Coupled Plasma Filtration Adsorption

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OUTLINE

• Definition and settings of Coupled Plasma Filtration Adsorption (CPFA);

• Report of clinical trials and rationale of the use of CPFA in septic shock patients;

• Other clinical applications and potential protective role of CPFA in septic and nephrotoxic AKI.
• Definition and settings of Coupled Plasma Filtration Adsorption (CPFA);

• Report of clinical trials and rationale of the use of CPFA in septic shock patients;

• Other clinical applications and potential protective role of CPFA in septic and nephrotoxic AKI.
**Conclusions:** Coupled plasmafiltration-adsorption was a feasible and safe extracorporeal treatment and exerted a remarkable improvement in hemodynamics, organ function and outcome of septic shock patients with or without concomitant AKI.
How does the resin work?

From micro

To nano

Large proteins will not enter the resin pores.
How does the resin work?

From micro to nano, small hydrophilic molecules will pass through.
How does the resin work?

From micro to nano, small hydrophilic molecules will pass through.
How does the resin work?

From micro

To nano

Hydrophobic proteins will adsorb to the resin
How does the resin work?

From micro to nano, hydrophobic proteins will adsorb to the resin.
How does the resin work?

From micro

To nano

Hydrophobic proteins will adsorb to the resin.
CPFA RESIN SIGNIFICANT ADSORPTION

- Interleukin 1b
- Interleukin 5
- Interleukin 6
- Interleukin 7
- Interleukin 8
- Interleukin 10(?)
- Interleukin 12p70
- Interleukin 16
- Interleukin 18

- Macrophage inflammatory protein-a (MIP-a)
- Macrophage inflammatory protein-b (MIP-b)
- Tumor necrosis factor-a (TNF-a)
- Monocyte chemotactic protein (MCP-1)
- RANTES
- Epithelial neutrophil activating peptide 78 (ENA-78)
- Angiogenin
LOW OR NON SIGNIFICANT ADSORPTION

**Non significant Adsorption**

- ALBUMIN
- HEPARIN
- CITRATE
- ANTIBODIES
- FERRITIN
- GM-CSF
- TIROXINE
- ADIPONECTIN
- VON WILLEBRAND FACTOR
- ENDOTOXIN

**Low Adsorption**

- INSULIN
- VEGF
- EGF
- ICAM
- VCAM
- MCP
An increasing body of evidence suggests that AKI can occur in the absence of hypoperfusion.

Sepsis induces profound alterations in microcirculatory flow in the entire organism, and the kidney is not the exception.

Sepsis is associated with the release of damage and pathogen associated molecular patterns (DAMPs and PAMPs) into the circulation.
Circulating plasma factors induce tubular and glomerular alterations in septic burns patients

Filippo Mariano, Vincenzo Cantaluppi, Maurizio Stella, Giuseppe Mauriello Romanazzi, Barbara Assenzio, Monica Cairo, Luigi Biancone, Giorgio Triolo, V Marco Ranieri, and Giovanni Camussi
Systemic inflammation is known to target tubular epithelial cells (TECs), leading to acute kidney injury.

Tubular cells have been implicated in the response to inflammatory mediators in ischaemic and septic renal damage.

Loss of tubular cells by apoptosis or epithelial-to-mesenchymal transition may ingenerate conditions that lead to progression towards chronic kidney disease.

TECs may actively contribute to the production of inflammatory mediators that may propagate the injury locally or in distant organs.
Extracorporeal Treatments in Patients with Acute Kidney Injury and Sepsis

Marita Marengo\textsuperscript{a} • Sergio Dellepiane\textsuperscript{b} • Vincenzo Cantaluppi\textsuperscript{c}
Definition and settings of Coupled Plasma Filtration Adsorption (CPFA);

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Coupled Plasma-Filtration Adsorption (CPFA)

