

Extracorporeal blood purification by adsorptive techniques

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Preface

Extracorporeal blood purification serves as therapeutic approach in a multitude of severe diseases from various fields of medicine. In some of these diseases the specific characteristics of the disease-causing agents or of the accumulating toxins require elimination processes different from conventional dialysis. "Therapeutic Apheresis" covers procedures like adsorption, precipitation and filtration. Due to their qualification and intense experience in performing extracorporeal therapy nephrologists often also carry out therapeutic apheresis besides standard dialysis in tight interdisciplinary co-operation.

This issue of Dialysis Update presents three different application areas of therapeutic apheresis. The study of Krisper et al. shows that "liver dialysis" by fractionated plasma separation and adsorption is capable of removing both water-solved and albumin-bound toxins effectively. Clearing the blood from atherogenic lipoproteins and cardiac autoantibodies respectively are further fields of application in patients who do not respond adequately to the conservative therapy. The efficacy of these therapeutic interventions could be demonstrated by the studies of Bosch et al. and Staudt et al. MB

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1. In vivo quantification of liver dialysis: Comparison of albumin dialysis and fractionated plasma separation

One critical issue of liver failure is the dramatic accumulation of toxins. The claim for effective therapies to overcome periods of decompensation or to bridge until transplantation has increased. The study by **Krisper et al.** compared two commercially available extracorporeal liver support devices in terms of their clearance capacity as a measure of detoxification efficiency and in terms of the reduction ratios (RR) of markers of albumin-bound and water-soluble toxins as a measure of delivered treatment dose. The two devices compared in this study were MARS[®], Molecular Adsorbents Recirculating System, from Gambro (at times of study performance from Teraklin) and Prometheus[®] from Fresenius Medical Care.

The MARS[®] system is based on the principle of albumin dialysis (AD system) where albumin bound as well as water-soluble toxins have to pass a special dialysis membrane surface-coated with protein before being removed by albumin containing dialysate. After then passing through a low-flux dialyser for removing the water-soluble toxins the albumin solution flows through two columns designed to extract the albumin-bound toxins, thus regenerating the solution so that it can return to the system for additional toxin removal. In contrast, in the Prometheus[®] system, based upon the method of fractionated plasma separation and adsorption (FPSA system), the patient's own albumin is separated from the blood and directly cleared from the toxins in two adsorbers before being readministered to the blood circuit where a high-flux dialysis follows.

Patients with acute-on-chronic liver failure were randomly assigned to start with the AD or with the FPSA system and then switched to the other device. This

study design allowed patients being their own control. Treatments were performed by experienced nephrology personnel either in the intensive care unit or in the dialysis unit when patients were clinically stable. Each treatment was performed for a duration of six hours at identical blood and dialysate flows for all patients. Eight patients completed at least one cycle of 4 treatments (2 with the AD and 2 with the FPSA system), so that a total of 32 treatments were available for analysis.

Before treatment a blood sample was drawn directly from the central venous catheter. 0.5, 1, 2, 4 and 6 hours after the start of the treatment blood samples were drawn from the inflow (arterial) and outflow (venous) lines of the extracorporeal circuit. Total, conjugated and unconjugated bilirubin (t-bili, c-bili and u-bili), ammonia and urea were measured. Clearance was calculated from paired arterial and venous samples and from effective blood flow. RR were calculated from pre- and post-treatment concentrations.

Clearance of all measured markers was higher with the FPSA system than with the AD system, though these differences lost significance beyond 4 hours for t-bili and c-bili. With both systems the clearance for u-bili, the more tightly albumin-bound fraction of bilirubin, was smaller than for the more loosely bound c-bili. In addition, clearance for all bilirubin parameters decreased during the six hour treatment with both systems which is an expected effect due to saturation of adsorbers. The clearance for urea remained stable throughout the treatment in both groups, as seen in haemodialysis. The clearance of ammonia decreased during the treatment with the AD system but not with the FPSA system. **Fig. 1** depicts the RR of the albumin-bound and water-soluble markers.

