CHAPTER 191

Extracorporeal Blood Purification Techniques Beyond Dialysis: Coupled Plasmafiltration-Adsorption

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OBJECTIVES

This chapter will:

1. Discuss the use of extracorporeal blood purification techniques within the clinical picture of sepsis.
2. Provide a rationale based on in vitro and animal studies for the use of coupled plasmafiltration-adsorption in human sepsis.
3. Analyze clinical results of this approach in terms of hemodynamics, respiratory function, immune status, and survival.
4. Update the technical feature of the new machine and the use of citrate as anticoagulant for the specific treatment.

Sepsis is one of the main causes of morbidity and mortality in intensive care units worldwide and the tenth leading cause of death in the United States.[1] Mortality of sepsis has been estimated to range from 20% to 80%—depending to a large extent on the severity of the clinical picture, the involvement of one or more organs (the so-called multiple organ dysfunction syndrome [MODS]), the study design (and reporting methods), and the timing of treatment initiation. MODS and renal failure often result from the exaggerated host response to infection.[2,3] Although several attempts have targeted specific components of the inflammatory cascade, no improvements in outcome have been reported in clinical trials.[4]

Sepsis is the leading cause of acute kidney injury (AKI), the prevalence of which ranges from 19% in sepsis, to 23% in severe sepsis, to 51% in septic shock.[5]

Sepsis involves two important pathways, the proinflammatory response and an immunosuppressive (or immunodysfunctional) response. The first is aimed at the delivery of mediators with a proinflammatory action, such as tumor necrosis factor-alpha (TNF-α), interleukin-1, interleukin-6, and the other releases cytokines with a predominant antiinflammatory activity, such as interleukin-10 and interleukin-4. Both responses may take place at the same time and not in sequence, as previously considered.[6]

It is hypothesized that inflammatory molecules are responsible for diffuse endothelial injury, inducing vasoparalysis and driving selective permeability with important ramifications on systemic hemodynamics and MODS. On the other hand, monocytes lose their ability to synthesize and deliver cytokines as a consequence of inflammatory stimuli, leading to an "immunoparalytic" state characterized by monocyte deactivation.[7,8] The substantial failure of the first interventional trials targeting specific components of the proinflammatory cascade, such as TNF-α, moved attention to different targets, for example, to blood purification techniques, which may remove several mediators simultaneously, positively affecting the outcome in septic shock.[9]

Of the extracorporeal treatments as a whole, "classic" continuous renal replacement therapies show intrinsic limitations tied to constrained exchange volumes and a low sieving coefficient of the molecules affected (with an approximate molecular weight ranging from 5 to 50 kDa), which leads to low removal rates and clearances.[10] In vitro and in vivo studies have shown that employing a large-pore membrane may enhance the convective transfer of soluble proinflammatory and antiinflammatory mediators, leading to increased clearance of nonselective cytokines.[11–14]

To overcome some of these problems, a new extracorporeal blood purification system was developed, coupled plasmafiltration adsorption (CPFA), which uses a resin cartridge along with a second hemofiltration system that allows convective exchange. The system exploits the nonselective removal of inflammatory mediators by means of a hydrophobic styrenic resin. The resin has high affinity and a large capacity for many cytokines and mediators.[15] The rationale for sorbent adsorption is to reinfuse the endogenous plasma after nonselective, simultaneous removal of different sepsis-associated mediators by means of processing it through a specific cartridge.[16]

CPFA currently is performed with the use of a four-pump modular treatment (Amplya, Bellco, Mirandola, Italy) consisting of a plasma filter—0.45 m^2 polyethersulfone with approximate cutoff of 800 kDa and absorption on a unselective hydrophobic resin cartridge (140 mL)—with a surface of about 700 m^2/g, and a final passage of the reconstituted blood through a synthetic, high-permeability, 1.4-m^2 polyethersulfone hemofilter in which convective exchanges may be applied in a postdilutional mode (Fig. 191.1).

The advantage in processing the plasma and not the blood through the sorbent cartridge is related to the fact that the plasma flow is lower than blood flow, allowing for a longer contact time with the sorbent.[17] Other advantages of using plasma are that there are no bioincompatibility issues and the problem of having to "coat" the resin with a biocompatible matrix, which often decreases efficacy, is avoided.

The postdilution reinfusion rate can be set for up to 4 L/hr. The blood flow is usually 150 to 180 mL/min, and the plasma filtration rate is maintained at a fractional filtration of the blood flow (approximately 15%–20%). The treatment usually is run for approximately 10 hours, after which the cartridge begins to show saturation by the mediators.

