0	0
6. Great vein perforation	0	0
7. Infection of the access site (including sepsis)	0	0
Cardio-vascular		
1. Transient weakness, nausea, chest pain	0	0
2. Hypotension	2	0
3. Short-term vasovagal reaction including syncope	2	0
4. Excessive fluid overload	0	0
5. Arrhythmia	0	0
Exchange solution effects		
1. Citrate toxicity		
a) facial paresthesia	6	0
b) muscular tension	1	0
2. Other solutions: pyrogenic (fever)	0	0
Other Reactions		
1. General signs (malaise, nausea, neurovegetative lability, chills, fever, headache)	11	3
2. Hypopotassemia	0	0
3. Hemolysis	0	0
4. Air embolism	0	0
5. Hypovolemia	0	0
6. Allergic reactions of unknown etiology (pruritus, rash)	0	0
7. Asthmatic attack	0	0
8. Difficulties caused by the rigid position assumed during examination	3	0
Late reactions		
1. Bleeding or thrombosis	0	0
2. Bacterial and viral infections	0	0
3. Immunological disturbances	0	0
Total	29	

The observed 29 side-effects were divided into early and late reactions. General signs were the most frequent.

Rep., the last columns shows the number of side-effects observed with the same case. One patient experienced headache twice, one patient experienced malaise twice and one had chills twice (observed during the period of 3 years).

Although great vein cannulation was unnecessary over the course of these procedures, at the beginning of our activity, we encountered several setbacks with venous access that eventually necessitated central cannulation. However, in such cases, we interrupted the procedure and repeated it later. In one of our patients, at that time, we implemented an arteriovenous shunt—a homozygous girl (15 years old) had the status of peripheral veins insufficient.

As for the troubles with citrate, only the most evident reactions have been recorded. A slight reaction occurs almost regularly, thus in our modified method we installed an input into the system which is filled with 4 ampoules of calcium gluconicum (Brown, Melsungen, Germany) in 50 mL of physiological solution. This solution can be slowly infused. The average consumption over the whole 4-h procedure is 25–35 mL; and it was only in a sensitive homozygote patient that we applied the entire 50 mL.

Feelings of tension and even slight edema, mainly in the legs, but sometimes also in the hands or eyelids are symptoms that almost unconditionally occur at the beginning of treatment. Thus, these problems are not mentioned in the synoptic table. These symptoms are accredited to a temporarily enhanced vascular permeability, not only in connection with the rapid changes in levels of lipoproteins, but also because of cytokine reaction on contact with sheep immunoglobulin. It has not yet been further scrutinized. Usually this reaction is very slight, not causing excessive inconvenience, lasting several hours, sometimes connected with increased tiredness, and not requiring special therapy. Amongst our patients, six had such reactions at the beginning of therapy, in two it persisted even after the procedure to date.

With regard to technical intricacy, these procedures belong to one of the most complex amongst hemapheresis therapeutic interventions. An important part depends on the theoretical proficiency and technical acumen of the personnel. These personnel were only considered well-trained after carrying out 100 procedures. Until then, minor technical faults did appear; however, in the past 3 years no such fault occurred.

The most critical personnel error would be to exchange the solutions leading to the intravenous application of disinfectant solution, with which the adsorbers are filled during storage. To prevent this, a protection was enforced. The columns are filled after the completion of each procedure and after the patient leaves the separator center. The disinfection solutions are stored separately. This error did not occur in our group.

Procedure tolerance

To attain a targeted lower level of cholesterol, it is necessary for the procedure to last for several hours. This justifies our main concern in following patient's subjective reactions towards longer procedures (those that lasted longer than 4 h especially). Our procedures lasted 230 ± 33 min, range 58–333, median 229 min (Plasma flow: 6654 ± 968 mL, range 1200–8734 mL, median 7000 mL.) These results show that procedures lasting longer than even 5 h were carried out exceptionally. Prolonged procedure tolerance as observed by the patient (namely in patients with atherosclerotic or other complications) is the deciding factor in this case. Six patients of our group did not find regular prolongation of the procedure (more than 4 h) to be advantageous. All eight patients did find the procedures longer than 5 h acceptable. Patients found the following inconvenient: the basic needs (drink or food possibility; WC; discomfort or even pain from the long and relatively stiff lying; and itching in various parts of the body, expectoration, sniffling and so on). Additionally, this procedure causes total dependence of the patient on personnel because both upper limbs have sampling tapping cannulae in place. Although personnel are constantly available during these treatments, the patient might still find this discomforting.

