Liver Support Devices

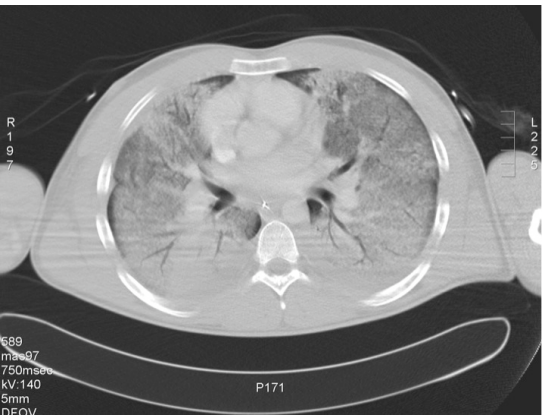
Michael Zimpfer - Andreas Bacher
Peter Faybik

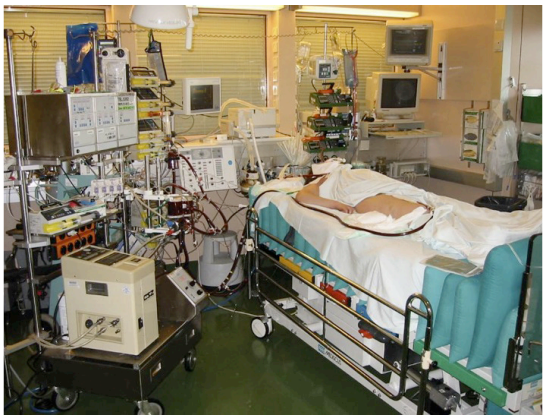
Department of Anesthesiology,
General Intensive Care and Pain Control

Medical University of Vienna,
General Hospital Vienna,
Vienna, Austria, Europe

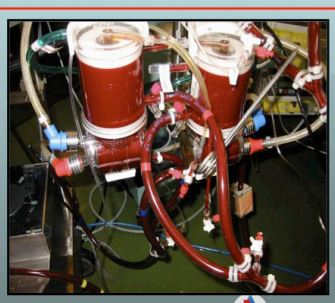
GENERAL HOSPITAL VIENNA

We are an extracorporeal organ support center

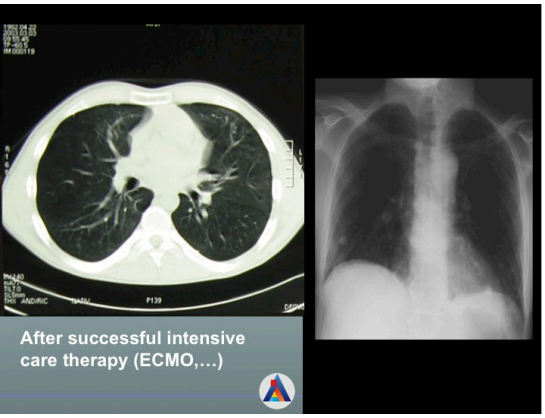




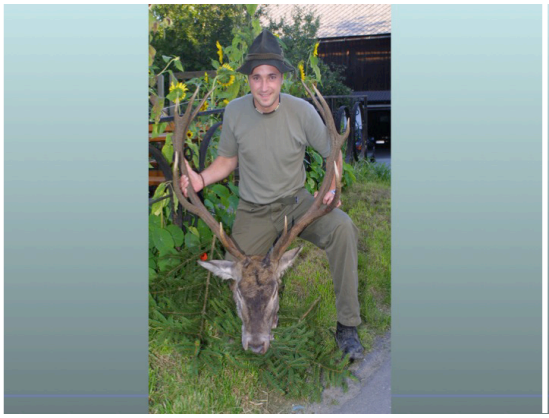
ECMO: Core element Oxygenator



- Hollow fiber system
- Supply pipes:
  - Oxygen
  - Compressed air
- 2 Oxygenators connected in parallel = SAFETY!



After successful intensive care therapy (ECMO,...)