Blood In 100-200 ml/min

Plasmafilter

Sorbent

Hemodiafilter

Blood Out

Plasm filtrate = 20 ml/min

Dialysate Out + Uf 2-8 ml/min

Dialysate In 30 ml/min

CYTOKINES CONCENTRATION IN BLOOD AND UF

- IL-1
- IL-8
- IL-6

Adsorption capacity for TNFα of two sorbent materials

Detoxyl (Uncoated charcoal)

Mediasorb (Hydrophobic resin)
Coupled plasma filtration-adsorption in a rabbit model of endotoxic shock Tetta C et al, Critical Care Med, 2000
Table 1. Main characteristics of treated patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>APACHE II Score</th>
<th>Failing Organs</th>
<th>Tx Sequence</th>
<th>NE (µg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>3</td>
<td>AB</td>
<td>0.19</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>4</td>
<td>AB</td>
<td>0.11</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>4</td>
<td>BA</td>
<td>0.15</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>3</td>
<td>AB</td>
<td>0.08</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>4</td>
<td>BA</td>
<td>0.16</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>4</td>
<td>BA</td>
<td>0.18</td>
</tr>
<tr>
<td>7</td>
<td>24</td>
<td>4</td>
<td>AB</td>
<td>0.22</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
<td>5</td>
<td>BA</td>
<td>0.19</td>
</tr>
<tr>
<td>9</td>
<td>27</td>
<td>4</td>
<td>AB</td>
<td>0.15</td>
</tr>
<tr>
<td>10</td>
<td>29</td>
<td>4</td>
<td>AB</td>
<td>0.12</td>
</tr>
</tbody>
</table>

APACHE, Acute Physiology and Chronic Health Evaluation; Tx, treatment; NE, norepinephrine; AB, treatment sequence of coupled plasma filtration adsorption plus hemodialysis, then continuous venovenous hemodiafiltration; BA, treatment sequence of continuous venovenous hemodiafiltration, then coupled plasma filtration adsorption plus hemodialysis.
Safe use of CPFA in ICU-hospitalized patients with septic shock independently of the presence of concomitant ARF. In this long-term study, we showed CPFA to be a safe and feasible treatment with significant improvement in hemodynamic stability, vasopressor requirement, pulmonary function, and 28- and 90-day survival. The 28 days survival rate was 90%, which was quite unexpected considering an Apache II-predicted mortality for these patients of about 40%.
Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: A multicenter randomised controlled clinical trial

Sergio Livigni, Guido Bertolini, Carlotta Rossi, Fiorenza Ferrari, Michele Giardino, Marco Pozzato, Giuseppe Remuzzi. GIVITI: Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (Italian Group for the Evaluation of Interventions in Intensive Care Medicine) is an independent collaboration network of Italian Intensive Care units

\[
\chi^2 \text{ test for general association, } 3.26; \ p = 0.20 \\
\text{Cochran-Armitage test for trend, } 1.82; \ p = 0.069
\]
Intensity of treatment, expressed by the Vp, was associated with an increased rate of survival of septic shock patients treated with CPFA, whereas its timing of initiation, that is, the interval of time elapsing between onset of symptoms and the beginning of plasma purification, did not appear to influence the outcome.

