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MARS and Prometheus in Acute-on-Chronic Liver Failure: Toxin Elimination and Outcome

Extracorporeal liver support by cell-free detoxification systems, such as the molecular adsorbents recirculating system (MARS) and fractionated plasma separation and adsorption (FPSA, Prometheus), has gained widespread interest during the last decade. Both devices effectively eliminate bilirubin, bile acids, and other albumin-bound substances accumulating in liver failure. However, it is less clear whether these systems exert a beneficial effect on factors believed to be important in the pathogenesis of liver failure such as proinflammatory cytokines or parameters of oxidative stress. While initial small studies on MARS in advanced liver failure indicated improved survival, preliminary data of two recent randomized trials of either MARS or Prometheus versus standard medical treatment demonstrated no survival benefit in large cohorts of patients with acute-on-chronic liver failure.

Key words: extracorporeal liver support, molecular adsorbents recirculating system (MARS), fractionated plasma separation and adsorption (FPSA)

MARS und Prometheus beim acute-on-chronic Lebersversagen: Entfernung von Toxinen und Ergebnisse

Die extrakorporale Leberunterstützung durch zellfreie Entgiftungssysteme wie z. B. das Molecular Adsorbent Recirculating System (MARS) und die fraktionierte Plasmaseparation und -adsorption (FPSA, Prometheus) hat in den vergangenen zehn Jahren großes Interesse gefunden. Mit beiden Geräten können Bilirubin, Gallensäuren und anderen albumingebundene Substanzen, die sich beim Lebersversagen anhäufen, wirksam entfernt werden. Es ist jedoch weniger klar, ob diese Systeme sich positiv auf Faktoren auswirken, die als wichtig in der Entstehung des Lebersversagens eingeschätzt werden, wie z. B. entzündungsfördernde Zytokine oder Parameter von oxidativem Stress. Während erste kleinere Studien zu MARS bei fortgeschrittenem Lebersversagen auf ein verbessertes Überleben hindeuten, zeigten vorläufige Ergebnisse aus zwei neueren randomisierten Studien zur Behandlung mit MARS bzw. mit Prometheus im Vergleich zu einer standardmäßigen medizinischen Behandlung keinen Überlebensvorteil in großen Patientenkohorten mit acute-on-chronic Lebersversagen.

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Schlüsselwörter: extrakorporale Leberunterstützung, Molecular Adsorbent Recirculating System (MARS), fraktionierte Plasmaseparation und -adsorption (FPSA)

Definition of Acute-on-Chronic Liver Failure (ACLF)

According to a working definition proposed by Jalan & Williams, acute-on-chronic liver failure (ACLF) is defined as acute deterioration of liver function in cirrhotic patients over a period of 2-4 weeks, usually precipitated by gastrointestinal bleeding, infection, binge drinking, or surgery, and associated with progressive jaundice, hepatic encephalopathy and/or hepatorenal syndrome, and signs of multi-organ dysfunction (1).

Pathogenesis and Natural History of ACLF

Pathogenesis of ACLF remains unclear at present. Putative mechanisms include accumulation of albumin-bound and water-soluble toxins, systemic inflammatory response with overproduction of proinflammatory cytokines, oxidative stress, and circulatory changes following the accumulation of vasodilators (1). ACLF has been shown to carry poor prognosis with an in-hospital mortality ranging from 50% to 66% (2, 3). Prognosis of ACLF may be estimated by the model of end-stage liver disease (MELD) or by composite prognostic ICU scores reflecting the degree of multi-organ dysfunction such as the sequential organ failure assessment (SOFA) score (2-4).

Extracorporeal Liver Support in ACLF

During the last four decades, several extracorporeal liver support systems have been designed and evaluated in the treatment of ACLF (5). Recently, research has focused on cell-free systems that provide elimination of albumin-bound toxins but do not replace hepatic synthetic function, such as the Molecular Adsorbent Recirculating System (MARS™, Gambro, Sweden) and the Fractionated Plasma Separation and Adsorption system (FPSA, Prometheus™, Fresenius Medical Care, Germany) (6, 7).