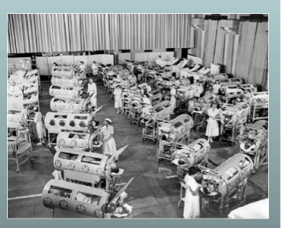
GENERAL HOSPITAL VIENNA

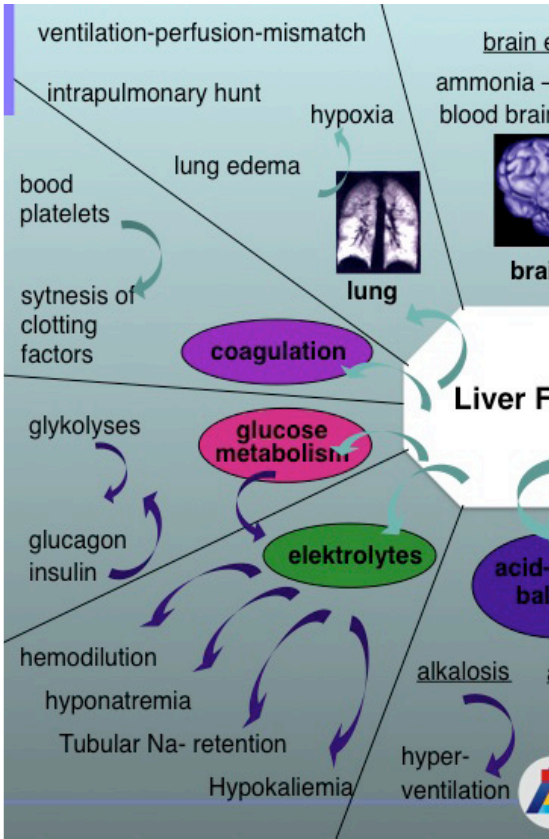
We are a liver transplant center

„The Willem Kolff Drum Kidney“ 1945-46

Iron Lung

Iron lung ward filled with Polio patients, Rancho Los Amigos Hospital, California (1953)



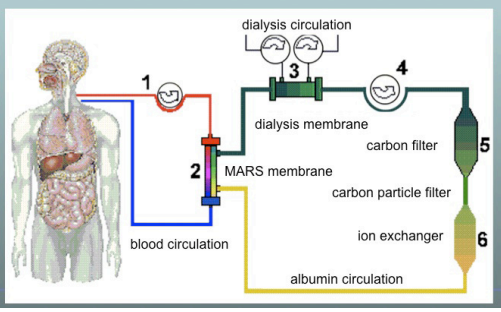


The ideal hepatic support device would replace the metabolic, synthetic and detoxification functions of the failing liver until the liver recovers from an offending insult or the liver transplantation is possible.

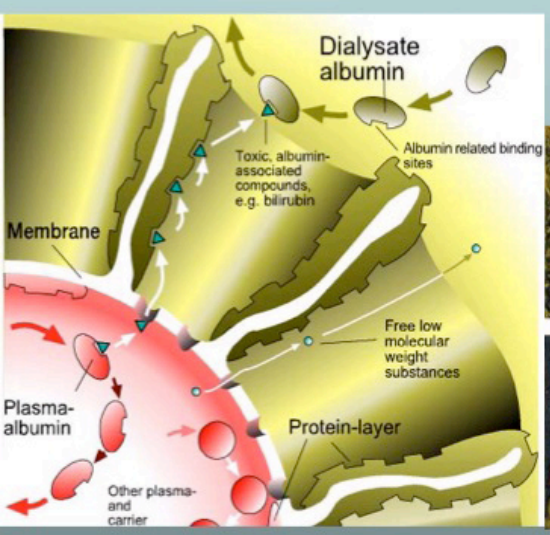
MARS®
Molecular Adsorbent Recirculating System

Extracorporeal albumin dialysis (ECAD) using the molecular adsorbent recirculating system (MARS) is a new method of hemodiafiltration whereby blood is dialyzed against an albumin-containing solution across a high flux membrane.