Based on the results of our observations we conclude that excessively prolonged procedures are unsuitable and, from the patient's point of view, might be difficult to tolerate. We found that 4 h is an acceptable limit, it is still possible to achieve a targeted cholesterol level, while still maintaining an acceptable patient tolerance.

DISCUSSION

Even though immunoapheresis is one of the most technically and time demanding of all hemapheresis procedures, we could not find a larger group of subjects in published material that dealt only (and as a main topic) with the problem of adverse effects of LDL-apheresis. Typically, there is work that mentions this problem, but this published material primarily deals with another topic. There is much published material (a very selective proportion of which is cited) that also mentions procedure-related complication and side-effects, however, they are rare. An important problem is that they exist neither generally accepted follow-up techniques, nor reporting systems for adverse events. So from study to study, the figures might differ significantly—the frequency of occurrence has been published as from 0 to 5%, and exceptionally 10% or even more. Some

results from previous reports mentioned document this concept.

While using the HELP method for instance, the authors present that long-term tolerance and safety parameters showed 'no significant difference' (14,15). Similarly, Splendiani et al. (3), while treating patients with myasthenia gravis using plasma-perfusion during columns containing tryptophan, did not observe any side-effects. Bambauer et al. discovered after 8 years of practice with various methods of extracorporeal elimination of lipoproteins, that the occurrence of severe side-effects such as shock or allergic reactions is very rare (0.3%) (5).

Sometimes a brief note on the subject suggests that a mere estimation of the frequency of such complications were presented. The authors also inconsistently evaluate the significance of the adverse effect, some do not include a weak citrate reaction amongst side-effects, as well as patient's complaints to the discomforting and long-lasting stiff positioning, etc. However, even routine hemapheresis in a healthy donor might have unexpected serious complications, e.g. cardiac arrest (16).

Our results have shown that modern methods of extracorporeal elimination of lipoproteins in the hands of experienced personnel can be a safe treatment method. Blessing et al. reported that the most frequent adverse effect were a drop in blood pressure. Long-term treatment is not reported in association with significant changes in blood cell component or other important blood constituents (e.g. total protein, albumin, immunoglobulins, hemoglobin, plasma electrolytes, hormones, and vitamins). The total incidence of adverse events reported to date was <5% (14). Our results are very similar to the Blessing's conclusions: During the treatment procedure, a detailed monitoring of the patient's clinical state including basic vital functions (pulse, BP, respiratory rate and ECG) was carried out by experienced personnel. The clinical state and the occurrence of side-effects were supplemented with monitoring basic biochemical markers, such as blood picture and differential, mineralogram, glycemia, creatinine, N urea, bilirubin, AST and ALT. These examinations were carried out at the beginning of the therapy and then repeated during long-term therapy in 3-month intervals. Up-to-date evaluations attest the fact that the changes in the followed parameters were not clinically significant and did not invariably condition apparent clinical reactions, symptomatology or disturbances in health state.

Severe reactions have been described with the use of dextran sulfate adsorbers, if the patient concurrently uses ACE inhibitors (9). In this case, it can lead to complement activation followed by mediator release and severe hypotension from an anaphylactoid reaction. This is mainly caused by a decreased breakdown of bradykinin and its increased production, induced by the negatively charged part of dextran sulfate. Hypotensive reaction during staphylococcal protein A column therapy in a patient with anomalous degradation of bradykinin was described in other published work (11). Thus, all patients and personnel are informed of this danger and prior to the procedure the personnel actively question the patients. These reactions did not occur in our group.

The course of the procedure can be considered in clinical practice as continual filtration, where the effluent plasma from the absorption columns has practically a zero concentration of LDL cholesterol, provided that the column is not oversaturated. The fall in concentration of cholesterol in plasma follows a curve that can be mathematically defined as follows: $C_x = C0\ (1 - 1/PV)^{Vp}$, where the concentration of cholesterol at point × is dependent on the initial concentration, PV represents the calculated volume of plasma (based on the hematocrit, weight and height of the patient) and Vp total volume of perfusion (17). We present a graph that depicts the drop in LDL cholesterol in plasma during continual separation in Fig. 2. To attain a targeted lower level of cholesterol it is necessary for the procedure to last several hours. This justifies our concern in patients' subjective reactions towards long procedures (patients' compliance and tolerance).

