Coupled Plasma Filtration Adsorption

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Italian Society of Nephrology (SIN)**

UNIVERSITÀ DEL PIEMONTE ORIENTALE

sin reni Società Italiana Nefrologia

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.**

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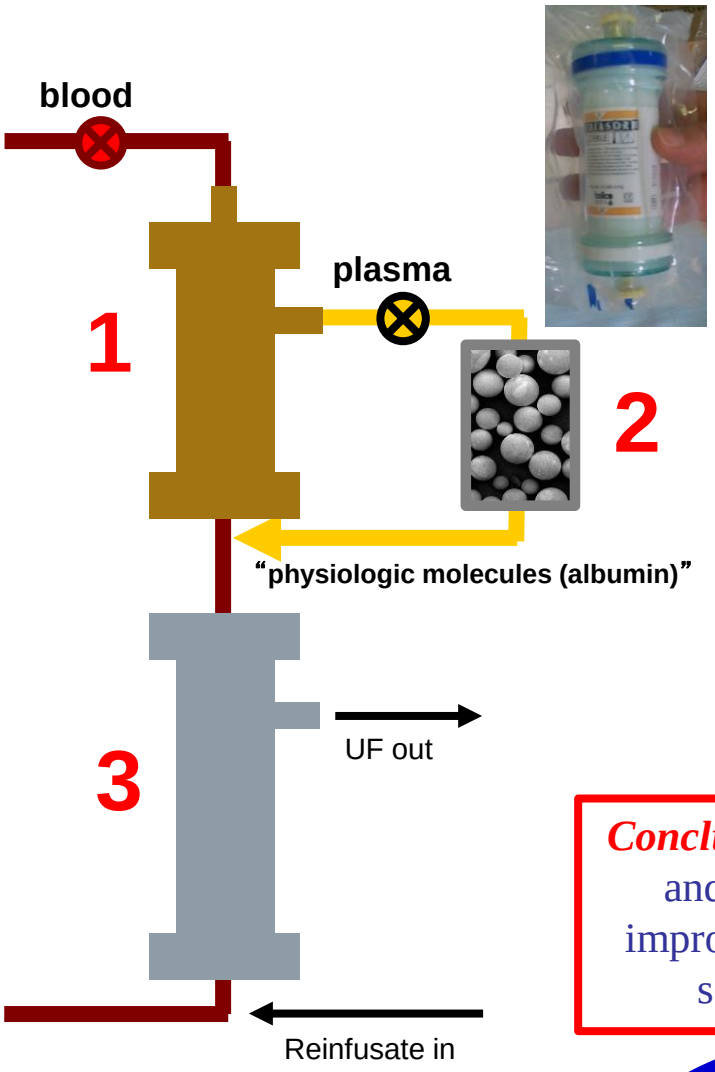
Coupled Plasma Filtration Adsorption



CPFA

1) PLASMAFILTER (POLYETHERSULPHONE 0.45 m^2 WITH A CUT-OFF OF 800 KDa)
2) SORBENT CARTRIDGE (HYDROPHOBIC STYRENIC RESIN)
3) HEMOFILTER/HEMODIAFILTER (POLYETHERSULPHONE 1.4 m^2)

BLOOD FLOW RATE 180-200 ml/min
PLASMA SEPARATION RATE 15-20%
ULTRAFILTRATION RATE 25-30 ml/Kg/hr

Hemodynamic response to CPFA in human septic shock — **Formica M et al.**

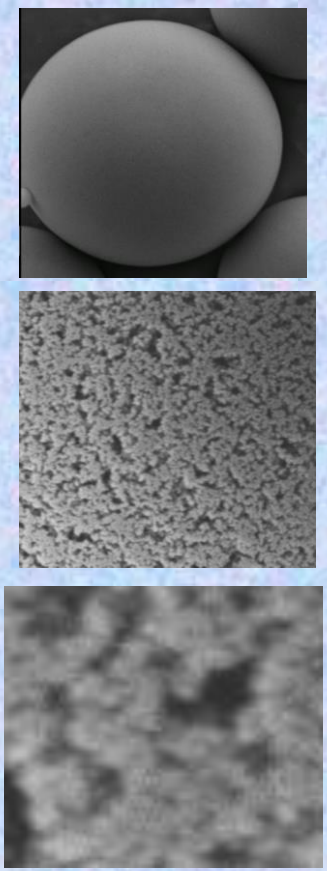
A pilot study of coupled plasma filtration with adsorption in septic shock — **Ronco C et al**

CRITICAL CARE

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.

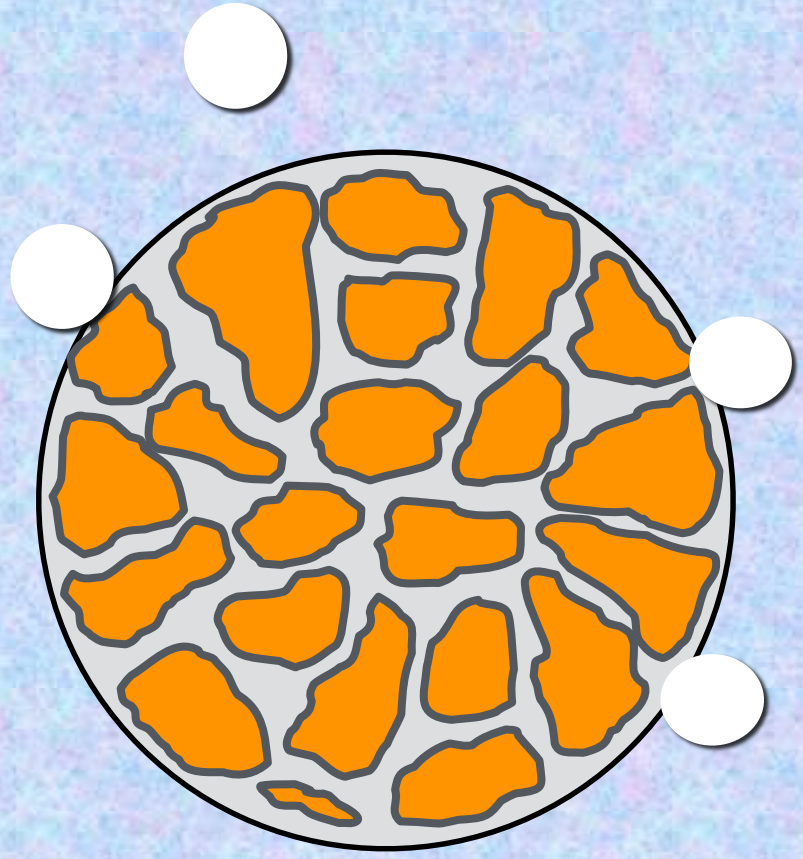
Simultaneous adsorption of several cytokines involved in systemic inflammation

How does the resin work?