MARS®
Molecular Adsorbent Recirculating System

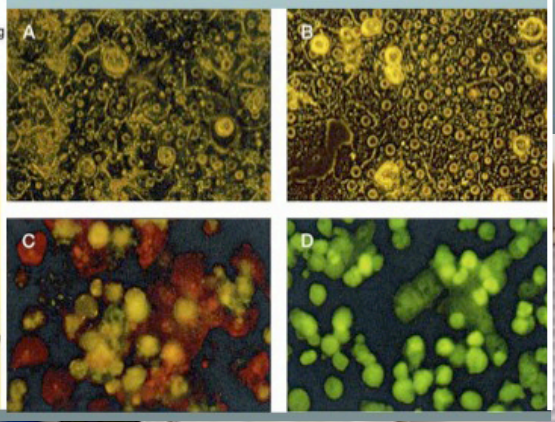


Extracorporeal Albumin Dialysis in Liver Dysfunction



Decreased Hepatotoxicity in vitro

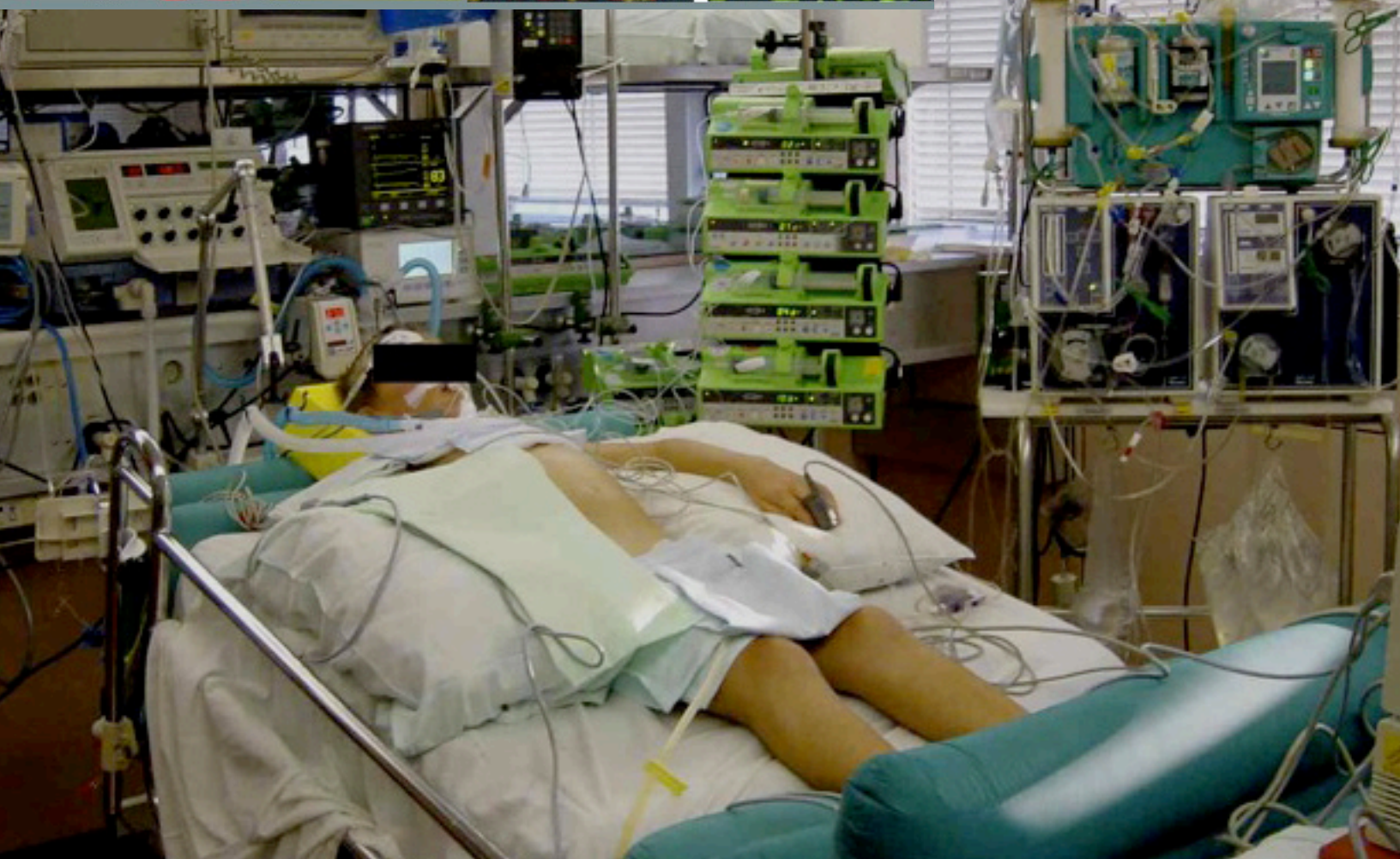
Before ECAD | After ECAD



Case: ALF in MOF

- 21-year old patient
- MOF because of abdominal sepsis
- SOFA score: 18
- bilirubin 20 mg/dl, ARF, paO_2/FiO_2 80 mmHg, severe hypotension, high vasopressor support (norepinephrin 0,6 $\mu g \cdot kg^{-1} \cdot min^{-1}$)
- NH_3 180 µmol/l, CCT: brain edema
- therapy of sepsis (supportive, surgical, antibiotics)
- 5 days of 8h-MARS therapy
- patient survived, complete recovery

Michael Zimpfer, MD, MBA - Handout 2/6

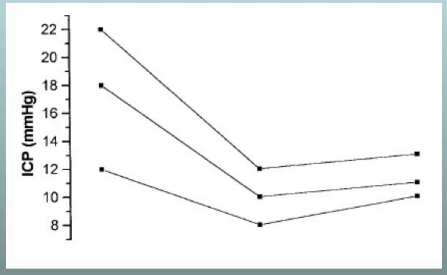


MARS

- 8 patients with Acute on Chronic Liver Failure with Hepatic Encephalopathy ≥3
- 3 patients were comatose and mechanically ventilated, ICP monitoring with intraparenchymal probes

Sorkine P, et al. Role of the molecular adsorbent recycling system (MARS) in the treatment of patients with acute exacerbation of chronic liver failure. Crit Care Med 2001;29:1332-6

MARS



Sorkine P, et al. Role of the molecular adsorbent recycling system (MARS) in the treatment of patients with acute exacerbation of chronic liver failure. Crit Care Med 2001;29:1332-6

MARS

- Phase I trial in 9 patients with FHF
- MARS treatment

Awad SS, et al. Results of a phase I trial evaluating a liver support device utilizing albumin dialysis. Surgery 2001;130:354-62