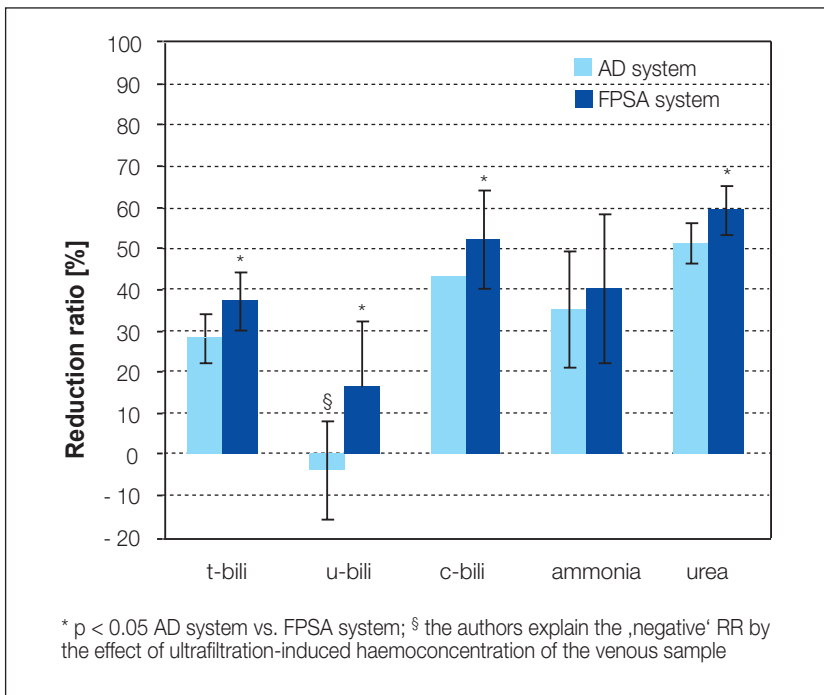


Fig. 1: Reduction ratios of the albumin-bound (total, conjugated and unconjugated bilirubin) and water-soluble markers (urea and ammonia); mean \pm SEM

Significantly higher RR for the FPSA system compared to the AD system were found for bilirubin and urea: 37 vs. 28% for t-bili, 16 vs. -4% for u-bili, 52 vs. 43% for c-bili and 59 vs. 51% for urea. Despite significantly higher ammonia clearance for the FPSA system, there was no significant difference in the ammonia RR: 40 vs. 35% for the FPSA and AD system, respectively. According to the authors relatively high rates of ammonia synthesis with rapid refilling from the extravascular compartments compared to elimination may be an explanation for these findings.

Despite overall higher clearances and RR with the FPSA system plasma levels did not differ significantly between both extracorporeal liver support systems. This would suggest that measurement of plasma levels alone is not sufficient for accurate quantification of the liver therapy. Thus, Krisper et al. recommend that RR of solutes could serve as an alternative to measure the delivered dose of therapy. However, when RR of solutes are evaluated their generation rates, transfer rates between multiple pools and possible post-treat-

ment rebound have to be considered. This would be especially indicated for ammonia and bilirubin. The additional measurement of the urea RR would thus assist an accurate assessment and quantification of the dose.

In conclusion, this comparison of the technical efficiency of an AD and FPSA system in eight acute-on-chronic liver failure patients revealed that the FPSA system provided a higher delivered treatment dose under identical study conditions. CL

Krisper P, Haditsch B, Stauber R, Jung A, Stadlbauer V, Trauner M, Holzer H, Schneditz D: In vivo quantification of liver dialysis: Comparison of albumin dialysis and fractionated plasma separation; J Hepatol 43, 451-457, 2005

2. Direct adsorption of low-density lipoprotein by DALI-LDL-apheresis: Results of a prospective long-term multicenter follow-up covering 12291 sessions

Raised levels of low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) (Lp(a)) are important risk factors in the development of atherosclerosis and coronary heart disease. Although most hypercholesterolemic patients can be treated effectively by conservative measures like physical exercise, diet, and drugs, some patients do not respond sufficiently to these therapeutic interventions. The removal of LDL-C by apheresis is thus indicated in these patients to reach the target values set by the scientific associations. Especially in patients who already suffered from a cardiovascular event, an aggressive LDL-C lowering therapy is recommended.