Early studies of CPFA used a prototype machine and cartridge with less resin that needed to be changed more often. Ronco et al.,[18] who tested the first clinical treatments of CPFA using the prototype machine, reported that a single CPFA

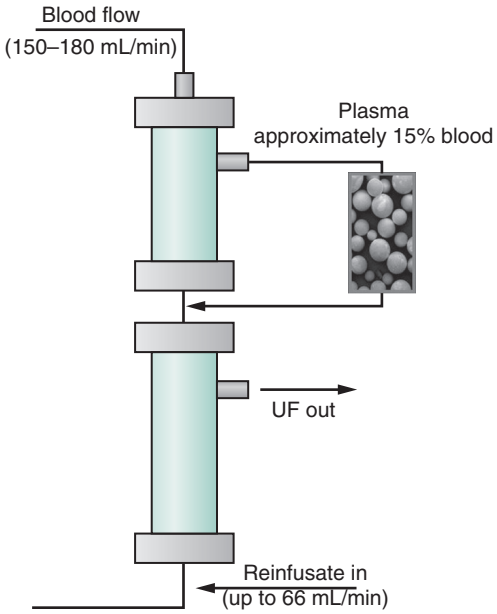


FIGURE 191.1 Schematic diagram of coupled plasmafiltration-adsorption.

treatment lasting 10 hours showed better hemodynamic improvement than continuous venovenous hemodiafiltration (referring to an improvement in mean arterial pressure and a decrease in norepinephrine requirement). Furthermore, this study provided very interesting biologic data: Monocytes in plasma drawn after passage through the sorbent cartridge were again able to respond to the lipopolysaccharide challenge with TNF-α production at a magnitude significantly greater than with continuous venovenous hemodiafiltration (Fig. 191.2). According to these preliminary data, CPFA was suggested to have a potential role for blood purification in septic shock treatment, modulating the immune response and resetting the balance between proinflammatory and antiinflammatory mediators. This concept was novel in that it suggested a role for extracorporeal therapies in actual purification of blood to remove inflammatory mediators, reaching beyond the traditional role of support for patients with renal failure.

Still employing the prototype machine, Formica et al.[19] evaluated the hemodynamic performance of CPFA. Their study had two unique features: (1) repeated application of the technique during the course of the septic shock (a mean of ten 10-hour sessions were applied) and (2) use in patients without concomitant AKI. Improvements have been reported in the main hemodynamic and respiratory parameters, such as mean arterial pressure, cardiac index, peripheral vascular resistance, and ratio of oxygen arterial pressure to inspired oxygen fraction ratio, as well as in levels of some mediators and severity of illness scores (Fig. 191.3). Norepinephrine was tapered progressively and stopped with different timings in the patient's population. Therefore it may have been stopped in one patient after three sessions and in another after eight sessions. The mean among the patients was five sessions.

No untoward clinical effects were recorded during the procedures, thus underlying the safety of the technique, which may be applied irrespective of the presence of AKI. The sessions had been planned originally for a duration of 10 hours, but the mean delivery time was about 8 hours, 45 minutes. Reasons for shorter sessions related to clinical requirements (radiologic procedures, emergency surgery) and to technical problems (circuit coagulation, plasma filter malfunction). The issue of coagulation with CPFA has been addressed further in a study performed in a particular AKI population.[20]

These technical problems have delayed significantly the introduction of a new machine that contained seven pressure transducers to monitor the transmembrane pressure and pressure drops of the plasma filter, hemofilter, and adsorptive cartridge in real time. Several pilot studies evaluated the role of mediator removal during barotraumas induced by mechanical ventilation and the role of CPFA versus pulsed high-volume hemofiltration in sepsis-induced apoptosis (C. Ronco, personal communication, 2006).