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Non-survivors</th>
<th>Significance, p value</th>
<th>Bonferroni, p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBW, kg, mean ± SD</td>
<td>67±13</td>
<td>74±9</td>
<td>0.164</td>
<td>1.000</td>
</tr>
<tr>
<td>SAPS II, median (IQR)</td>
<td>47 (43–54)</td>
<td>44 (41–58)</td>
<td>0.591</td>
<td>1.000</td>
</tr>
<tr>
<td>Charlson Comorbidity Index, median (IQR)</td>
<td>1 (0–3)</td>
<td>2 (1–3)</td>
<td>0.699</td>
<td>1.000</td>
</tr>
<tr>
<td>Timing of CPFA initiation, h, median (IQR)</td>
<td>25 (18–31)</td>
<td>27 (22–32)</td>
<td>0.573</td>
<td>1.000</td>
</tr>
<tr>
<td>Number of CPFA sessions, median (IQR)</td>
<td>5 (4–5)</td>
<td>4 (4–5)</td>
<td>0.271</td>
<td>1.000</td>
</tr>
<tr>
<td>Total Vp, L, median (IQR)</td>
<td>85 (60–98)</td>
<td>54 (43–68)</td>
<td>0.007</td>
<td>0.102</td>
</tr>
<tr>
<td>Total Vp/IBW, L/kg, mean ± SD</td>
<td>1.23±0.37</td>
<td>0.76±0.29</td>
<td>0.002</td>
<td>0.032</td>
</tr>
<tr>
<td>Vp/IBW, L/session/kg, mean ± SD</td>
<td>0.25±0.06</td>
<td>0.17±0.03</td>
<td>&lt;0.001</td>
<td>0.009</td>
</tr>
<tr>
<td>SOFA before CPFA, median (IQR)</td>
<td>11 (9–13)</td>
<td>12 (10–15)</td>
<td>0.617</td>
<td>1.000</td>
</tr>
<tr>
<td>MAP before CPFA, mm Hg, mean ± SD</td>
<td>61±7</td>
<td>57±10</td>
<td>0.205</td>
<td>1.000</td>
</tr>
<tr>
<td>Norepinephrine dose before CPFA, μg/kg/min, median (IQR)</td>
<td>1.09 (0.76–1.51)</td>
<td>1.62 (1.22–2.03)</td>
<td>0.137</td>
<td>1.000</td>
</tr>
<tr>
<td>CI before CPFA, μg/kg/min, median (IQR)</td>
<td>109 (76–151)</td>
<td>162 (122–213)</td>
<td>0.123</td>
<td>1.000</td>
</tr>
<tr>
<td>PACI before CPFA, μg/kg/min/mm Hg, median (IQR)</td>
<td>1.83 (1.16–2.81)</td>
<td>2.36 (2.05–4.14)</td>
<td>0.123</td>
<td>1.000</td>
</tr>
</tbody>
</table>
CPFA, citrate and outcome

Considering that previous studies demonstrated (a) a dose-effect relationship between the volume of plasma processed and the outcome, which is better when this variable exceeds 0.20 L/kg/session, and (b) the superiority of RCA over intravenous heparin in patients undergoing renal replacement therapy in terms of duration of the extracorporeal circuit, systemic bleeding and transfusion requirements. Moreover, in septic patients, finding the right dose of heparin can be challenging due to a number of conditions such as the presence of possible sources of hemorrhage, the low levels of Antithrombin III and the hypercoagulable state determined by the interaction between inflammatory mediators and coagulation factors.

For these reasons and a few citrate contraindications, RCA has been recommended even in the absence of an increased risk of bleeding.

The recent COMPACT II study, which has been prematurely suspended due to an excess mortality rate in the treatment group, required the use of RCA instead of heparin during the CPFA
Low concentrations of citrate reduce complement and granulocyte activation in vitro in human whole blood.

Also, the effects were further enhanced with increasing citrate concentration.

Dialysis fluids containing citrate are promising alternatives for acetate dialysis fluids showing improved biocompatibility dialysis, hopefully with less adverse effects for the patients.
Increased mortality in CPFA group vs control, especially during the first days of treatment.

In septic shock patients enrolled in the study, a clinical poor outcome in the CPFA group was observed.

COMPACT-2 was prematurely interrupted and GiViTI did not recommend the use of CPFA for septic shock patients.
Sepsis and alteration of microvascular flow

Principal mechanisms implicated in the development of microcirculatory alterations

- Endothelial dysfunction (impaired sensitivity of vasoconstrictive/vasodilating substances)
- Altered glycocalyx
- Impaired RBC deformability
- Rolling and adhesion of RBC and WBC to endothelium
- Impaired backward communication
- Flow $>>$ O$_2$ needs $\Rightarrow$ High SvO$_2$
- Flow $<<$ O$_2$ needs $\Rightarrow$ Hypoxia