With this investigation **Bosch et al.** performed the largest open, prospective, multicenter long-term clinical follow-up to date with the DALI system (Fresenius Medical Care, Bad Homburg, Germany), the first system for direct adsorption of LDL-C and Lp(a) from whole blood. During an observation period of 5-years 12291 DALI sessions were documented in 158 hypercholesterolemic atherosclerosis patients from 28 apheresis centers. The included patients had persistently elevated plasma LDL-C levels > 30% above the target level despite maximal conservative therapy. The aim of

the study was to evaluate the efficacy (target of $\geq 60\%$ LDL-C reduction per session which is set by the German guidelines of good clinical practice), the selectivity (i.e. HDL-C recovery) and the safety of DALI. From 93 patients demographic data were available. 66.7% of them were male and their mean age was 47 ± 14 years. 76.3% suffered from the heterozygous form of familial hypercholesterolemia, 10.8% from the homozygous form, 5.4% from non-familial hypercholesterolemia, 5.4% from combined hypercholesterolemia and 2.2% from an isolated Lp(a) elevation. In order to reach the target of $\geq 60\%$ LDL-C reduction per session four different adsorber sizes were available: DALI 500, 750, 1000, and 1250.

The mean patient follow-up was 25 ± 16 months and the number of sessions averaged 78 ± 53 per patient. Most of them were carried out at weekly or biweekly intervals. The percentage reductions during a session, i.e. acute reductions, of the measured parameters by DALI are shown in **Fig. 2**.

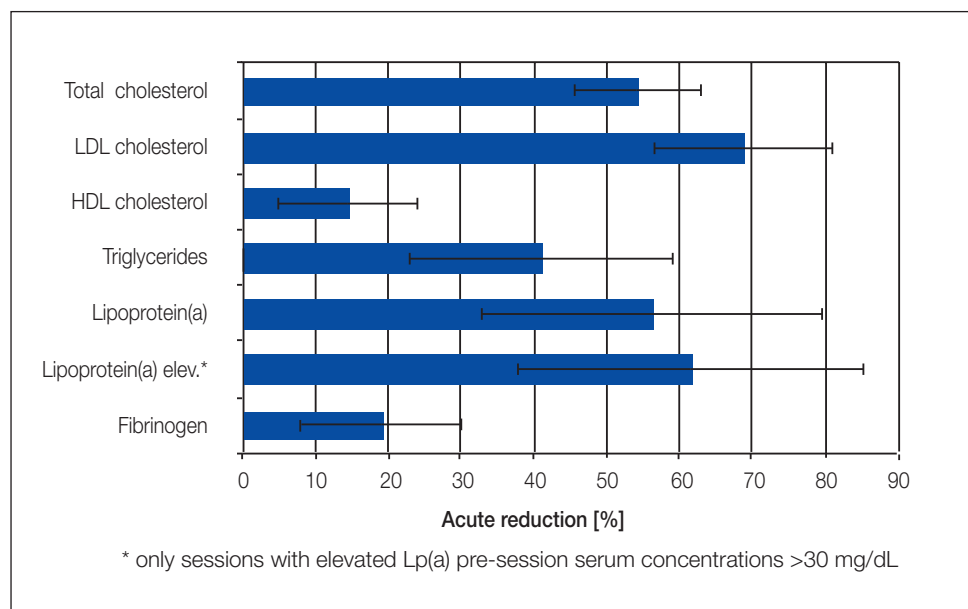


Fig. 2: Acute reductions in serum lipoproteins and fibrinogen by the DALI sessions

Reductions of LDL-C and Lp(a) in patients with elevated Lp(a) levels averaged 68.8% (from 188 ± 77 to 59 ± 35 mg/dl) and 61.5%, respectively. In contrast, HDL-C was reduced on average by only 14.5%, showing the high efficacy and selectivity of the DALI technique. Increasing the adsorber size markedly improved the reduction of LDL-C and Lp(a) as well as to a lesser extent also of triglycerides and fibrinogen while HDL-C losses remained constant at less than 15%. Long-term mean reductions calculated from baseline levels prior to the first DALI session and the averaged inter-apheresis levels of the last three sessions were 40% for LDL-C, 16% for HDL-C, 11% for triglycerides, 35% for Lp(a), and -3% for fibrinogen.