MARS

- 70 pts., grade 3 or 4 HE, treated with MARS (n=39) vs. standard therapy (n=31)
- endpoint: improvement of HE by 2 grades
- MARS: 34% (median 30%)
- standard therapy: 19% (median 0%)
- improvement significantly faster in MARS-treated patients

Hassanein TI, et al. Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. Hepatology. 2007;46:1853-62

MARS

- 7 pts. with FHF, 5 pts. with aocHF; all HE
- one 6h-period with MARS
- Kety-Schmidt-^{133}Xe-Technique for CBF
- HPLC for amino acid concentration measurements
- arterial and jugular venous amino acid concentration measurements

Schmidt LE, et al. Effect of treatment with the molecular adsorbents recirculating system on arterial amino acid levels and cerebral amino acid metabolism in patients with hepatic encephalopathy. Scand J Gastroenterol. 2004;39:974-80

MARS

Table III. Effects of ECHS on hepatic toxins (n = 9)

Lab	*Baseline*	*Post ECHS*	P *value*
Total bilirubin (mg/dL)	20.3 ± 2.5	17.6 ± 2.7	.40
NH_3 (mg/dL)	130 ± 24	64 ± 16	.01
Fischer ratio*	0.98 ± 0.2	2.2 ± 0.5	.038
Free fatty acids (mg/dL) (n = 3)	1313 ± 240	571 ± 137	.055

ECHS, Extracorporeal hepatic support; NH_3, ammonia;
*Fischer ratio, (Valine + Leucine + Isoleucine)/(Phenylalanine + Tyrosine).

Table IV. Effects of ECHS on neurological parameters

Test	*Baseline*	*Post ECHS*	P *value*
HES	3.8 ± 0.1	2 ± 0.7	.02
ICP (mm Hg)	37 ± 3.9	13.3 ± 2.8	.048

HES, Hepatic encephalopathy score; *ICP*, intracranial pressure.

Awad SS, Swaniker F, Magee J, Punch J, Bartlett RH. Results of a phase I trial evaluating a liver support device utilizing albumin dialysis. Surgery 2001;130:354-62

MARS

- total arterial amino acid concentration: 20%-decrease (normalization)
- correlation total AA-conc./NH_3-conc.
- Fischer's ratio (valin+leucin+isoleucin/phenylalanin +tyrosin): 25%-increase from a low value (0.73±0.47 to 0.91±0.54)
- net cerebral efflux of amino acids not influenced by MARS
- no effect of cerebral metabolic rate of any amino acid

Schmidt LE, et al. Effect of treatment with the molecular adsorbents recirculating system on arterial amino acid levels and cerebral amino acid metabolism in patients with hepatic encephalopathy. Scand J Gastroenterol. 2004;39:974-80

MARS Standard Anticoagulation

- 33 pts., 61 MARS treatments
- 15 ALF, 8 AOCLF, 5 septic ALF, 3 liver graft dysfunctions, 2 cholestasis
- anticoagulation:
  - 3-5 ng·kg^{-1}·min^{-1} PGI2 in all pts.
  - additionally 100-600 units of unfractioned heparin in 17 pts.

Faybik P, et al. Molecular adsorbent recirculating system and hemostasis in patients at high risk of bleeding: an observational study. Crit Care 2006;10:R24

MARS

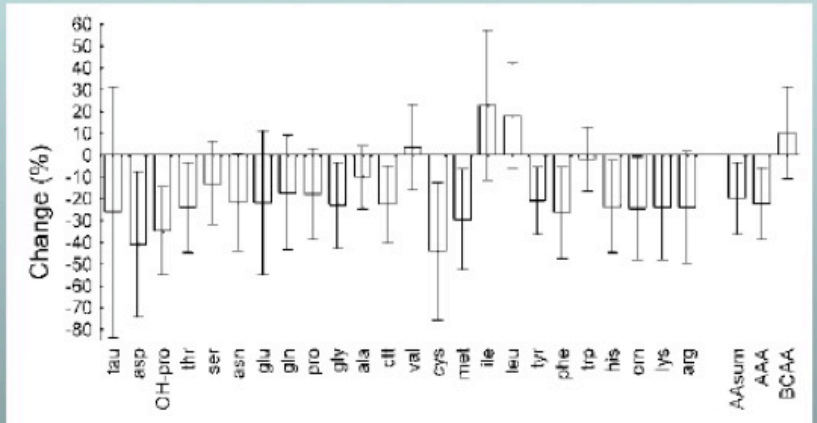


Fig. 2. Change in percentage in arterial amino acid concentration during Molecular Adsorbents Recirculating System (MARS) treatment. Minus denotes a decrease in concentration. Whiskers indicate 95% CI. AA = amino acid; AAA = aromatic amino acid; BCAA = branched-chain amino acid.