In 2007 a randomized multicenter clinical trial was performed in 18 adult intensive care units (ICUs) that regularly used CPFA in the treatment of septic shock to assess the efficacy of CPFA in reducing mortality of critically ill patients with septic shock (COMPACT study). Patients more than 18 years of age with septic shock either at or during their admission to the ICU were eligible for study entry, provided that CPFA could be started within 6 hours from the occurrence of hypotension refractory to fluid resuscitation. Between January 2007 and November 2010, a total of 192 patients had been randomized. Recruitment in each ICU lasted a median of 22 months (IQR 13–26). Unfortunately, issues of circuit coagulation constrain the volume of treated plasma leading to numerous protocol violations. No statistical difference was found in hospital mortality with 47.3% dying in the control group (44/93) versus 45.1% dying in the CPFA group (41/91, $p = .76$), with an absolute risk difference of 2.2% (95% CI –12.2% to 16.6%).[21] The 90-day survival curves of the two groups substantially overlapped (LOG-RANK test, $p = .48$; Fig. 191.4). Secondary end points did not differ statistically; the occurrence of new organ failure was 55.9% in the control versus 56% for CPFA patients ($p = .99$); the free ICU days during the first 30 days postrandomization were 6.8 in the control group versus 7.5 in the CPFA group ($p = .35$). Hospital mortality in patients with septic shock on ICU admission was comparable (16/39 [41%] for control vs. 19/43 [44.2%] for CPFA; $p = .77$). The same was observed for the subgroup of patients who developed septic shock during their ICU stay (27/53 [50.9%] control vs. 21/47 [44.7%] CPFA; $p = .53$).

The per-protocol analysis revealed a nonsignificant trend in hospital mortality according to the tertiles of volume of plasma treated per kilogram per day over the first 5 days. The logistic regression model, aimed at adjusting for possible confounders, verified that hospital mortality in patients falling within the third tertile (≥0.18 L/kg/day of plasma treated over the first 5 days) was statistically lower than in the control group (OR 0.36, 95% CI 0.13 to 0.99; Fig. 191.5). Two sensitivity analyses were performed, namely limiting the evaluation of the volume of plasma treated to the first 3 days and excluding from the control and treated groups patients who died in the first 24 hours postrandomization. The first analysis was aimed at assessing whether any possible benefit of CPFA was obtained before 5 days; the second was intended to minimize any possible selection bias as patients who died early could not have entered the highest tertile of treated plasma because of insufficient time. Both sensitivity analyses confirmed the same estimates, even though statistical significance was lost for lack of power.

The subgroup analysis was suggestive of efficacy, provided that a high volume of plasma was treated. Given the new availability of citrate regional anticoagulation, it has been designed a confirmatory, adaptive trial whose first step will be to prove this new technique easily allows