From micro

To nano



Large proteins will not enter the resin pores

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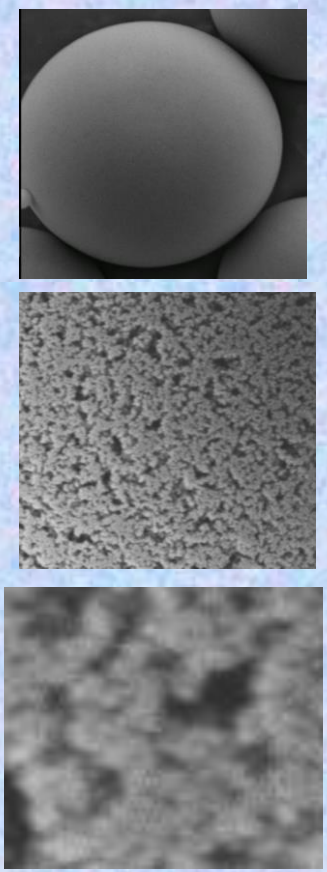

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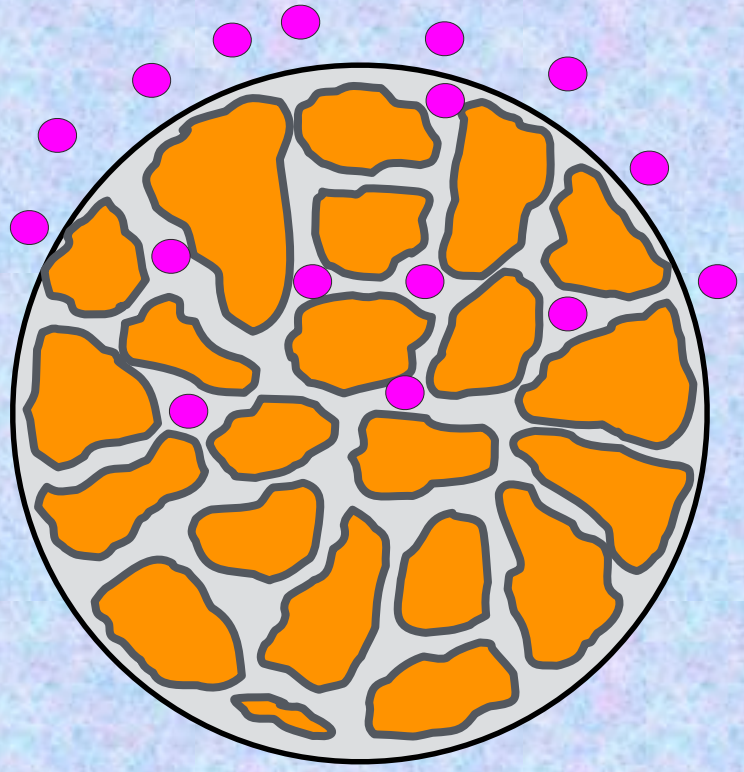
small hydrophilic molecules will pass through



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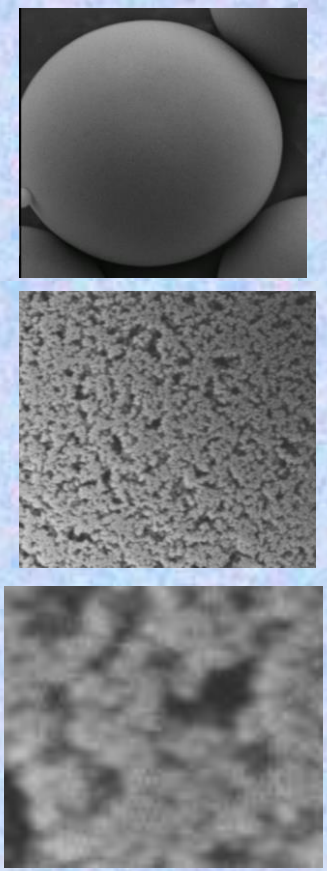

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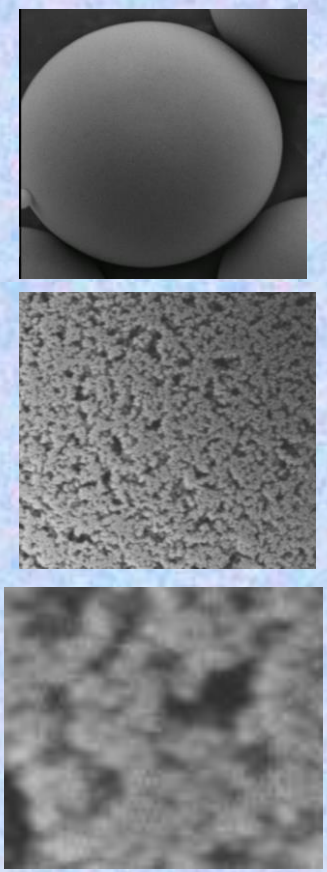

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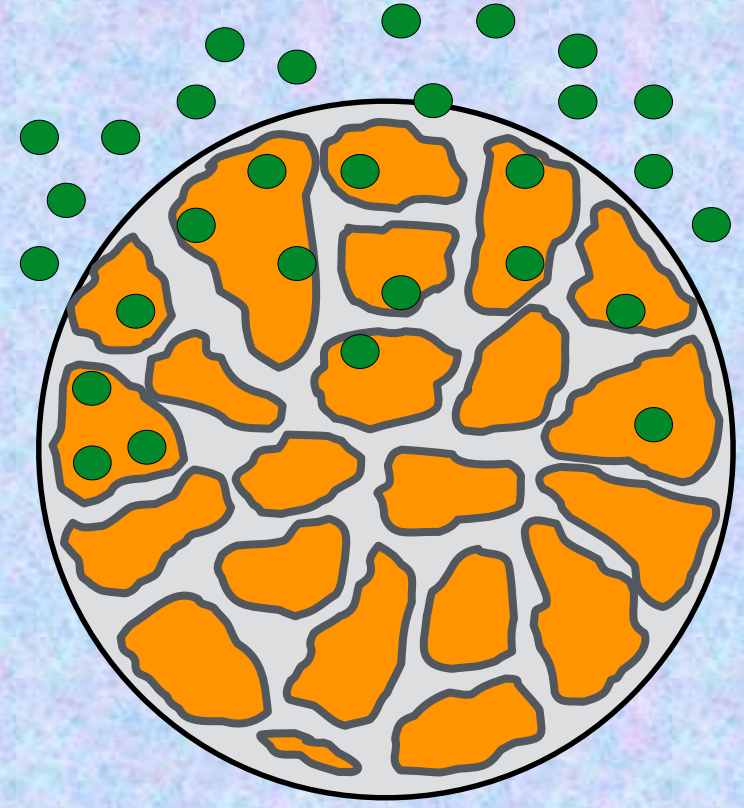