Schmidt LE, et al. Effect of treatment with the molecular adsorbents recirculating system on arterial amino acid levels and cerebral amino acid metabolism in patients with hepatic encephalopathy. Scand J Gastroenterol. 2004;39:974-80

MARS Standard Anticoagulation

- 3 bleeding complications (3-4 RPCs) in 3 pts.

standard coagulation tests

Parameter	Before MARS treatment		After MARS treatment		p
	Median (interquartile range)	Range	Median (interquartile range)	Range	
PT (%)	28 (16–40.2)	5–129	27 (17.5–46.2)	5–92	0.93
aPTT (s)	57.6 (49.5–68.2)	32–103	54 (46.9–70.5)	33–121	0.94
TT (s)	16.7 (14.8–20.1)	10–120	17.6 (15.1–21.1)	11.4–60	0.02
Fibrinogen (mg/dl)	145 (91.7–312)	42–1,120	142 (74.7–319)	13–1,020	0.006
AT (%)	43 (27–61)	12–127	42 (26.7–59.2)	8–120	0.14
Platelets (G/l)	60.5 (28.5–85.5)	8–352	44 (23–77.5)	6–254	<0.0001
Hematocrit (%)	30 (27–33)	22–45	30 (27–32.5)	19–40	0.95

TEG

	TP1	TP2	TP3	p
Reaction time (mm)	16.7 (13.3–21.6)	17.5 (13.8–21.1)	17.4 (12.9–21.3)	0.84
Coagulation time (mm)	12 (7.3–25.1)	13.7 (7.5–33.2)	15.0 (5.85–33.0)	0.07
Maximal amplitude (mm)	38.5 (26.8–48.8)	35.5 (25.1–50.2)	34.0 (22.7–48.2)	0.0003
Angle alpha (degree)	35 (24.5–51.1)	42 (23.7–54.8)	30.0 (17.8–53.5)	0.002
Clot lysis (percent)	100 (98.7–100)	100 (99.1–100)	100 (98.4–100)	0.68
Coagulation index	-0.68 (-6.3–3.9)	-1.0 (-6.3–3.6)	-1.5 (-7.7–4.6)	0.81
R_{HEP}(mm)	0.7 (-0.5–2.6)	2.9 (0.125–5)	1.4 (0.2–4.1)	0.07
MA_{PLT} (mm)	24 (12.5–31.1)	20 (13.6–28.6)	19 (8.1–29.5)	0.3

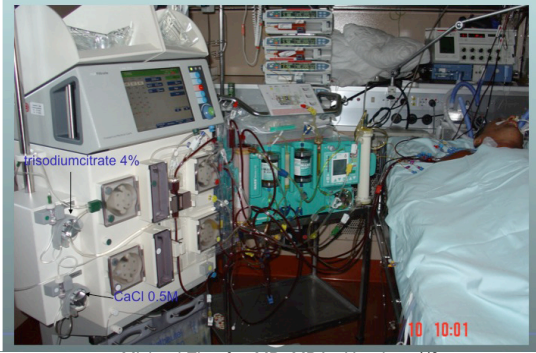
MA_{PLT}, difference between standard and abximimab-fab-modified maximal amplitude (MA) reflecting solely the platelet function. R_{HEP}, difference between standard and heparinase modified reaction time (R), reflecting the effects of endogenous/exogenous heparinoids on plasmatic coagulation. TP, time point.

Faybik P, et al. Molecular adsorbent recirculating system and hemostasis in patients at high risk of bleeding: an observational study. Crit Care 2006;10:R24

MARS Anticoagulation

- possibility of using sodiumcitrate for regional anticoagulation of extracorporeal circulation
- reversion of regional anticoagulation with calciumchloride
- problem: increase in citrate-calcium chelate may lead to increase in total calcium concentration (= albumin-bound Ca^{++} + ionized Ca^{++} + citrate-calcium)

MARS Citrate Anticoagulation



MARS Citrate Antigoagulation

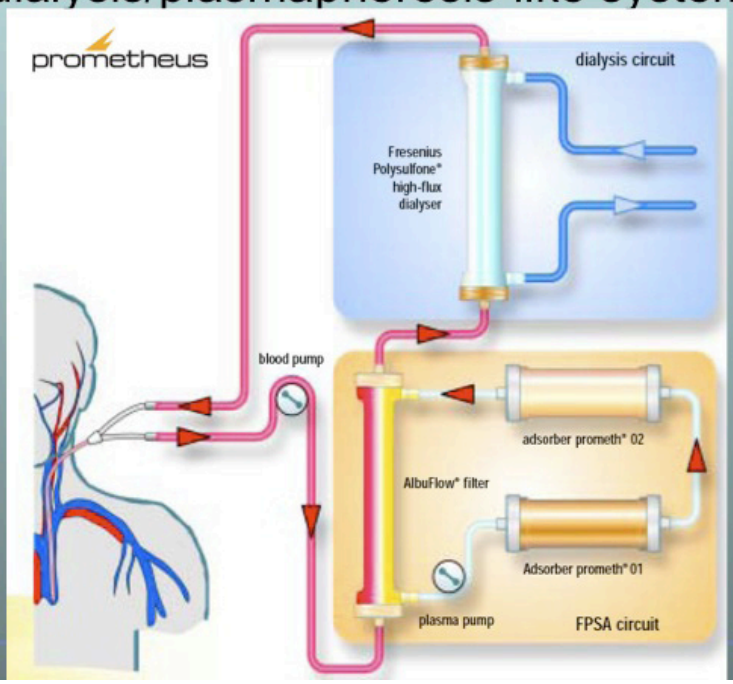
- 20 pts., 77 MARS treatments
- anticoagulation: solely with trisodiumcitrate 4% administered to the arterial line of the dialysis machine
- reversal of antigoagulation: CaCl 0.5M administered to the venous line of dialysis machine