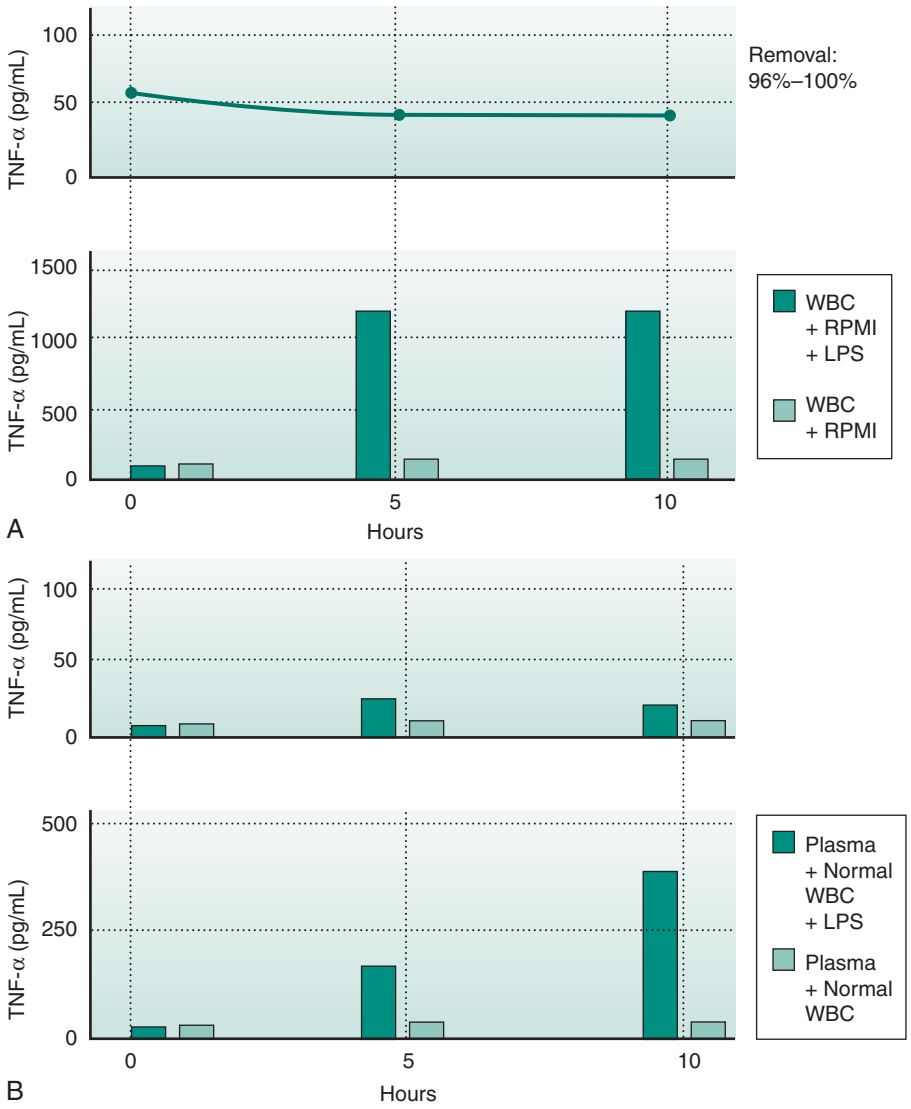


FIGURE 191.2 A, In vitro production of tumor necrosis factor-alpha (TNF-α) after lipopolysaccharide challenge at different times during coupled plasmafiltration-adsorption (CPFA). *Top,* Plasma TNF-α level; *bottom,* in vitro production. *Dark green bar* indicates white blood cells plus lipopolysaccharide; *light green bar* indicates white blood cells plus RPMI medium only. B, Effect of septic plasma on normal white blood cell production of TNF-α during CPFA treatment. *Top,* Precartridge plasma; *bottom,* postcartridge plasma. *Dark green bar* indicates plasma plus normal white blood cells plus lipopolysaccharides; *light green bar* indicates plasma plus normal white blood cells. (Data from Ronco C, Brendolan A, Lonnemann G, et al. A pilot study of coupled plasma filtration with adsorption in septic shock. *Crit Care Med.* 2002;30:1250–1255.)

high volume of plasma treated with CPFA, identified by the acronym COMPACT-2 (COMbined Plasmafiltration and Adsorption Clinical Trial)—registered on ClinicalTrials.gov with the identifier NCT01639664. The study objective is to clarify whether the application of high doses CPFA in addition to the current clinical practice is able to reduce hospital mortality in septic shock patients in ICU. Secondary objectives are the resolution of septic shock and the reduction of ICU length of stay. According to the rationale of the study, a lower mortality is expected in patients treated with CPFA to higher doses than patients treated according to current medical practice. The study will then be conducted according to the adaptive scheme, in which two intermediate evaluations of the results are foreseen, which will determine the continuation or not of randomization. If the study will exceed both of these interim evaluations, enrollment will continue until the size expected for the analysis of mortality.

REGIONAL CITRATE ANTICOAGULATION IN COUPLED PLASMAFILTRATION-ADSORPTION

Citrate has been used successfully for the first time in CPFA in 13 septic patients with ARF and high risk of bleeding or active bleeding,[20] confirming the superiority of citrate compared to heparin, allowing lower intra-cartridge pressure thus preventing circuit coagulation.

Citrate levels in the plasma taken before and after the cartridge were comparable, suggesting that citrate is not retained by the hydrophobic resin.[20] A remarkable stability of blood ionized calcium and acid-base parameters was observed during the whole length of the RCA-CPFA session.

The citrate has been used in patients with septic shock treated with CPFA in recent years in other centers, with achievement of doses of plasma filtrate more than other