Pre- and post-session concentrations of all measured parameters but Lp(a) and HDL-C were significantly higher ($p < 0.001$), Lp(a) was lower (ns) and HDL-C was virtually identical in homozygous compared to heterozygous patients. Also the acute reductions for total cholesterol, LDL-C, triglycerides and Lp(a) were lower in homozygous patients with the exception of HDL-C for which a higher reduction rate was found ($p < 0.001$). Bosch et al. speculate that in this patient group the DALI adsorbers may be saturated earlier due to the higher baseline levels. Fibrinogen reduction was nearly identical in both groups.

Adverse events occurred only in 3.9% of the sessions with hypotension, paraesthesia and pain being the most common clinical problems. According to the authors, possible explanations for the hypotension might be hypovolemia, loss of oncotic pressure due to lipoprotein removal, vasovagal reactions and decreases in ionized calcium levels caused by the citrate anticoagulation. Furthermore, negatively charged adsorber surfaces give rise to bradykinin activation which might also contribute to hypotension. However, after two or three sessions the incidence of adverse events had decreased to a low level, indicating a growing experience in the DALI system of both the patients and the treating physicians.

In conclusion, this large prospective multicenter follow-up could demonstrate that direct adsorption of lipoproteins from whole blood with the DALI system is safe, effective, and highly selective for the harmful lipoprotein fractions LDL cholesterol and lipoprotein(a).

MB

Bosch T, Gahr S, Belschner U, Schaefer C, Lennertz A, and Rammo J for the DALI Study Group: Direct adsorption of low-density lipoprotein by DALI-LDL-apheresis: Results of a prospective long-term multicenter follow-up covering 12291 sessions; Ther Apher Dial 10, 210-218, 2006

3. Effects of immunoabsorption on the nt-BNP and nt-ANP plasma levels of patients suffering from dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is a primary myocardial disease characterised by dilation of the heart and impaired systolic function of mostly the left ventricle with decreased ejection fraction. Even with different pharmacological therapy options like angiotensin converting enzyme inhibitors or β -blockers the mortality rate is still high. Different etiological factors have been identified so far including hereditary as well as virus or alcohol associated forms of DCM. One of the main mechanisms in idiopathic DCM might be autoimmunity, as several antibodies e.g. against cardiac proteins have been identified. Therefore, immunoabsorption – effectively removing cardiac antibodies from plasma – is seen as a potential additional therapeutic approach in DCM patients.

In the present case-control study Staudt et al. included 30 stable patients with severe DCM (left ventricular ejection fraction (LVEF) < 35%). Additionally to their pharmacological therapy 15 patients received immunoabsorption and were retrospectively compared with the findings of 15 DCM patients without additional immunoabsorption therapy. Medication and dosage for the treatment group did not differ from that for the control group. The immunoabsorption therapy schedule (Immunosorba, Fresenius Medical Care AG, Bad Homburg, Germany) consisted of four courses at monthly intervals until month 3. All four courses were carried out on 5 consecutive days. After the final immunoabsorption session of each course, the patients of both groups received polyclonal immunoglobulin G (IgG) to restore IgG plasma levels.

As the neurohormones nt-ANP (inactive fragment of atrial natriuretic peptide) and nt-BNP (inactive fragment of brain natriuretic peptide) have been described

to increase in proportion to the severity of chronic heart failure and to independently predict morbidity and mortality in those patients, the investigators analysed the influence of immunoabsorption on nt-ANP and nt-BNP plasma levels, as well as on LVEF. In the immunoabsorption group LVEF was measured at baseline, after the first immunoabsorption treatment course and before and after the last treatment course (after 3 months) and nt-ANP and nt-BNP were additionally analysed before and after each treatment course. In the controls LVEF, plasma nt-ANP and nt-BNP were measured at baseline and after at least 3 months.