MARS Citrate Antigoagulation

- Only two premature terminations in 77 treatment cycles (one due to HIT2, one due to withdrawal of treatment in a hopeless case)!
- Exact adjustment of dialysis dosage, dosage of citrate and CaCl successfully avoided increase in total serum Ca concentrations after MARS:
  - total calcium corrected (mmol/l): 2.70±0.31 to 2.80±0.39
  - ionized calcium (mmol/l): 1.16±0.15 to 1.13±0.15
  - total calcium/ionized calcium ratio: 2.04±0.32 to 2.17±0.35

Prometheus

dialysis/plasmapheresis-like system



Prometheus

- case report: cocaine/ecstasy intoxication
- no LTX planned because of untreated drug abuse
- severe HE, with menacing cerebral herniation
- patient survived

Kramer L, et al. Successful treatment of refractory cerebral oedema in ecstasy/cocaine-induced fulminant hepatic failure using a new high-efficacy liver detoxification device (FPSA-Prometheus). Wien Klin Wochenschr 2003;115:599-603

Prometheus

- case report: 15 year old pt., Wilson's disease, AHF with hemolysis, multiorgan failure, listed for HU LTX
- meanwhile: three 6h-treatments on three consecutive days
- improvement of:
  hemolysis
  mental state
- discharge without LTX, normalization of all laboratory variables after 4 months

AAgaard NK, et al. Blood Purif 2009;28:102-107

Prometheus and ICP

- ALF model in pigs: one group treated with Prometheus vs. one control ALF-group
- results:

bilirubin (mmol/l): at 6h: 13±7 vs 30±10
at 9h: 12±4 vs 30±12
at 12h: 14±6 versus 26±12

ICP (mmHg): at 9h: 19±4 vs 24±3
at 12h: 24±5 vs 30±6

Ryska M, et al. Eur Surg Res 2009;42:230-5

Prometheus Protein Adsorption

- Mass spectrometric analysis of proteins removed from plasma in a patient receiving a 6h Prometheus treatment due to alcoholic cirrhosis

Mares J, et al. Journal of Proeteome Research 2009; 8:1756-64

Prometheus Anticoagulation

- 17 pts., 15 treatments with heparin, 22 treatments with heparin+epoprostenol
- in 24% of treatments filter exchange due to clotting necessary
- three patients: severe bleeding complications within 24 h of treatment
- no thrombotic events in patients
- 23%-decrease in protein C, no effect on protein S or thrombin-antithrombin complex
- no difference between heparin vs heparin +epoprostenol

Krisper P, et al. Artif Organs 2009

Prometheus Protein Adsorption

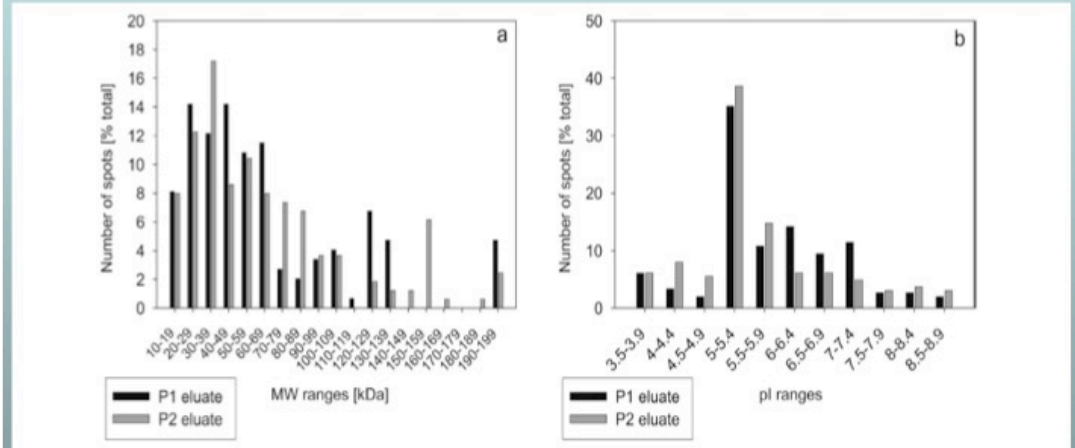


Figure 2. Molecular weight (a) and p/ (b) distributions in Prometh 1 eluate (P1) and Prometh 2 eluate (P2). Percentage per category of total spot number is given. MW = molecular weight.