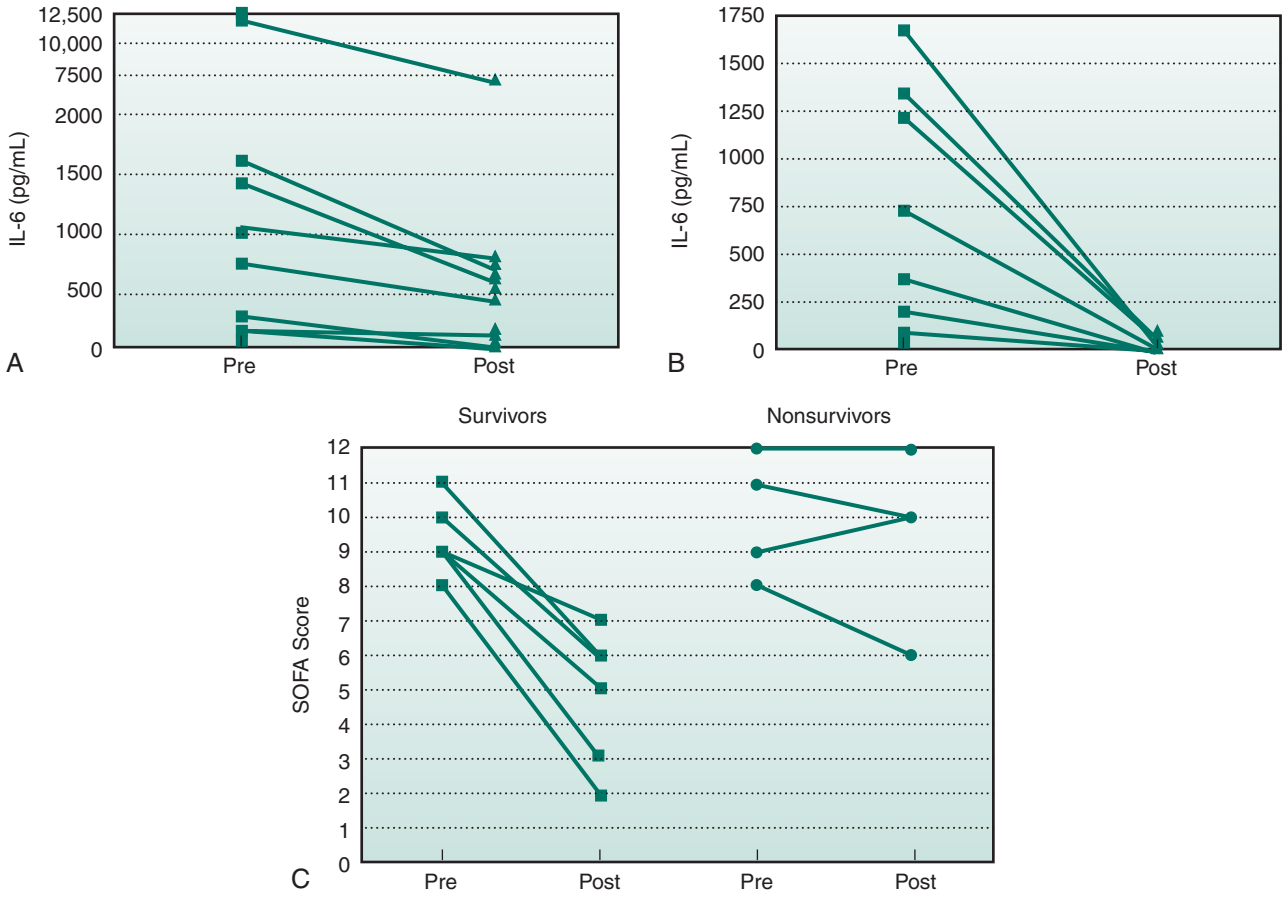
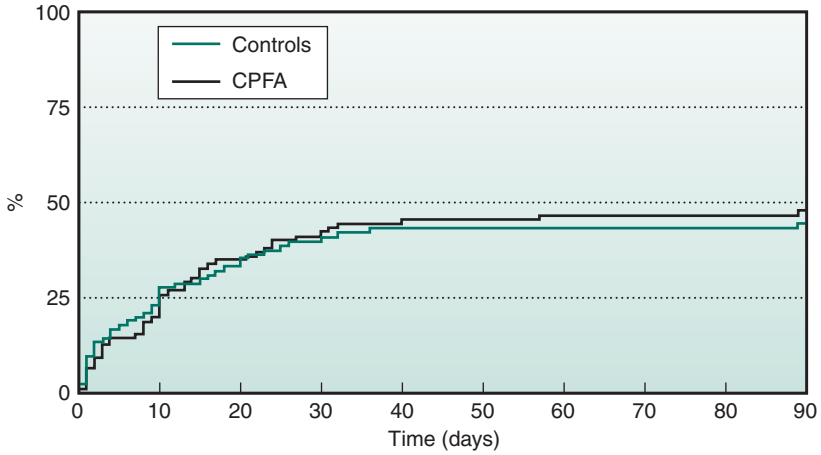


FIGURE 191.3 A, Interleukin-6 (IL-6) blood concentration before (Pre) and after (Post) a session of coupled plasmafiltration-adsorption (CPFA). B, Precartridge and postcartridge plasma IL-6 concentrations. C, Sequential Organ Failure Assessment (SOFA) scores before (Pre) and after (Post) CPFA treatment in survivors and nonsurvivors. (Data from Formica M, Olivieri C, Livigni S, et al. Hemodynamic response to coupled plasmafiltration-adsorption in human septic shock. *Intensive Care Med.* 2003;29:703–708.)