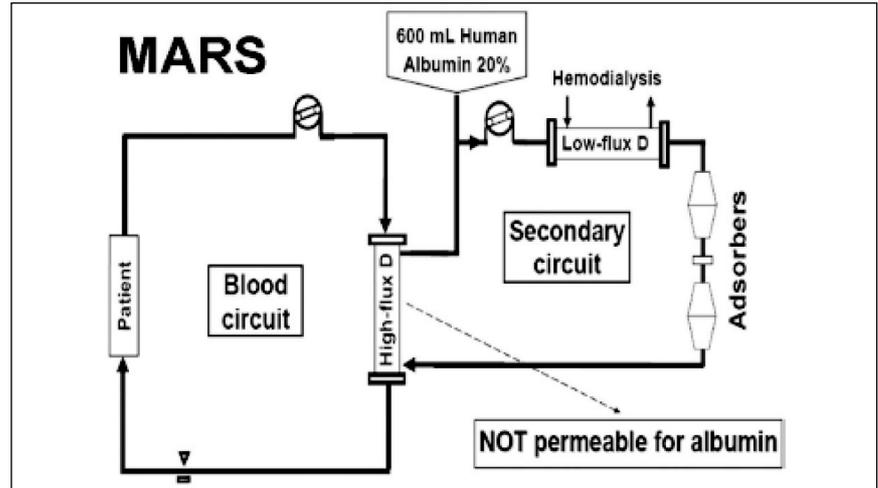


Fig. 1a: MARS (molecular adsorbents recirculating system) is based on albumin dialysis, using an albumin-impermeable high-flux dialyzer and a secondary circuit pre-filled with 20% albumin solution, and additional low-flux dialysis in the secondary circuit (8).

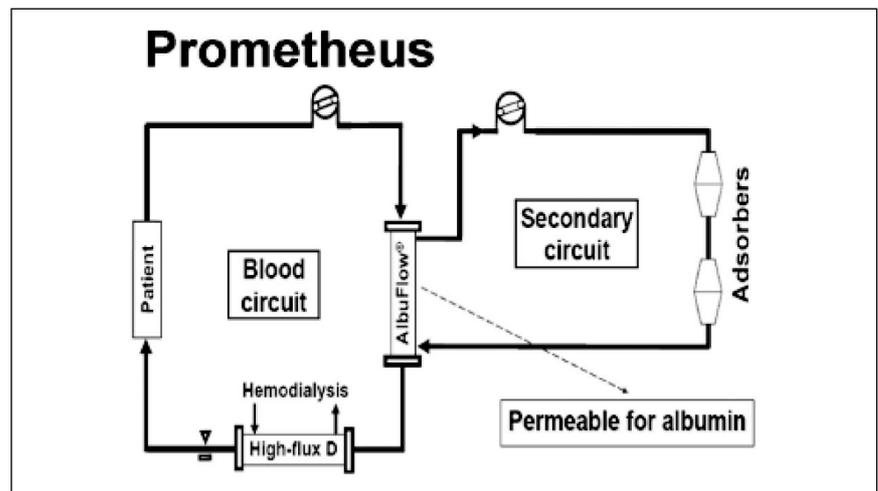


Fig. 1b: Prometheus (FPSA, fractionated plasma separation and adsorption) is based on fractionated plasma separation across an albumin-permeable filter (AlbuFlow) and high-flux dialysis in the blood circuit (8).

MARS

In MARS, blood is dialyzed across an albumin-impermeable membrane with a molecular weight cut-off of 60 kDa against 20% human serum albumin, which is continuously cleansed by subsequent passage through columns of charcoal and an anion exchange resin. Water soluble substances such as NH_4^+ are removed by a low-flux dialyzer connected to the secondary circuit (7, 9).

Prometheus

In Prometheus, the patient's plasma is separated by a membrane with a molecular weight cut-off of approximately

250 kDa and this albumin containing fraction is passed over two columns containing different adsorbents. Water soluble substances are cleared by a high-flux dialyzer directly inserted into the blood circuit (6, 10-12).

Toxin Elimination by MARS and Prometheus

Several studies using MARS or Prometheus demonstrated elimination of albumin-bound and water-soluble substances accumulating in liver failure such as bilirubin, bile acids, and ammonia (8, 10, 13-17). Few studies have directly compared the relative efficacy of

both systems with respect to toxin elimination (8, 14, 18-20).