- highest clearance: prealbumin, retinol binding protein, anionic trypsin, prothrombin, hyaluronan-binding protein 2
- Clinical consequences? Disturbed retinol transport? Disturbed thyroxin transport? Coagulation disorders aggravated?

Mares J, et al. Journal of Proeteome Research 2009; 8:1756-64

Prometheus Anticoagulation

TABLE 1. *Patient characteristics*

	Group A (Hannover)	Group B (Graz)
Age (years)	49.4 ± 2.6	57.8 ± 1.7*
Gender (m/f)	4/4	3/6
Child-Pugh score	12 ± 1	12 ± 1
MELD†	23 ± 2	25 ± 4
Bilirubin (mg/dL)	27.1 ± 6.9	29.3 ± 3.1
Albumin (g/L)	27 ± 2	29 ± 1
Creatinine (mg/dL)	2.5 ± 0.5	2.0 ± 0.6
INR	2.2 ± 0.2	2.2 ± 0.3
Dead/alive	5/3	6/3

*Significant difference between the two groups.
†MELD score was obtained using the MELD calculator at the Website of the Mayo Clinic (http://www.mayoclinic.org/gi-rst/mayomodel5.html).
MELD, model for end-stage liver disease; INR, international normalized ratio.

Krisper P, et al. Artif Organs 2009

TABLE 2. *Standard coagulation tests before, during, and after Prometheus*

	Group A (Hannover: heparin)			Group B (Graz: heparin + epoprostenol)		
	Before	During	After	Before	During	After
aPTT (s)	71.5 (±38.3)	93.8 (±41.2)	70.8 (±39.2)	70.2 (±27.1)	105.6* (±38.5)	102.4* (±42.1)
PT (%)	36.8 (±15.2)	35.2 (±15.2)	38.3 (±17.2)	45.6 (±21.6)	36.9 (±19.5)	30.9* (±17.0)
AT3 (%)	37.3 (±18.0)	33.7 (±15.6)	34.4 (±15.8)	39.1 (±25.9)	29.8 (±23.3)	34.5 (±25.3)
Platelet count (G/L)	55.1 (±25.2)	55.3 (±24.6)	54.3 (±26.1)	85.4 (±64.7)	71.3 (±78.6)	67.7 (±44.9)

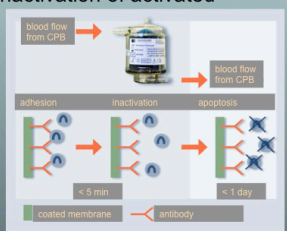
*Significant difference to baseline.

Future Aspects of Detoxification Devices

leukocyte inhibition module (LIM):

– specific binding and inactivation of activated leukocytes

– possible indications:
- sepsis, SIRS
- CPB
- autoimmune disease



LIM

leukocyte inhibition module (LIM):

– thermoplastic housing (160 ml)
– open porous polyurethane foam
– coated with immobilized agonistic IgM anti-Fas antibodies (clone CH11)

LIM in Pig Model CPB

- 12 pigs, CPB (60 min including 30 min myocardial ischemia)
- LIM in arterial line of CPB
- hemodynamics (PAC, ventricular conductance catheter)
- leukocyte labeling (99mTc-Exametazime) and scintigraphy

Abdel-Rahman U, et al. Inhibition of neutrophil activity improves cardiac function after cardiopulmonary bypass. J Inflamm (Lond) 2007;4:21

LIM and CPB: Results

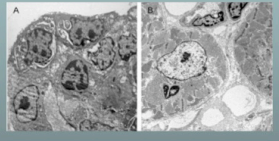
Perioperative inflammatory and tissue damage markers

	Pre-CPB		Post-CPB	
	Control	LIM	Control	LIM
Neutrophils (×10³/µl)	5.9 ± 0.8	6.4 ± 0.3	13.4 ± 2.3	7.2 ± 1.8
PBL (×10³/µl)	7.5 ± 2.1	7.9 ± 1.1	8.8 ± 0.4	8.2 ± 0.9
TNF-α (pg/ml)	68.4 ± 38.9	89.0 ± 25.3	255.3 ± 64.1	112.4 ± 55.7
CK (U/l)	418.1 ± 39.3	397.6 ± 22.0	727.9 ± 75.7	645.8 ± 89.4
CK-MB (U/l)	339.8 ± 44.7	384.9 ± 77.3	592.6 ± 79.3	517.5 ± 69.6

Abdel-Rahman U, et al. Inhibition of neutrophil activity improves cardiac function after cardiopulmonary bypass. J Inflamm (Lond) 2007;4:21

LIM and CPB: Results

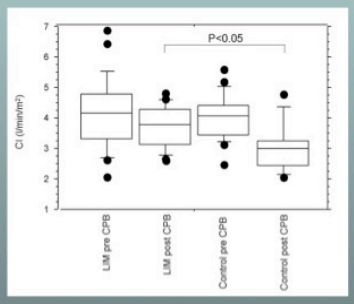
Electron microscopic microphotographs of accumulated neutrophils within the epicardium (A) and within the left ventricular heart muscle (B) after CPB.