Patients at risk:

Controls	93	75	61	55	51	50	48	48	47	46
CPFA	91	70	61	54	48	47	46	44	44	43

FIGURE 191.4 90-day survival curves of the two groups of the COMPACT study. *CPFA,* Coupled Plasmafiltration-Adsorption; *COMPACT,* COMbined Plasmafiltration and Adsorption Clinical Trial.

types of anticoagulation such as heparin, heparin-protamine + prostacyclin, and dermatan sulphate.[22]

To obtain optimal anticoagulation of the circuit, a concentration of citrate equal to 3 mmol/L (normal concentration of citrate in the blood is 0.05 mmol/L) has been reached. Infusing citrate at the beginning of the extracorporeal circuit, ionized calcium (iCa^{++}) was chelated and its concentration in the circuit has been decreased from 1 to 1.2 mmol/L to 0.2 to 0.4 mmol/L.

CPFA was conducted using the locoregional anticoagulation with citrate-calcium chloride with the following prescriptive parameters (Fig. 191.6):

- Blood flow (Qb) of 150 mL/min
- Plasma flow(Qp) of 30 mL/min (maximum of 40 mL/min)

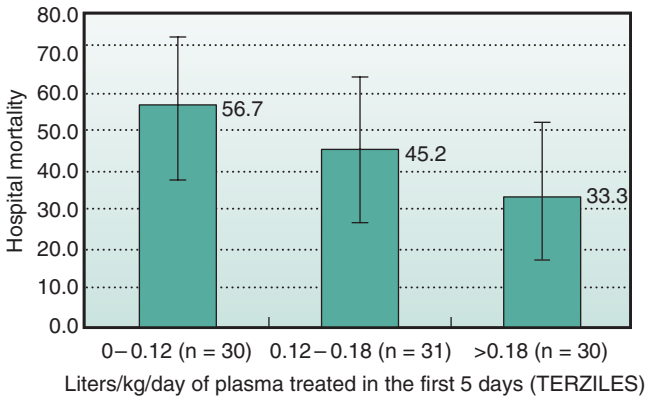


FIGURE 191.5 Hospital mortality according to the quantity of treated plasma volume.

- Predilution solution (Na^+ 136 mmol/L, citrate 10 mmol/L, citric acid 2 mmol/L) to maintain citratemia in the circuit of 3 mmol/L
- Postdilution solutions:
  1. HAB32 (Na^+ 140 mmol/L, K^+ 2.5 mmol/L, Ca^{++} 1.5 mmol/L, Mg^{++} 0.75 mmol/L, Cl^- 115 mmol/L, HCO_3^- 32 mmol/L, glucose 5.55 mmol/L)
  2. HAB34 (Na^+ 138 mmol/L, K^+ 3.5 mmol/L, Ca^{++} 1.5 mmol/L, Mg^{++} 0.75 mmol/L, Cl^- 112 mmol/L, HCO_3^- 34 mmol/L, glucose 5.55 mmol/L)
  3. HAB36 (Na^+ 140 mmol/L, K^+ 4 mmol/L, Ca^{++} 1.5 mmol/L, Mg^{++} 1.0 mmol/L, Cl^- 113 mmol/L, HCO_3^- 36 mmol/L, glucose 5.55 mmol/L)
- 10% $CaCl_2$ infusion in postdilution monitored and adjusted according to the patient's needs.
- Minimum plasma dose to treat for single treatment 0.20 L × kg predicted body weight (PBW)