Hydrophobic proteins will adsorb to the resin

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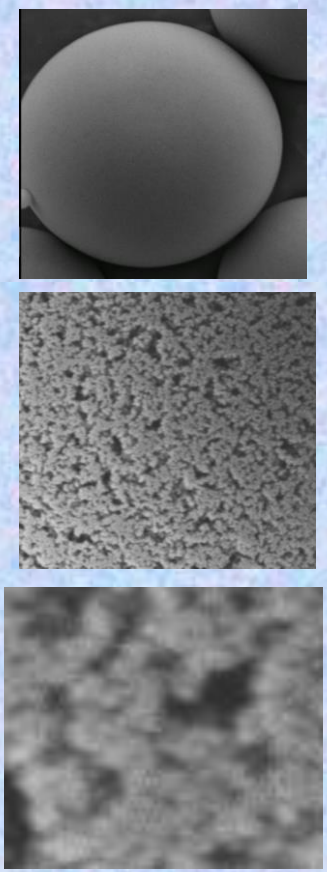

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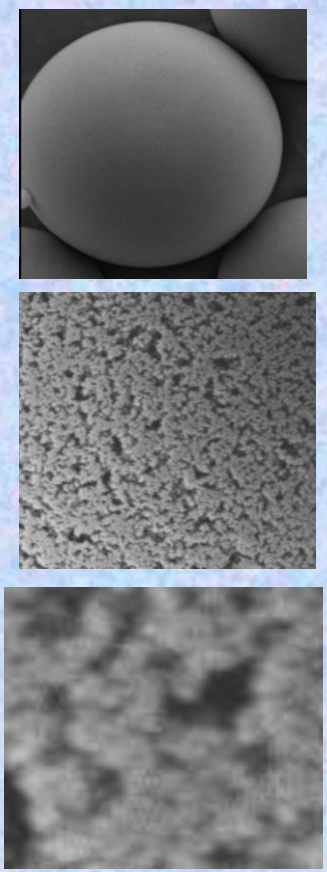

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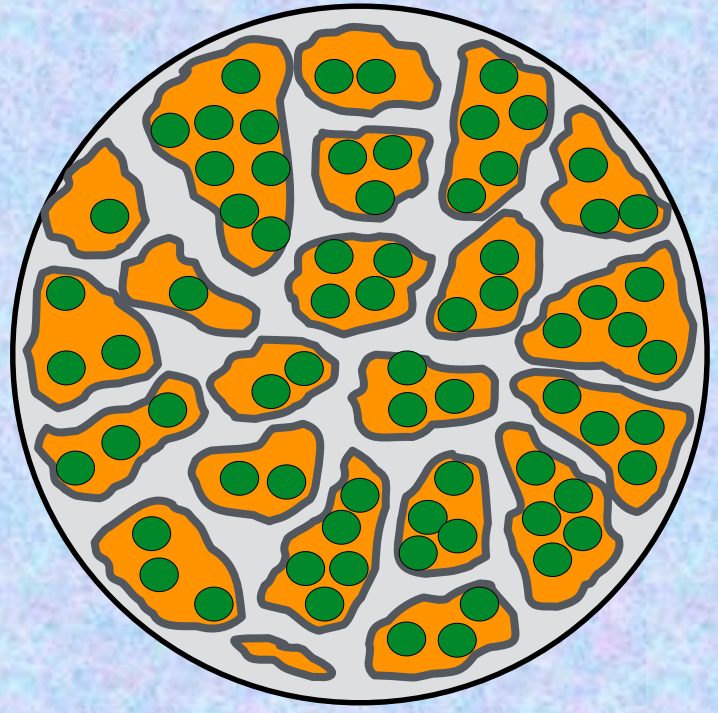
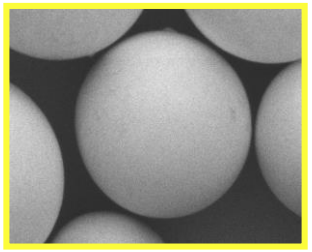


Hydrophobic proteins will adsorb to the resin

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-aTNF-a**
- **Monocyte chemotactic protein (MCP-1)**
- **RANTES**
- Epithelial neutrophil activating peptide 78 (ENA-78)
- Angiogenin