- Capillary density
- Number of stopped-flow and intermittent-flow capillaries

↓ surface for O$_2$ exchange
Changes in microvascular blood flow during coupled plasma filtration and adsorption- CPFA

CPFA and Sublingual Blood Flow

Pre CPFA  2 h after CPFA initiation  1 after Stop CPFA

LPS removal reduces CD80-mediated albuminuria in critically ill patients with Gram-negative sepsis

Effects of extracorporeal treatments CPFA on cytokine removal.
LPS removal reduces CD80-mediated albuminuria in critically ill patients with Gram-negative sepsis

Effects of CPFA on markers of Gram-negative infection and glomerular permeability

Extracorporeal treatment with CPFA significantly reduced the levels of EEA, as compared with control group.

Baseline proteinuria and albuminuria were significantly high in Gram-negative septic patients, but the reduction in circulating LPS levels by CPFA induced a reduction in glomerular permeability to plasma proteins, as demonstrated by the reduction of proteinuria and albuminuria levels.

Baseline urine CD80/creatinine ratio was elevated in Gram-negative septic patients.

Removal of LPS by CPFA induced a statistically significant reduction in urinary CD80 excretion as compared with control group.
LPS removal reduces CD80-mediated albuminuria in critically ill patients with Gram-negative sepsis

Confocal analysis of frozen renal tissues showed absence of CD80 glomerular expression in control pigs not exposed to LPS (Fig. 5, A–D).

The experimental group exposed to LPS, but not treated with CPFA, showed marked increase of CD80 expression at the podocyte level, as demonstrated by the colocalization with the podocyte marker WT-1 (Fig. 5, E–H).

CPFA treatment reduced podocyte expression of CD80 after LPS exposure, reaching a level comparable to the experimental group not exposed to LPS (Fig. 5, I–L), as shown by the image analysis.

CPFA treatment, while reducing LPS levels and inhibiting CD80 induction at the podocyte level, was also able to reduce glomerular permeability to proteins.

Crit Care 2010

Amberchrom CG161M resin (Rohm and Haas Co. Philadelphia, PA)
Maladaptative repair following AKI

Maladaptive repair

Progressive scarring

Healthy kidney

AKI

CKD

DNA damage
Increasing age
Previous AKI/CKD
Sustained cell stress

G2/M cycle arrest

Progressive fibrosis

Maladaptative repair

Injured, adhesive endothelium

Apoptotic tubular cell

Necrotic tubular cell

M1 macrophage recruitment

Neutrophil recruitment

Pericyte/capillary dissociation

Macrophages

G2/M-arrested tubular cells

Myofibroblast

Collagen deposition

Secretion of profibrotic factors by G2/M cells

Chronic inflammation

Tubular loss
Definition and settings of Coupled Plasma Filtration Adsorption (CPFA);

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Other clinical applications and potential protective role of CPFA in septic and nephrotoxic AKI.
The question......

CPFA: other clinical applications?
Rhabdomyolysis and Acute Kidney Injury

Xavier Bosch, M.D., Ph.D., Esteban Poch, M.D., Ph.D., and Josep M. Grau, M.D., Ph.D.

Renal injury related with Myoglobin:

1) ISCHEMIA
2) CAST NEPHROPATHY
3) OXIDATIVE INJURY
The experience of CPFA in rhabdomyolysis is limited. The use of CPFA in rhabdomyolysis resulting in kidney transplantation has been described. In a limited number of cases, described the use of CPFA in post-traumatic rhabdomyolysis with renal damage, elevated blood levels of creatinine and contraction or absence of diuresis. Used CPFA early in order to prevent kidney damage, 6 h after the surgical revascularization along with the infusion therapy, diuretic, and correction of metabolic acidosis.

The serum creatinine and potassium values remained normal. Diuresis has always been present, and the blood levels of CK and myoglobin decreased rapidly. The patient recovered without sequelae.
Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction.

Bilirubin may contribute to AKI in patients with severe liver dysfunction for a direct toxic and pro-apoptotic effect on tubular epithelial cells.