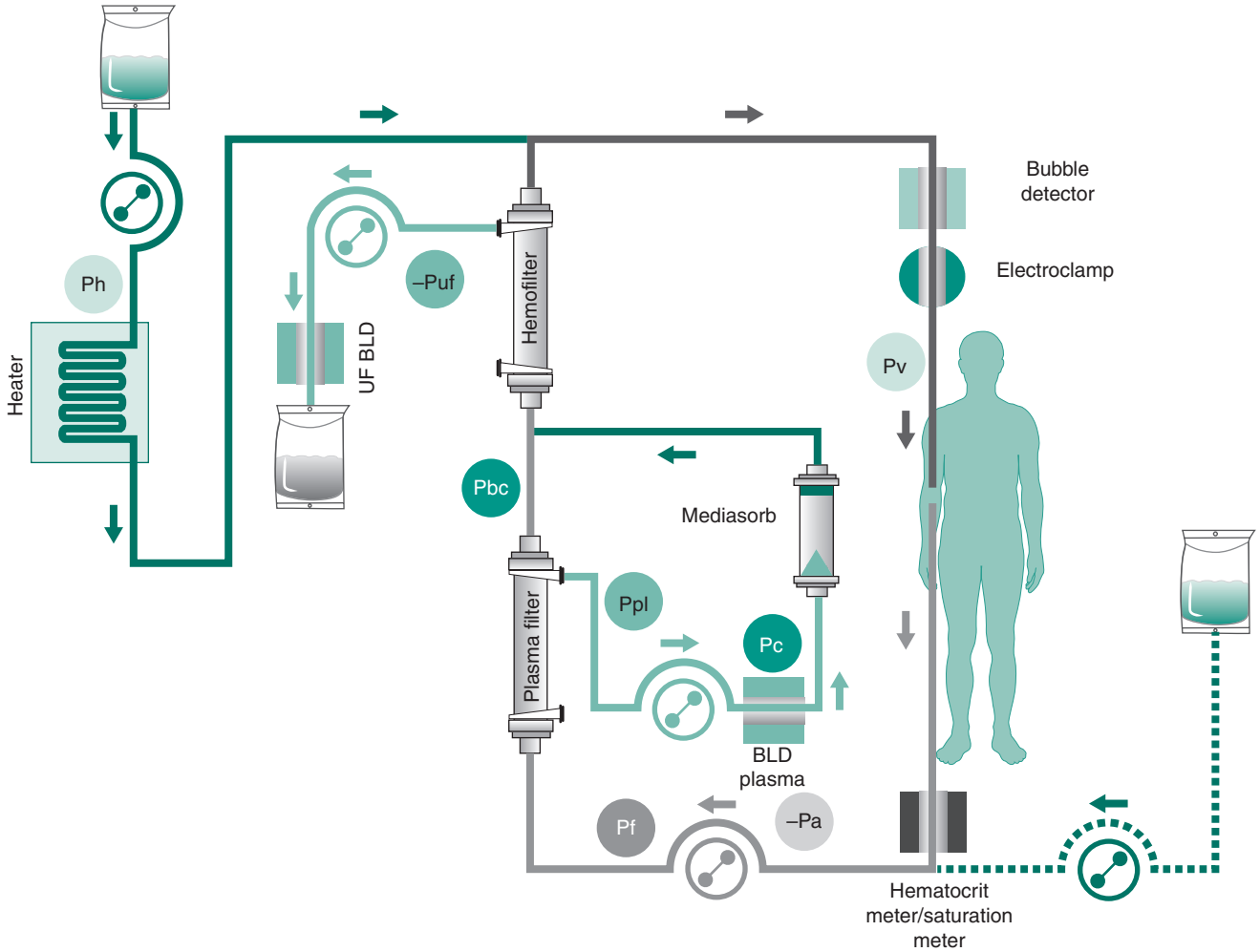


FIGURE 191.6 Schematic diagram of regional citrate anticoagulation in coupled plasma filtration adsorption. The figure shows the blood pump and the blood flow on the access side in *light grey*; the blood flow on the return side in *dark grey*; the infusion pump, the bags, and the infusion flow in *(solid line)* on the left; the predilution pump, the bags, and the predilution flow in *(dashed line)* on the right; and the ultrafiltration or UF pump, the bags, and the UF (plasma water) flow in *light green* on the left. The center shows the plasma flow into the Mediasorb cartridge in *light green* the plasma flow out of the Mediasorb cartridge in *(solid line)* the plasma pump in *dark grey* and the hemofilter, the plasma filter and the Mediasorb cartridge, the heater, the sensors (saturation meter/hematocrit meter, UF BLD and plasma BLD, venous air bubble detector) and the venous electroclamp. The pressures measured directly or indirectly are access (Pa), return (Pv), plasma filter inlet (Pf), hemofilter inlet or plasma filter outlet or Mediasorb outlet (Pbc), infusion pump outlet (Ph), UF pump inlet (Puf), Mediasorb inlet (Pc), and plasma pump inlet (Ppl).