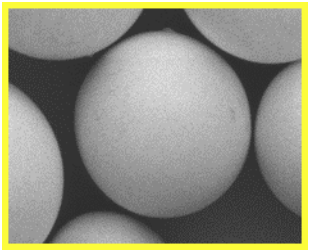
LOW OR NON SIGNIFICANT ADSORPTION

Non significant Adsorption

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

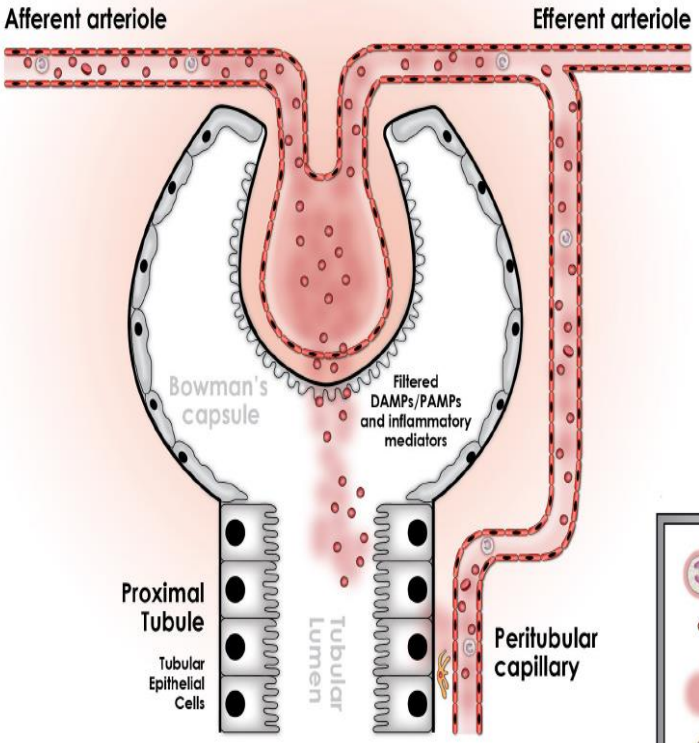
Low Adsorption

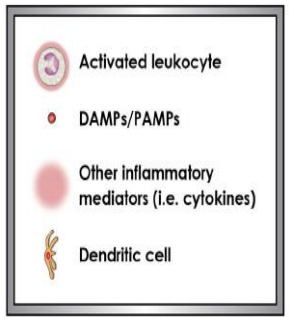
- INSULIN
- VEGF
- EGF
- ICAM
- VCAM
- MCP

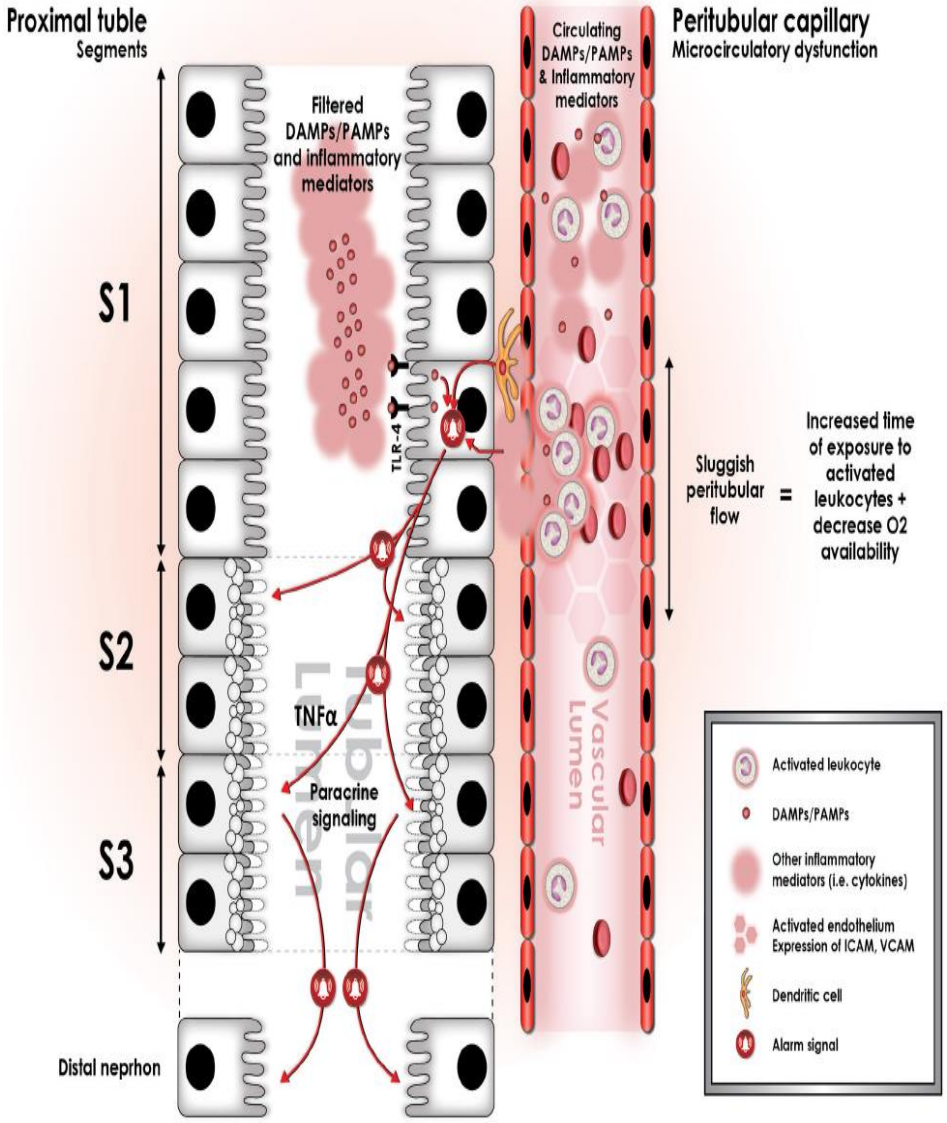


A Unified Theory of Sepsis-Induced Acute Kidney Injury: Inflammation, microcirculatory dysfunction, bioenergetics and the tubular cell adaptation to injury

Hernando Gomez, MD[*,†], Can Ince, PhD[†], Daniel De Backer, MD[‡], Peter Pickkers, MD[§], Didier Payen, MD[‖], John Hotchkiss, MD[*], and John A. Kellum, MD[*,†]







An increasing body of evidence suggests that AKI can occur in the absence of hypoperfusion.

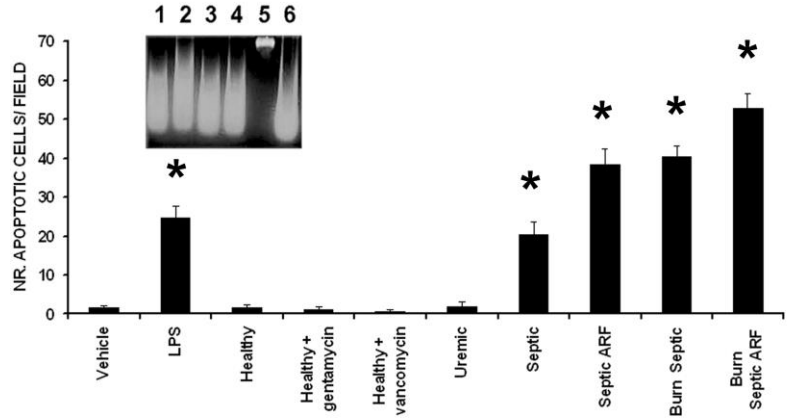
Sepsis induces profound alterations in microcirculatory flow in the entire organism, and the kidney is not the exception

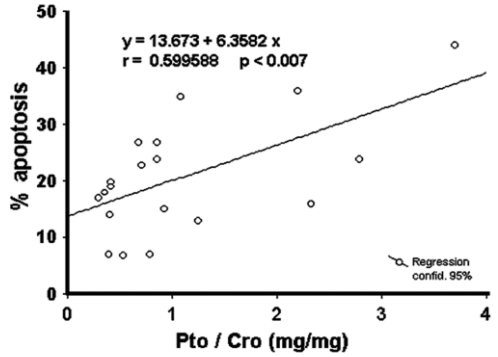
Sepsis is associated with the release of damage and pathogen associated molecular patterns (DAMPs and PAMPs) into the circulation.