We believe that the views on the cause of hypotension are yet to be uniform. Our results with the two short periods of low, insignificant drop of blood pressure do not give any significant answer, but a number of authors believe that they are typical vasovagal reactions, however, others point out the significance

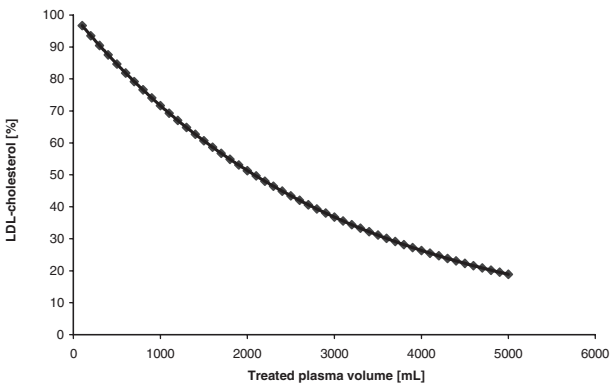

FIG. 2. Drop in LDL cholesterol in plasma during continual separation.

of complement activation, cytokine reaction, etc. (18). The complement activation might be connected with the incidence of nausea, fever, vomiting, muscular pains and dyspnoea, especially in immunoadsorption utilizing staphylococcal protein A, that directly activates complement (19). Vasculitis has also been described in connection with the use of these methods (cited from Pták, 2004–18).

Schuff-Werner evaluated an extensive group of 59 121 procedures with the extracorporeal apheresis system HELP. He recorded 2734 (4.6%) adverse effects in 622 patients. Even so, he believed that to define adverse effects directly related to the HELP procedure and adverse effects from concomitant drugs administered require careful consideration. Thus, the incidence of adverse effects directly attributable to HELP does not exceed 1–2% (2).

Carsten et al. evaluated the side-effects of extracorporeal elimination of lipoprotein with the aid of dextran sulfate columns. From 93 procedures carried out, 11 adverse events were recorded, adding up to 11.2%. From these, five were medical and six technical. The medical adverse events were mild, and LDL apheresis was continued in each case. From the medical events, three symptoms of hypocalcemia that reacted well to the application of calcium and two episodes of arterial hypotension were corrected by a reduction in blood flow (20).

Silvestro et al. assessed records from an Italian register, in which there were more than 164 943 various hemapheresis. The comparison of hemapheresis and LDL-apheresis is not correct, but it is interesting that they uncovered almost the same incidence of side-effects as we recorded during LDL-apheresis—a total of 6.75% adverse reactions during therapeutic procedures (whereas during donor procedures there were only 0.59% (21).

Pták evaluated adverse reactions during immunoapheresis carried out with Adsopak columns (Pocard) from sheep antibodies, adsorbing IgG (the only work which was carried out exclusively with columns from the same manufacturer as in our work). It was found that from the 245 treatment procedures there was a single case of mild hypotension and two technical breakdowns in the secondary equipment leading to the interruption of the procedure. The other 10 events were difficulties with venous access (18).

With the use of reusable immunoadsorption columns, some curious anecdotal cases have been published. For example, Kaiser et al. described a transmission of hepatitis C in patients treated with immunoadsorption columns with sheep antibodies in the case of a patient treated with antibodies against hemophilia A. The transmission probably occurred from the blood on the cuff of a sphygmomanometer. The blood was from another patient who was positive for hepatitis C and was treated for in the same room (22).

The total number of side-effects recorded in the present study was 29 of 463 procedures in the treatment of eight patients. The side-effects observed in the same cases are included in the number of side-effects (Table 2). The rate of side-effects could be strongly influenced by a patient's individual sensitivity. The analysis of this fact is shown in the last column in Table 2. It depicts the number of side-effects observed with the same case. One patient had a headache twice, one patient had a short period of malaise twice and one had weak chills twice (all were observed during the whole period of 3 years).

Our conclusions must be confirmed after further observation on a larger group of cases.

CONCLUSION

In our work, the invaluable modification treatment with LDL-apheresis can be considered to be safe in the hands of experienced personnel. By adhering to the rules mentioned above there were only 6.26% of non-serious complications. Even the tolerance of the procedure is acceptable. We confirm that 4 h is an acceptable limit because it is possible to achieve a targeted cholesterol level while still maintaining an acceptable patient tolerance.