To explain the minimum plasma dose to treat for single treatment of 0.20 L × kg PBW, the data of COMPACT-1 study were followed.[21]

CONCLUSION

The prognosis of patients admitted to intensive care units with septic shock and MODS still has a burden of high mortality, and all attempts to find a "magic bullet" to restore the immune derangements have failed, owing to the complex interactions between proinflammatory and antiinflammatory responses during sepsis, along with the clinical course of the disease.

Interest in the use of extracorporeal blood purification techniques in sepsis has been growing.[23] Of all techniques, CPFA has been demonstrated to be a feasible and safe treatment, with positive results in terms of improved systemic hemodynamics and respiratory functions paralleled by a quick tapering of the need for vasoactive drugs. Also of interest is the improvement in splanchnic perfusion, evaluated by means of tonometry of gastric-mucosal P_{CO_2} diffusion, which could emphasize further the resolution of the hyperdynamic-vasoparalytic state displayed in septic shock.[24]

Thus CPFA is a treatment targeted to the nonselective removal of soluble mediators involved in the septic shock scenario. One can speculate further that the association of different removal mechanisms (diffusion/convection/adsorption) in this modality may play a role in reestablishing a new immune balance *(immunomodulation)* with a significant reduction in acute-phase reactants achieved by hampering their peak levels.[25,26] The results may be related to the ability to restore leukocyte responsiveness to immunoactive stimuli, which may be clinically beneficial because of the link to hemodynamic improvement.[18,27] In consideration of the still high morbidity and mortality rates in patients admitted to ICUs with septic shock, this new blood purification technique seems to exert its benefits best when applied early in the course of sepsis and also when used in patients without concomitant AKI, suggesting that it can be performed to prevent rather than treat AKI.[19] With these premises, if confirmed, it is reasonable to propose to extend this technique also to early stages of septic shock (such as severe sepsis or systemic inflammatory response syndrome—along with pancreatitis).

Despite the fact that some clinical results of CPFA treatment appear good, they must be regarded with caution because of the negative COMPACT-1 trial that could not confirm that CPFA is able to reduce mortality in patients with septic shock. The current results[21] discourage the use of CPFA in the everyday clinical practice, as it was implemented in the COMPACT study.

Two randomized prospective studies are ongoing: the COMPACT-2 and the Mortality Reduction in Septic Shock by Plasma Adsorption (ROMPA) to test the effectiveness of high doses CPFA with AMPLYA Bellco, Italy of more than 0.20 L/kg/day of plasma treated in the first days after randomization.

Citrate has been used successfully in CPFA in septic patients with ARF and high risk of bleeding or active bleeding,[20] confirming the superiority of citrate compared to heparin, allowing lower intra-cartridge pressure thus preventing circuit coagulation.

Regional citrate anticoagulation is a feasible and effective alternative to heparin anticoagulation during CPFA, which can reduce CPFA session interruptions resulting from circuit clotting, thus allowing achievement of higher targets of plasma volume treated per day with good control of patients' coagulation, serum calcium, electrolyte, and acid-base balance.[28]

Key Points

1. Continuous plasmafiltration-adsorption is a feasible, safe, and well-tolerated treatment for critically ill patients with sepsis.
2. This procedure has been shown to improve hemodynamics (mean arterial pressure, cardiac index, vascular peripheral resistance) and pulmonary function (ratio of oxygen arterial pressure to inspired oxygen fraction), to reduce norepinephrine requirement, and to restore immune balance (improvement of monocyte deactivation).
3. Continuous plasmafiltration-adsorption allows a nonselective binding of a wide array of proinflammatory and antiinflammatory mediators, cutting down their peak concentrations and showing an effective body clearance beyond a reduced inflammatory state.
4. This technique can be used in combination with other therapies, such as continuous venovenous hemofiltration, but it also may be of use in patients without acute kidney injury to *prevent* the renal involvement.
5. Up to now we have no clear data to support that CPFA is able to reduce mortality in patients with septic shock. More large-scale trials are needed to support the potential benefits of continuous plasmafiltration-adsorption in treating septic patients.
6. RCA is a feasible and effective alternative to heparin anticoagulation during CPFA, which can reduce CPFA session interruptions resulting from circuit clotting, thus allowing achievement of higher targets of plasma volume treated per day.
7. The availability of citrate protocols for CPFA and the introduction of newer generation machines could facilitate a safe implementation of RCA also in this setting.

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