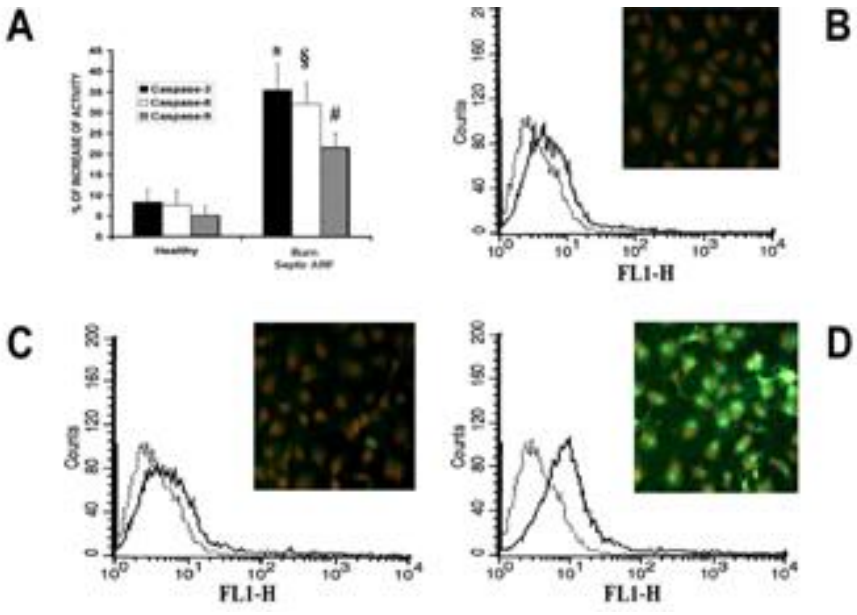
Circulating plasma factors induce tubular and glomerular alterations in septic burns patients

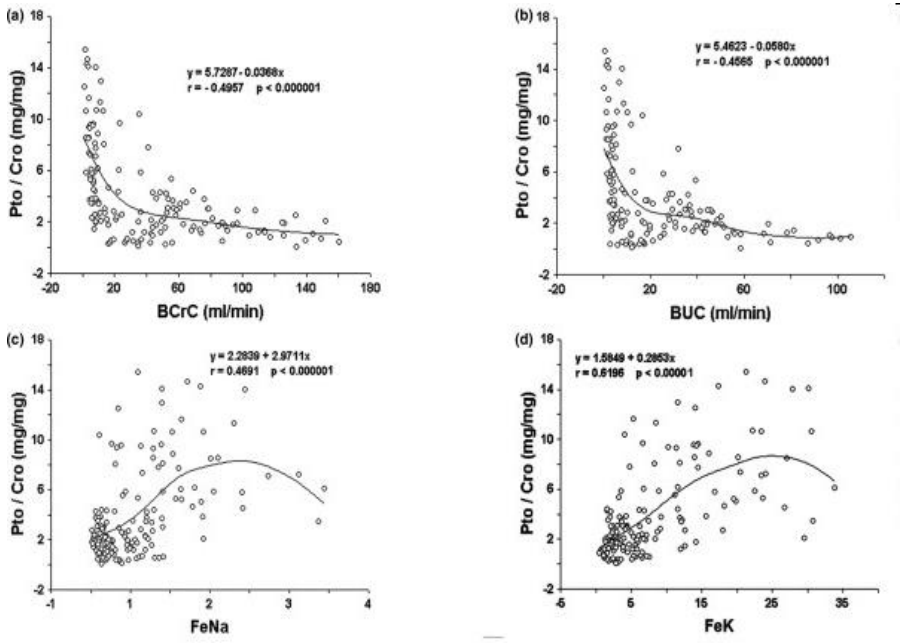
Filippo Mariano,[#] Vincenzo Cantaluppi,[#] Maurizio Stella, Giuseppe Mauriello Romanazzi, Barbara Assenzio, Monica Cairo, Luigi Biancone, Giorgio Triolo, V Marco Ranieri, and Giovanni Camussi