Comparative Trial of MARS and Prometheus

From 2003 to 2005 we performed a randomized cross-over trial of MARS and Prometheus in 8 consecutive patients with ACLF as defined above. In 4 patients alcoholic hepatitis on the background of alcoholic liver cirrhosis was the precipitating event. Using sealed envelopes, patients were randomly assigned to start with either MARS or Prometheus and underwent alternating MARS and Prometheus treatments on 2-8 consecutive days depending on the clinical course. MARS and Prometheus treatments were performed for 6 hours at identical blood and dialysate flows in all patients (200 and 300 ml/min, respectively) and the same dialysis machine (4008 H, Fresenius Medical Care) was used during the entire study. The flow in the secondary circuit was set to 200 ml/min in MARS and 300 ml/min in Prometheus as recommended by the manufacturers. Heparin, epoprostenol (Flolan®, 4 ng/kg/min) or both were used for anticoagulation and activated partial thromboplastin time (aPTT) was aimed to remain below 100 sec.

Bilirubin

While hyperbilirubinemia is a hallmark of advanced liver failure and its height is related to prognosis, bilirubin is not considered as a toxin but rather a surrogate parameter of liver failure. We compared the elimination capacity of both systems for individual bilirubin fractions and found superior plasma clearance of bilirubin (especially of its unconjugated fraction) by Prometheus (8, 14). However, the corresponding difference in plasma levels did not reach statistical significance (Figure 2).

Bile Acids

Bile acids are another example of albumin-bound substances that accumulate in liver failure. Hydrophobic bile acids are cytotoxic at high concentrations and their accumulation within hepatocytes may lead to apoptosis or necrosis. In addition, elevated plasma bile acids are

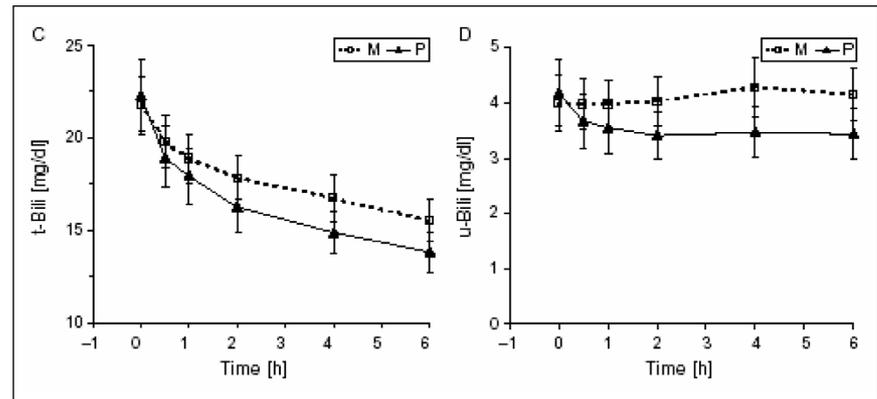


Fig. 2: Plasma levels (mean SEM) for MARS (M, dotted line) and Prometheus (P, solid line) at different time points of treatment for total bilirubin (C) and unconjugated bilirubin (D). No significant differences were found between M and P (14).

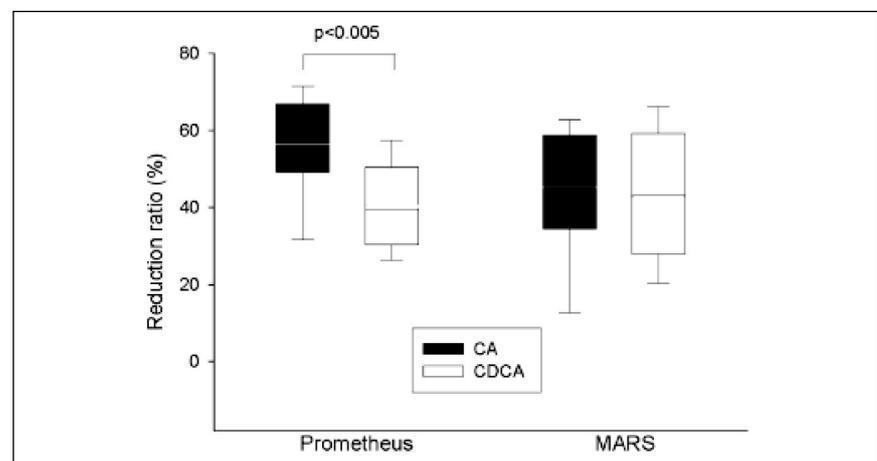


Fig. 3: Reduction ratio (1-post/pre) of cholic acid (CA) and chenodeoxycholic acid (CDCA) during Prometheus and MARS treatments. Box plots indicate mean, first quartile, third quartile, and whiskers indicate 5th and 95th percentiles (8).

linked to cholestatic pruritus and their elimination by albumin dialysis was associated with an improvement in pruritus.