Mechanisms of tubular cell injury are similar to those observed in presence of Ig light chains during multiple myeloma and of myoglobin during rhabdomyolysis: role of the endocytic receptor megalin.

Megalin is an endocytic receptor expressed on the luminal surface of the renal proximal tubules.

Megalin plays a crucial role together with cubilin in re-adsorption of filtered vitamin/carrier complexes.
In vitro data: kinetics of bilirubin and albumin adsorption during CPFA

Experimental set-up

Qp: 30 ml/min

Vol = 1L 1:1 Albumin Bilirubin

Pre-cartridge

Post-cartridge

Coupled plasma filtration adsorption reduces serum bilirubin in a case of acute hypoxic hepatitis secondary to cardiogenic shock

Courtesy by Wratten ML,

Hyperbilirubinemia After Liver Transplantation: The Role of Coupled Plasma Filtration Adsorption

Liver-type fatty acid binding protein (L-FABP) is a 14KDa protein belonging to calycin family acting as an iron carrier (like NGAL).

L-FABP is also able to bind with high affinity to hydrophobic molecules including free fatty acids, bile acids and bilirubin.

L-FABP is released into the bloodstream and patients with liver damage have elevated plasma L-FABP levels.

L-FABP is also present in kidney tubular epithelial cells and its expression is increased during ischemic and nephrotoxic AKI.
Evidence for megalin-mediated proximal tubular uptake of L-FABP, a carrier of potentially nephrotoxic molecules

Yuko Oyama¹, Tetsuro Takeda¹,², Hitomi Hama¹, Abuhito Tanuma¹, Noriaki Ino¹, Kiyoko Sato¹, Ryohsei Kaseda¹, Motokazu Maki¹, Tadashi Yamamoto⁶, Hiroshi Fujii¹, Junichiro I Kazama¹, Shoji Odani¹, Yoshio Terada³, Kunihiro Mizuta³, Fumitake Gojyo⁴ and Akihiko Saito¹,²

L-FABP is uptaken by kidney proximal tubular epithelial cells by the endocytic receptor megalin

L-FABP may have a role as carrier of nephrotoxic molecules in tubular epithelial cells
Effect of CPFA treatment on L-FABP adsorption

*In vitro* L-FABP adsorption on polystirenic resin:
100% after 15 min;
still 60% after 10 hrs.

Data confirmed in vivo in septic patients

![Diagram showing Qp: 30 ml/min and pre-cartridge, post-cartridge]
Bilirubin and L-FABP levels after CPFA treatment

Bilirubin (< 15 mg/dl) and L-FABP (9 ng/ml) decrease was associated with an increase of urinary output.
Effect of CPFA on low molecular weight proteinuria and urinary NGAL levels

After CPFA treatment, we observed a reduction of urinary levels of low molecular weight proteins (α1-microglobulin, Retinol Binding Protein), NGAL (uNGAL) and tubular cells (tubular score) at urine microscopy.

Diagnostic Value of Urine Microscopy for Differential Diagnosis of Acute Kidney Injury in Hospitalized Patients

Mark A. Perazella, Steven G. Coca, Mehmet Kanbay, Ursula C. Brewster, and Chirag R. Parikh
Effect of septic plasma on kidney tubular epithelial cells (TEC): apoptosis

CPFA significantly reduced *in vitro* TEC apoptosis (TUNEL assay detecting DNA fragmentation)
CONCLUSIONS

- Coupled Plasma Filtration Adsorption (CPFA) is a safe and feasible extracorporeal therapy;

- Clinical trials (Compact-Compact 2) did not support the rationale of CPFA use in septic shock patients;

- Experimental data suggest a protective effect on sepsis-associated AKI through the inhibition of endothelial and tubular epithelial cell injury induced by inflammatory mediators;

- Myoglobin- and bilirubin-associated cast nephrotopathy and AKI are other potential clinical applications for CPFA.
Coupled Plasma Filtration Adsorption

Thank you for the attention

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