Continuous modalities of renal replacement therapy. Review of selected aspects

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Abstract

Severe clinical course of acute renal and acute liver failure is recognized as life-threatening condition, often developing in critically ill patients, demanding intensive care. Continuous renal replacement techniques, including veno-venous hemodialysis/hemofiltration/hemodialfiltration/ /ultrafiltration (CVVHD/CVVHF/CVVHDF/SCUF) are becoming the therapeutic modality of choice in unstable patients with acute renal failure. Recently introduced new technique – albumin dialysis (MARS – Molecular Adsorbent Recirculating System) is a very useful extracorporeal method of detoxication in patients with acute liver or kidney/liver failure. It may also serve as bridge to liver transplantation in patients with rapidly deteriorating chronic liver failure. Indications, benefit/risk ratio and specific clinical and technical aspects are briefly described in this review paper.

Key words: continuous hemodialysis-hemodiafiltration, albumin dialysis, MARS.

Continuous renal replacement therapy (CRRT)

Acute renal failure in unstable patients is the main indication for continuous renal replacement techniques (CRRT). There are four types of these modalities, including veno-venous hemodialysis/hemofiltration/hemodialfiltration/ /ultrafiltration (CVVHD/CVVHF/CVVHDF/SCUF). The arterio-venous variant of hemofiltration is now abandoned in most centres, due to technical and clinical superiority of veno-venous techniques [1,2]. Advantages and contraindications are summarized in *Tab. 1*.

Standard vascular access required to perform veno-venous CRRT techniques is regular double-lumen hemodialysis catheter, introduced to the central vein by Seldinger technique or (in specific cases) surgically. Currently available CRRT machines offer advanced electronic control of several technical parameters, crucial for efficacy and safety of the procedure and friendly for the medical staff. The blood flow driving force is almost independent from the patients current blood pressure values and both ultrafiltration/supplementation rates planned by physician are actively created and monitored by machine. Fully integrated electronic system adjusts all the required parameters to desired balance.

Depending on specific clinical conditions – different techniques are used, with the same device. The options are summarized in *Tab. 2*.

In terms to follow new clinical requirements, the initially introduced technique may be extended. If e.g. patients treated by SCUF develop uremic toxicity, the modality may be extended to CVVHD or CVVHDF, simply by adding supplementation or dialysate flow. The higher flow of these fluids – the higher efficacy of detoxication. The range of fluid flow rates depends on patients body weight (volume distribution) and severity of uremic toxicity. Both (supplement and dialysate) may be given with velocity from 100 to 1500 ml/h. Commercially available fluids contain ions and buffers in concentration resembling physiological plasma water. The exception is potassium, which (depending on current kaliemia) must be added to the fluid, if required [3-7].

According to several reports, potentially advantageous effect of CVVHF in septic patients is based not only on uremic toxins/water elimination, but also cytokines (range of 10000--50000 daltons) and bacterial endotoxins removal. Tumor

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***Table 1*. Continuous renal replacement techniques in acute renal failure (ARF)**

Modality	Main indications	Contraindications	Advantages	Disadvantages Common complications
CVVHF CVVHD CVVHDF SCUF	– ARF with massive overhydration – ARF in nephrotic patients – parenteral nutrition in anuric patients – ARF in patients with congenital defects or surgery-related damage of abdomen cavity and wall (contraindication for peritoneal dialysis) – ARF with extreme BUN concentration and coma (high risk of brain oedema)	– poor quality of vascular acess * – severe coagulation defects ** – severe active bleeding, especially to CNS ** * relative problem, solved by change of access ** relative problem, solved by reduction or withdrawing of heparinisation	– gentle, slow detoxication – well, automatically controlled ultrafiltration rate – performable in unstable patients with heart failure, or with septic shock, remaining on catecholamines	– problems with maintaining vascular access with prolonged therapy – thrombocytopenia with prolonged heparinisation – high dialysate consumption in hypercatabolic cases – long immobilization of the patient with all side-effects of this condition

***Table 2*. Specific indications for different CRRT modalities**

Specific indication	Recommended CRRT modality
Overhydration, low uremic toxicity (e.g. ARF in nephrotic patients)	SCUF
ARF in septic patients (potential advantage of cytokines removal)	CVVHF/CVVHDF
High BUN, hypercatabolic patients, parenteral nutrition	CVVHD/CVVHDF

necrosis factor (TNFα), interferon-γ and several interleukins (IL-1, -2, -6) are considered candidates. The reliability of this aspect is controversial, as no extended, controlled studies are available [8,9].