Abdel-Rahman U, et al. Inhibition of neutrophil activity improves cardiac function after cardiopulmonary bypass. J Inflamm (Lond) 2007;4:21

LIM and CPB: Results

Boxplot depiction of Cardiac index values obtained for the control group and for the LIM group, pre- and postoperatively. In the control group, but not in the LIM group, the difference between pre- and post CPB values was statistically significant ($p < 0.01$). The post-CPB intergroup difference was also statistically significant ($p < 0.05$).



Abdel-Rahman U, et al. Inhibition of neutrophil activity improves cardiac function after cardiopulmonary bypass. J Inflamm (Lond) 2007;4:21

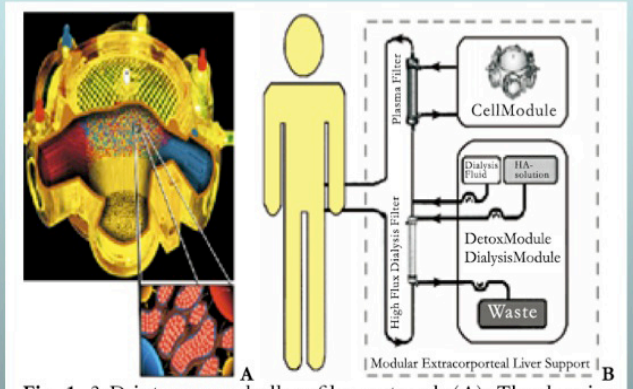


Fig. 1. 3-D interwoven hollow fiber network (**A**). The drawing illustrates the MELS bioreactor system, a CellModule bioreactor with human liver cells, a DetoxModule enabling albumin dialysis, and a DialysisModule for continuous venovenous hemodiafiltration (**B**) [Adapted from Sauer et al, 2002].

Source: Cheng-Bo Yu et al, Hepatobiliary Pancreat Dis Int 2009; 8: 134-140

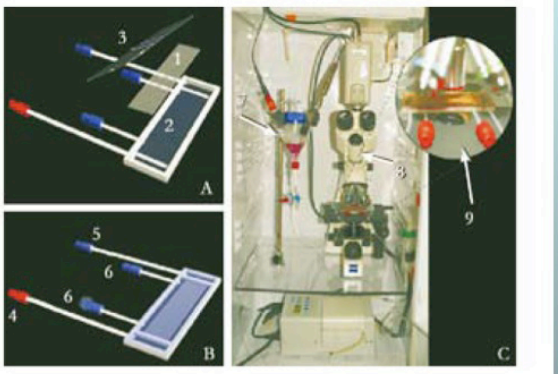


Fig. 2. A: The hollow fiber (1) between the two slides (2, 3) which form the cell compartment; **B:** The perfused tubes (4, 5) connect the hollow fibers and the short tubes (6) are accessible to the cell compartment; **C:** Experimental set-up comprises control unit (7), microscope and camera (8) and the SlideReactor (9) [Adapted from Schwartlander et al, 2007].

Source: Cheng-Bo Yu et al, Hepatobiliary Pancreat Dis Int 2009; 8: 134-140

SUMMARY (1)

Liver support devices, in terms of long lasting, nearly complete liver support, as compared to, e.g., renal replacement with hemodialysis, are far from being ready. Thus, no available system is able to replace the dysfunction of hepatocytes resulting in loss of the synthetic metabolic and detoxification pathways of the liver.

SUMMARY (2)

Liver transplantation remains the only effective treatment for end-stage liver disease. However, liver assist devices can temporarily support the patient until the native liver recovers or can serve as a bridge to orthotopic liver transplantation by detoxifying blood, improving cerebral circulation and reducing brain edema.

Contact

Michael Zimpfer, MD, MBA

Professor and Chairman
Department of Anesthesiology, General Intensive Care and Pain Control
Medical University of Vienna – General Hospital Vienna
18-20 Waehringer Guertel
1090 Vienna - AUSTRIA - EUROPE

Private Office
Health Care Center Doebling
44 Doeblinger Hauptstrasse
1190 Vienna
AUSTRIA – EUROPE

Phone: xx 43 1 369 40 40 Cell: xx 43 664 35 666 99 Fax: xx 43 1 369 40 30

e-mail: michael@zimpfer.at www.anaesthesiology.at www.zimpfer.at

This handout is available for download at www.zimpfer.at