CRITICAL CARE





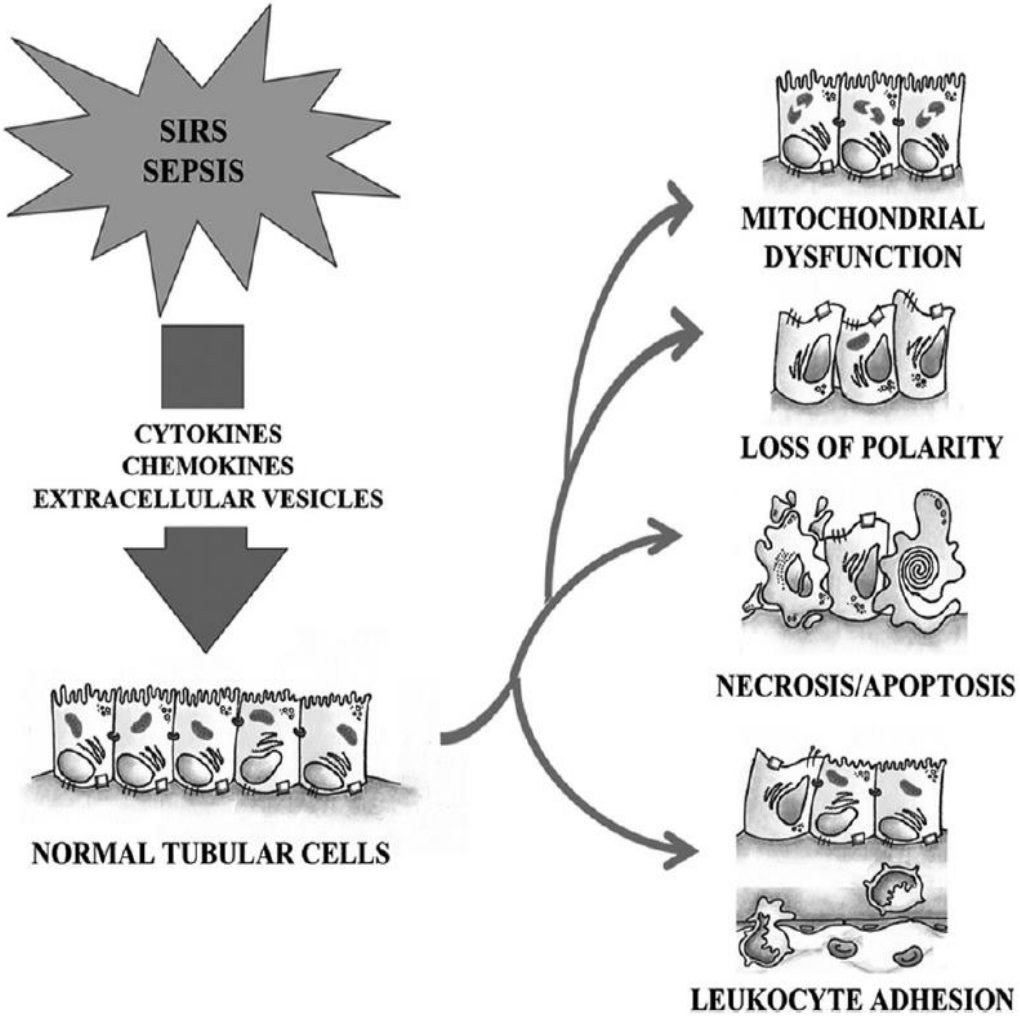




Interaction between systemic inflammation and renal tubular epithelial cells

Vincenzo Cantaluppi, Alessandro Domenico Quercia, Sergio Dellepiane, Silvia Ferrario, Giovanni Camussi and Luigi Biancone

ndt Nephrology Dialysis Transplantation



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.

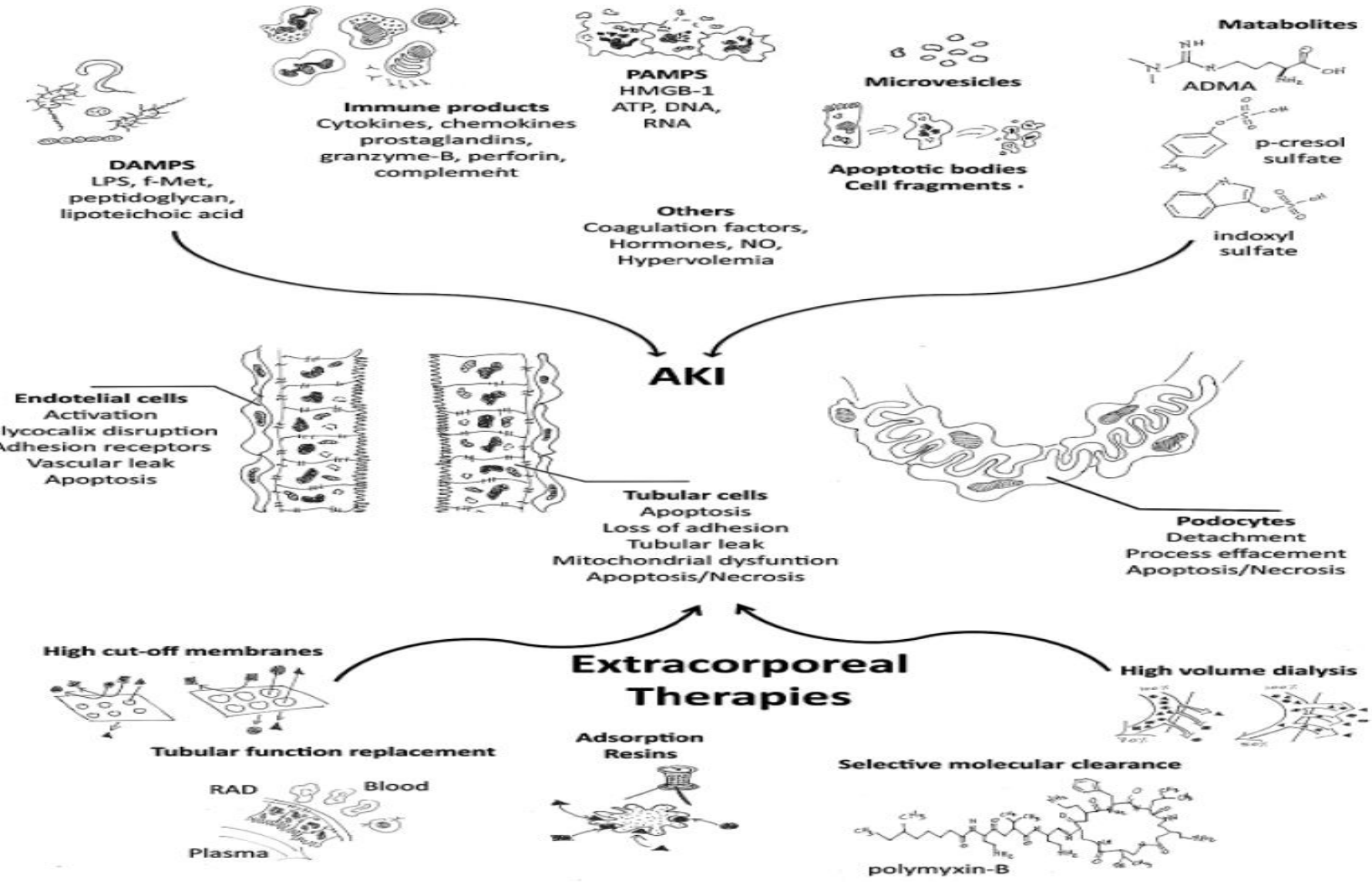
Loss of tubular cells by apoptosis or epithelial-to-mesenchymal transition may ingenerate conditions that lead to progression towards chronic kidney disease.