As all extracorporeal techniques, CRRT modalities require heparinisation, applied up to personal experience. If non-fractioned heparin is selected – bolus dose of 0.3-0.5 mg (30-50 u.)/kg/dose, followed by continuous infusion of 0.1-0.2 mg (10-20 u.)/kg/h is recommended. Activated coagulation time (ACT) must be monitored, to maintain a target range of 170-200 s. Low molecular-weight heparin (LMWH) iv., at repeated doses of 50-100 j.antyXa./kg/6 h may be administered alternatively. Thrombocytopenia is specific complication in patients treated with CRRT during several, following days. Obviously, in patients at bleeding-risk the heparinisation should be reduced or withdrawn.

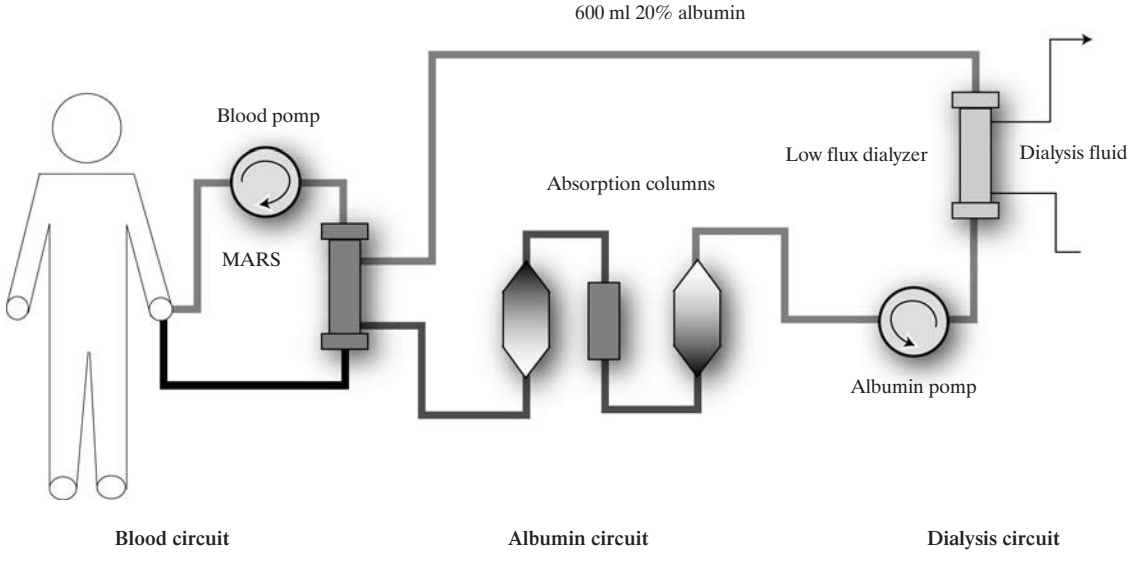
Continuous liver-renal replacement therapy Albumin dialysis – MARS (Molecular Adsorbent Recirculating System)