After 3 months LVEF increased in the immunoabsorption group from $29.7 \pm 1\%$ to $38.6 \pm 2\%$ ($p < 0.001$). No improvement was seen in the control group. The New York Heart Association (NYHA) classification – the functional classification system that relates symptoms to everyday activities – improved significantly in the immunoabsorption group from 3.1 ± 0.1 to 1.7 ± 0.2 . In contrast, control patients experienced no significant NYHA class improvement. A significant decrease in the prognostic parameter nt-ANP paralleled the increase of left ventricular function in the immunoabsorption group (Fig. 3A). Similarly, nt-BNP levels acutely fell during the first immunoabsorption course and still were decreased after 3 months (Fig. 3B). In the control group, nt-ANP and nt-BNP levels remained relatively stable during the 3 months of the study observation. For the authors it remains unclear whether the improvement of the left ventricular function and the reduction of nt-ANP and nt-BNP during immunoabsorption was caused by direct improvement of myocardial function, and/or was the result of vasodilation.

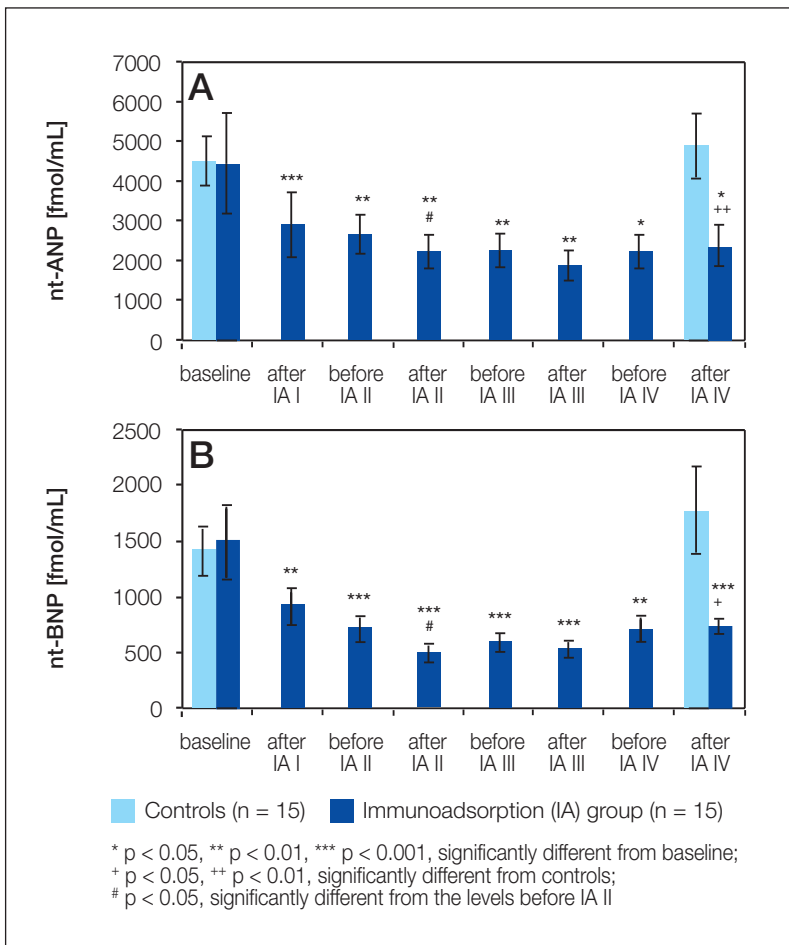


Fig. 3: Changes in nt-ANP (A) and nt-BNP (B) plasma levels in controls and the immunoadsorption group

All patients tolerated the immunoadsorption well and no major complications occurred. Neither clinical examination nor laboratory data showed any signs of infection in either group.

The study of Staudt et al. analysed for the first time the influence of immunoadsorption on plasma levels of the prognostic markers nt-ANP and nt-BNP in patients with heart failure due to DCM. The investigators could show that immunoadsorption not only improves left ventricular function in those patients, but might also reduce nt-ANP and nt-BNP plasma levels. AR

Staudt A, Staudt Y, Hummel A, Empen K, Dörr M, Trimpert C, Birkenmeier K, Köhl U, Noutsias M, Russ D, Felix SB: Effects of immunoadsorption on the nt-BNP and the nt-ANP plasma levels of patients suffering from dilated cardiomyopathy; Ther Apher Dial 10, 42-48, 2006



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