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[a] · Sergio Dellepiane[b] · Vincenzo Cantaluppi[c]

Blood Purification



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

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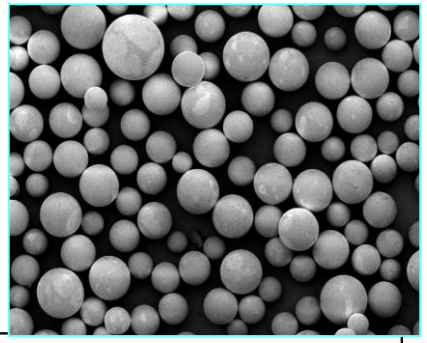
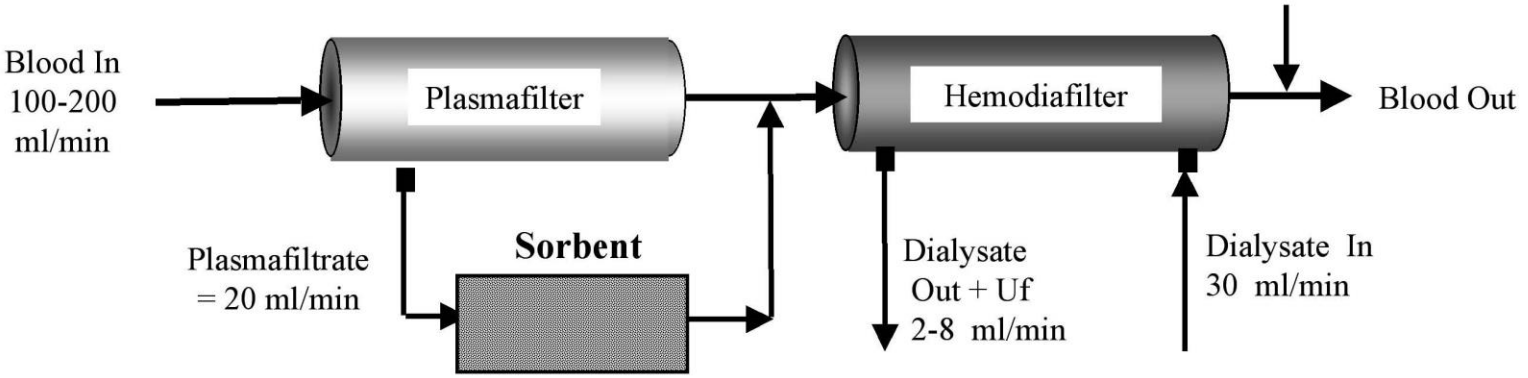
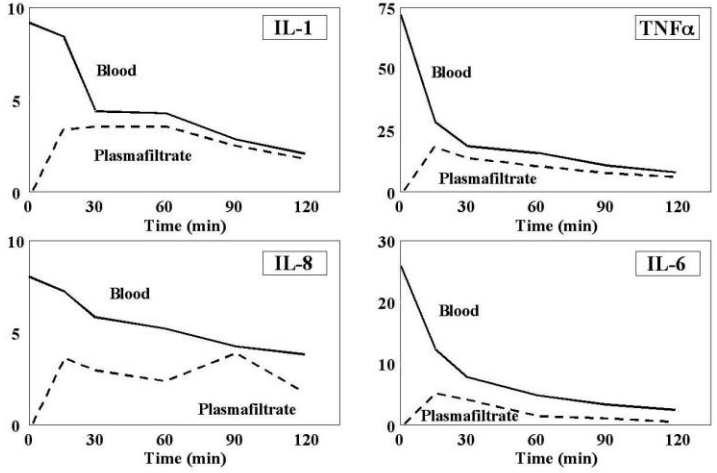
Coupled Plasma-Filtration Adsorption (CPFA)