Indication for MARS therapy is liver failure with hepatic encephalopathy and liver-kidney failure in cases of hepato-renal syndrome [10,11]. Hepatic encephalopathy is a neuropsychiatric syndrome occurring in several patients with both acute and chronic liver failure. It is characterized by altered sleep-wake cycle, confusion and disorientation, asterixis, hyperreflexia and slowing of the dominant rhythm on electroencephalography. It is potentially reversible, if liver function improves, spontaneously or under specific treatment and in cases, when the liver transplantation is successfully performed on time. Hepatic encephalopathy usually develops slowly in chronic, cirrhotic patients, but in cases of acute liver failure the onset is sudden and it may progress very rapidly. Coma and brain herniation are the main life-threatening complications. Encephalopathy is one of the major determinants of very high mortality and irreversible brain damage in acute liver failure. The pathogenesis of hepatic encephalopathy is multifactorial. One of the mechanisms is the systemic accumulation of several neuroactive and neurotoxic substances, normally metabolised and cleared by the liver. Massive astrocytes swelling is the cause of brain oedema and, if is not overcome, fatal brain herniation. Arterial ammonia concentration seems to correlate with occurrence of increase of intracranial pressure and cerebral herniation. Other important substances include cerebral benzodiazepines, serotonin, manganese, inflammatory cytokines and bilirubin. Many of these substances, as bound by plasma albumins, are water-insoluble. Extracorporeal removal of liver toxins is the target of specific therapeutic modalities. The aim of such therapy is either to avoid hepatic encephalopathy or ameliorate existing condition, while awaiting spontaneous improvement of hepatic function or liver transplantation. It must be stressed, that urgent liver transplantation is the optimal therapeutic option for patients with hepatic encephalopathy, unless irreversible brain damage occurs [12].

Recently a new method designed for the selective removal of albumin-bound substances MARS (Molecular Adsorbent Recirculating System), originally developed by Dr Jan Stange and Dr Steffen Mitzner from University of Rostock (Germany), became available [13-17].

The aim of MARS technology is continuous selective

Figure 1. **MARS – circulating systems**



removal of small and medium sized molecules from blood. The special polysulfone high-permeability MARS membrane absorbs lipophilic, protein-bound toxin from patient's blood onto one side and is simultaneously cleaned by selective molecular adsorbents (albumin dialysate) from the other side. Small – sized and water – soluble substances are also dialyzed through this membrane, as during conventional hemodialysis. Therefore MARS therapy enables specific simultaneous elimination of the liver failure albumin – bound toxins and water – soluble uremic toxins, using "intelligent" membrane transport [18].

Technical aspect of the procedure is similar to all other extracorporeal modalities. The patient's blood flows through a catheter via an extracorporeal circuit into blood compartment of capillary MARS-flux dialyzer. The outside of MARS membrane is cleansed by a recirculating human albumin 20% solution (albumin "dialysate"). As the "liver toxins" are transported by bounding proteins, this mechanism produces the driving force across the MARS membrane. Albumin dialysate is then regenerated in closed circuit. It flows through the blood compartment of the second dialyzer (DIA-flux) and undergoes regeneration by bicarbonate-buffered dialysate in open-loop, single pass dialysate circuit ("renal detoxification" – water and small soluble toxins are removed). On the next step the albumin dialysate is passing through two sequential columns; the first containing uncoated charcoal to bind non-ionic toxins and the second – an anion exchanger resin to remove the toxins still bound to albumin ("hepatic detoxification"). After this regeneration purified albumin dialysate returns to clean MARS membrane in closed circuit. The MARS Monitor is connected to the hemodialysis machine, allowing continuous flow of albumin dialysate through dialyzer MARS-flux and its regeneration in DIA-flux dialyzer and two adsorbers. It can cooperate with majority of standard dialysis machines and machines for continuous renal replacement therapy (CRRT) [18].

MARS procedure effectively removes several substances from the patient's blood: albumin bound – bilirubine, bile acids, aromatic amino acids, benzodiazepin like substances, short and middle chain fatty acids and water soluble – ammonia, creatinine, urea, copper, iron. The procedure is usually performed in continuous manner – the time of single session ranges from 8 to 24 hours. The absorbing capacity of columns decreases with time, so depending on basic concentration of toxic substances – the circuit must be exchanged, once the columns are saturated. Slow and gentle removal of several toxins improves the clinical safety, especially in cases at risk of brain herniation. Patients with severe coagulation defects require no heparinisation during MARS procedure, however with gradual improvement of liver insufficiency – ACT must be checked regularly and unfractioned heparin should be added to the circuit, to maintain ACT within the range 170-200 s.

MARS therapy has a positive impact on patient's survival, systemic hemodynamics, neurological status, course of hepatic encephalopathy, cerebral blood flow velocity, intracranial pressure, intrahepatic cholestasis, kidney and liver function, toxin load, albumin binding capacity, electrolyte and acid-base balance.

It must be stressed, that MARS therapy should be used by specialized centers, able to proceed all the steps of management, required by critically ill patients with liver or multiorgan failure [19,20].

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