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REFERENCES

1. Bambauer R. Is lipoprotein (a)—apheresis useful? *Ther Apher* 2005;9:142–7.
2. Schuff-Werner P. Clinical long-term results of H.E.L.P-apheresis. *Z Kardiol* 2003;92:III28–9.
3. Splendiani G, Cipriani S, Passalacqua S et al. Plasma perfusion on tryptophan columns can improve the clinical outcome of patients affected with myasthenia gravis. *Artif Cell-Blood Substit Immobil Biotechnol* 2003;31:69–79.
4. Seidel D, Armstrong VW, Schuff-Werner P. The HELP-LDL-Apheresis Multicentre Study, an angiographically assessed trial on the role of LDL-apheresis in the secondary prevention of coronary heart disease. I. Evaluation of safety and cholesterol-lowering affects during the first 12 month. *Eur J Clin Invest* 1991;21:375–83.5.
5. Bambauer R, Schiel R, Latza R. Low-density lipoprotein apheresis: an overview. *Ther Apher Dial* 2003;7:391–6.
6. Gordon BR, Stein E, Jones P, Illingworth DR. Indications for low-density lipoprotein apheresis. *Am J Cardiol* 1994;74:1109–12.
7. Bláha V, Zadák Z, Bláha M et al. Recommended indication criteria for LDL-apheresis treatment (in Czech). *Cas Lek Ces* 1998;137:424–9.

8. Bláha V, Zadák Z, Bláha M, Havel E, Vyroubal P, Malý J. LDL-apheresis: history and current practice in Czech Republic (in Czech). *Kapit Kardiol* 2001;3:72–6.
9. Bláha V, Solichová D, Zadák Z et al. Immunoadsorption LDL-apheresis in the treatment of severe hypercholesterolemia (in Czech). In: Bláha V, ed. *Nutritive and Metabolic Support in Critical Cases and Organ Failure.* Praha: Galén, 2001; 159–62.
10. Bláha M. Therapy of myeloma and other paraproteinemias by plasmapheresis. In: Sakalová A, Bláha M, Tichy M, eds. *Multiple Myeloma and Paraproteinemias*. Bratislava, Slovak Republic: Slovak Academic Press. 1995;121–5.
11. Molinaro R, Adam A, Lepage Y, Hammerschmidt D, Koenigbauer U, Eastlund T. Hypotensive reaction during staphylococcal A column therapy in a patient with anomalous degradation of bradykinin and Des-Arg—bradykinin after contact activation. *Transfusion* 2002;42:1458–65.
12. Borberg H. Results of an open, longitudinal multicenter LDL-apheresis trial. *Transf Sci* 2000;20:83–94.
13. Bláha M, Zadák Z, Bláha V, Malý J et al. The importance and mutual correlation between the indicators of atheromatosis activity after LDL-apheresis. *Acta Med (Hradec Králové)* 2002;45:48.
14. Blessing F, Wang Y, Nagel D, Seidel D. The efficacy and safety of the new heparin-induced extracorporeal low-density lipoprotein precipitation system (Plasmat Futura) in comparison with the currently used system (Plasmat Secura). *Ther Apher Dial* 2004;8:33–8.
15. Blessing F, Wang Y, Walli AK, Seidel D. Heparin-induced extracorporeal low-density lipoprotein precipitation: rationale for a specific adjuvant therapy in cardiovascular disease. *Transf Sci* 2004;30:255–66.
16. Cassens U, Baumann C, Hilamnn H et al. Circulatory arrest during PBPC apheresis in an unrelated donor. *Transfusion* 2003;43:736–41.
17. Bláha M, Mašín V, Stránský P, Bláha V et al. Optimization of therapeutic procedure during LDL-apheresis—a computerized model. *Transf Sci* 2005;32:149–56.
18. Pták J. *Immunoadsorption in the Therapy of Myasthenia Gravis (In Czech.).* Praha: Galén, 2005.
19. Toepfer M, Sitter T, Burchardi C. Klinische Immunoadsorption. *Dtsch Med Wochenschr* 1999;124:461–5.
20. Carsten O, Kern P, Bambauer R, Kallert S, Schwandt P, Parhofer KG. Efficacy and safety of a new whole-blood-low-density lipoprotein apheresis system (Liposorber D) in severe hypercholesterolemia. *Artif Organs* 2003;27:1116–22.
21. Silvestro DG, Marson P, Russo GE, Vicarioto M, Donadel C. National Survey of apheresis activity in Italy (2000). *Transf Sci* 2004;30:61–71.
22. Kaiser R, Geulen O, Matz B. Risk of hepatitis C after immunoadsorption. *Infect Control Hosp Epidemiol* 2002;23: 342–3.