In our comparative trial we evaluated the elimination capacity of MARS and Prometheus for individual bile acids measured by gas chromatography. Removal of total bile acids was equally effective in MARS and Prometheus treatments. Detailed analysis of individual bile acids revealed that Prometheus but not MARS altered the bile acid profile (preferential removal of cholic acid by Prometheus) (Figure 3) (8, 14).

Cytokines

Systemic inflammatory reaction, characterized by a predominantly proinflammatory cytokine profile, may cause the transition from stable cirrhosis to ACLF (21). Proinflammatory cytokines

are believed to mediate hepatic inflammation, apoptosis and necrosis of liver cells, cholestasis, and fibrosis (22). Therefore, it has been hypothesized that removal of proinflammatory cytokines could be beneficial in patients with ACLF (23). However, data on the effect of extracorporeal liver assist devices on serum cytokine levels are controversial (23-30).

We therefore evaluated the effect of MARS and Prometheus on elimination of several pro- and antiinflammatory cytokines (IL6, IL8, IL10, TNF α , and sTNF α R1). While both MARS and Prometheus showed a measurable clearance of all cytokines mentioned above, neither system was able to reduce serum levels of these cytokines (Figure 4), presumably due to high production rates (18).

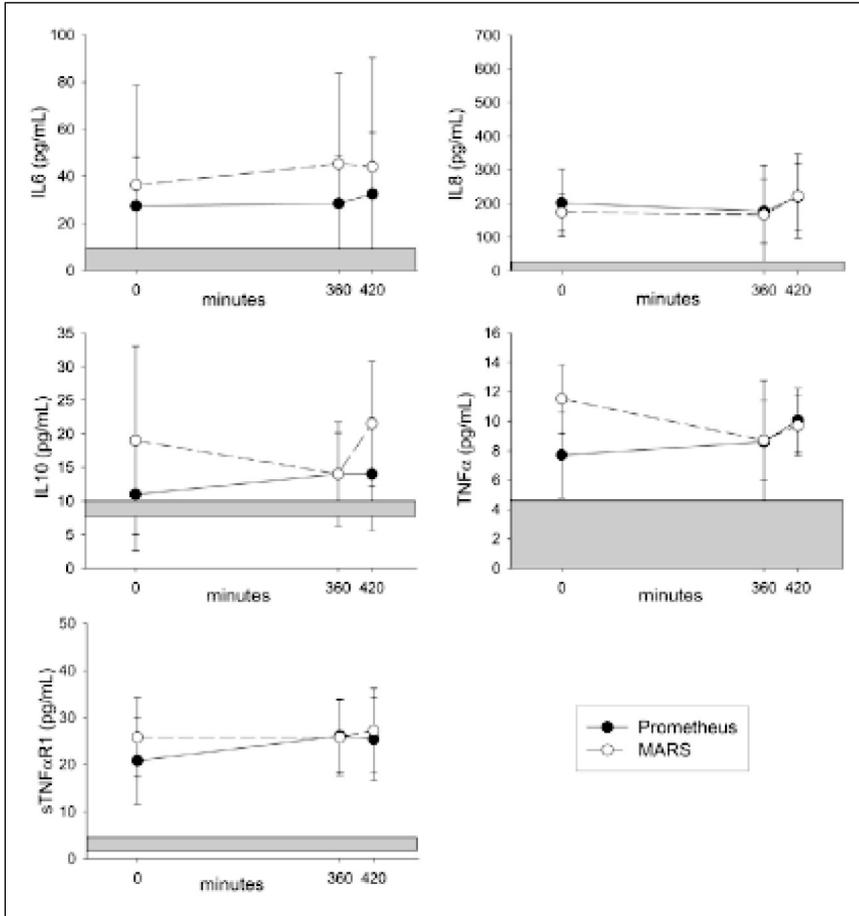


Fig. 4: Serum cytokine levels at the beginning of, the end of, and 60 min after 6-hour treatments with Prometheus or MARS. Values are expressed as median (Q1, Q3). Shaded areas indicate normal range. No significant changes of any cytokine levels were found (18).

Vasodilators

Advanced chronic liver disease is characterized by a hyperdynamic circulation following systemic vasodilation which is mediated by several vasodilators accumulating in chronic liver failure. This circulatory changes play an important role in the pathogenesis in life-threatening complications such as hepatorenal syndrome. In a comparative trial of MARS and Prometheus in patients with alcoholic cirrhosis and superimposed alcoholic hepatitis, Laleman et al. demonstrated that MARS but not Prometheus increased mean arterial pressure and systemic vascular resistance and this improvement was paralleled by a decrease in plasma renin activity, aldosterone, norepinephrine, vasopressin, and NOx levels (19). This differential result on blood pressure and hemodynamic markers may be in part due to a loss of serum albumin in Prometheus treatments leading to a reduction in colloid osmotic pressure that

might blunt the beneficial effects observed in MARS treatments (31).

Redox State of Albumin

Oxidative stress is believed to play an important role in acute-on-chronic liver failure (ACLF). Albumin, an important transport vehicle, was found to be severely oxidized in ACLF patients (32). Recently we evaluated the effect of MARS and Prometheus on the redox state of serum albumin by measuring the fractions of human mercaptalbumin (HMA, non-oxidized), human nonmercaptalbumin-1 (HNA1, reversibly oxidized) and human nonmercaptalbumin-2 (HNA2, irreversibly oxidized) before and after MARS and Prometheus treatments and during follow-up (20). In ACLF patients oxidized fractions of albumin, HNA1 and HNA2, were markedly increased. Both MARS and Prometheus treatments resulted in a shift of HNA1 to HMA while HNA2

was not significantly affected. This shift in albumin fractions was transient and disappeared within 24 hours after treatment. There were no significant differences between MARS and Prometheus treatments with respect to the redox state of albumin.

Effect of MARS and Prometheus on the Outcome of ACLF

Until recently, only limited data were available on the effect of MARS and Prometheus on survival. Three randomized controlled trials of MARS have been published as full papers (33-35). A small study randomized 13 patients with hepatorenal syndrome to MARS or hemodiafiltration and demonstrated a significant survival benefit in the MARS group (33). Another small study in 24 patients with excretory liver failure (most of whom had acute alcoholic hepatitis) again showed a significant survival benefit by MARS vs. standard medical treatment (SMT) (34). In contrast, a larger study in 70 patients with advanced hepatic encephalopathy who were randomized to either daily 6-hour MARS sessions on five consecutive days or SMT revealed significant improvements in hepatic encephalopathy but failed to show a survival benefit (35).

Recently, preliminary data of two large randomized trials were presented (36, 37). The MARS RELIEF trial enrolled 189 patients with acute-on-chronic liver failure (defined as bilirubin >5 mg/dl and at least one of the following: HE grade II-IV, hepatorenal syndrome or bilirubin >20 mg/dl) who were randomized to MARS (up to 10 sessions of 6-8 hours during 3 weeks) or SMT. The result was disappointing: survival at day 28 (the primary endpoint) was identical in both groups (59% vs. 60%) (36). The HELIOS trial enrolled 145 patients with acute-on-chronic liver failure who were randomized to SMT+Prometheus or SMT alone. Prometheus treatments were intended for 8-11 sessions of at least 4 hours during 3 weeks. Again, overall, survival was not different at day 28 (66% vs. 63%) or on day 90 (47% vs. 38%), although significant survival benefits were observed in predefined subgroups of more severely ill

patients with hepatorenal syndrome type 1 or with a MELD score >30 (37).

Conclusions

Both artificial liver support systems, MARS and Prometheus, can remove a variety of albumin bound and water solved toxins accumulating in liver failure. Due to its design Prometheus provides more effective removal of tightly albumin-bound substances, such as unconjugated bilirubin, but lacks favorable hemodynamic effects compared to MARS. With respect to cytokines, both MARS and Prometheus fail to reduce serum levels due to their low removal capacity when compared to cytokine production rates. Both systems can provide transient improvements of oxidative stress as indicated by the redox state of serum albumin.

The beneficial effects mentioned above have not yet been translated into a clear clinical benefit in patients with ACLF. While initial small randomized trials with MARS demonstrated significant survival benefits, preliminary data of two recent studies using MARS or Prometheus, respectively, in large cohorts of patients with ACLF failed to prove a survival benefit by either system when compared to standard medical treatment. Importantly, current extracorporeal liver support neither improves inflammation nor completely restores albumin function. Therefore alternative concepts are warranted to design new liver support systems with more powerful and selective toxin elimination (e.g. by cytokine-specific adsorbents) and/or replacement of defective albumin while preserving other important plasma proteins.

Based on the preliminary data of recent randomized trials, we conclude that detoxification with current liver support systems is insufficient to improve overall survival in ACLF. These findings should temper a liberal use of MARS and Prometheus in these patients. Instead alternative methods of extracorporeal liver support should be developed and evaluated in well-designed clinical trials.

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