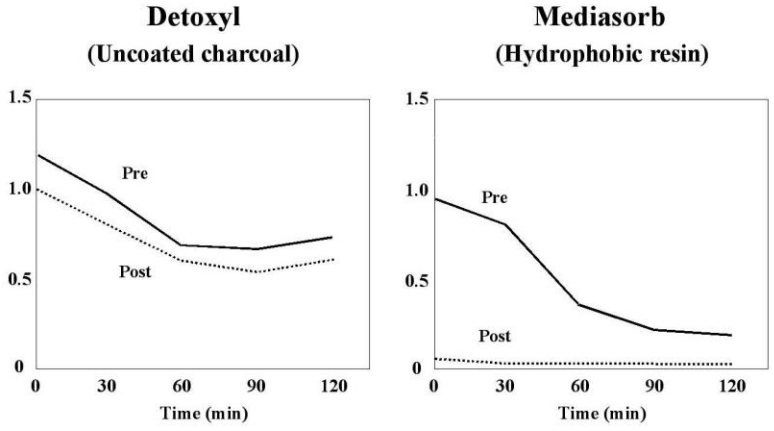




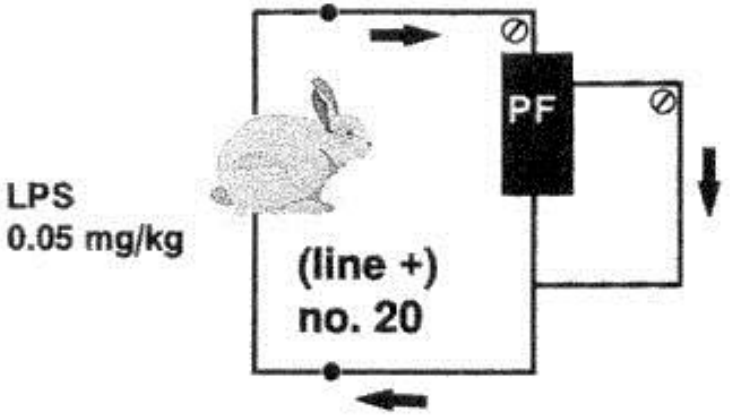
CYTOKINES CONCENTRATION IN BLOOD AND UF

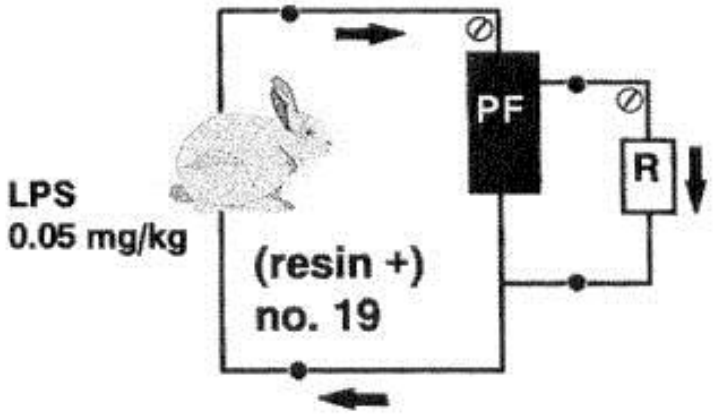


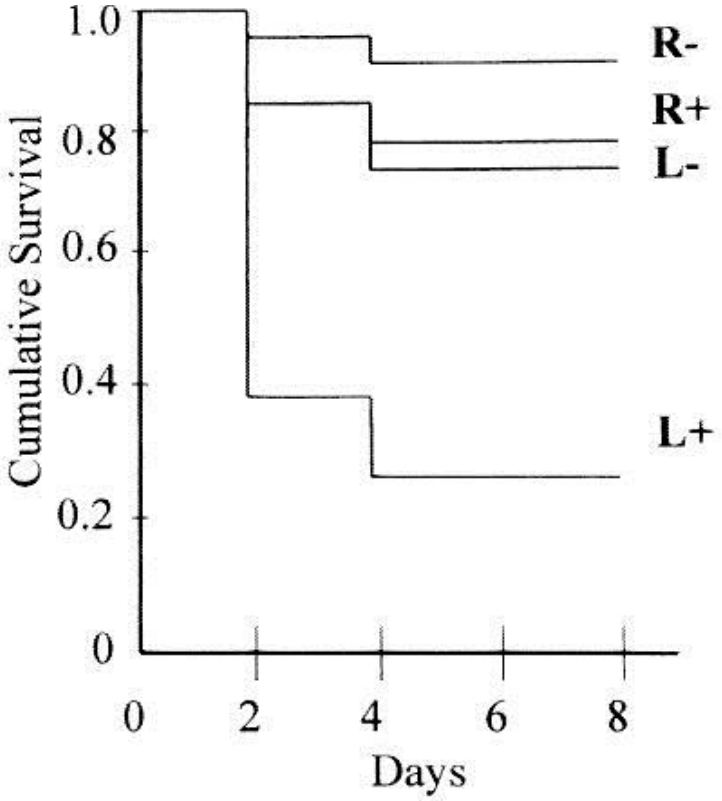
Adsorption capacity for TNFα of two sorbent materials

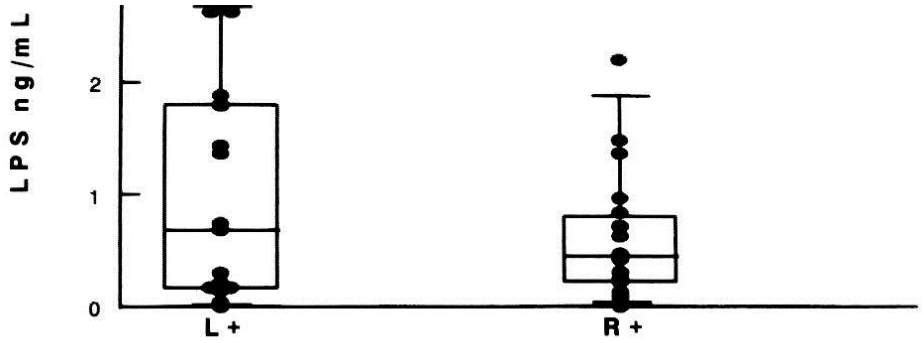


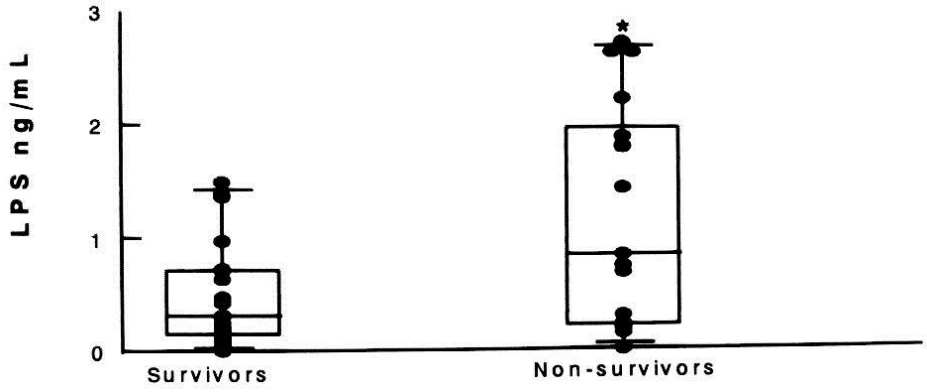
Coupled plasma filtration-adsorption in a rabbit model of endotoxic shock Tetta C et al, Critical Care Med, 2000











A pilot study of coupled plasma filtration with adsorption in septic shock Ronco C et al, Crit Care Med, 2002*

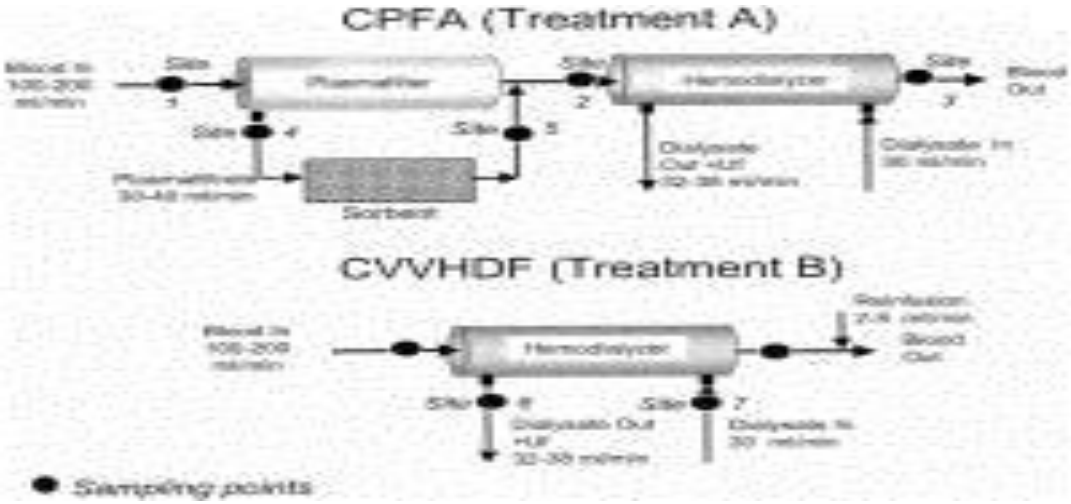
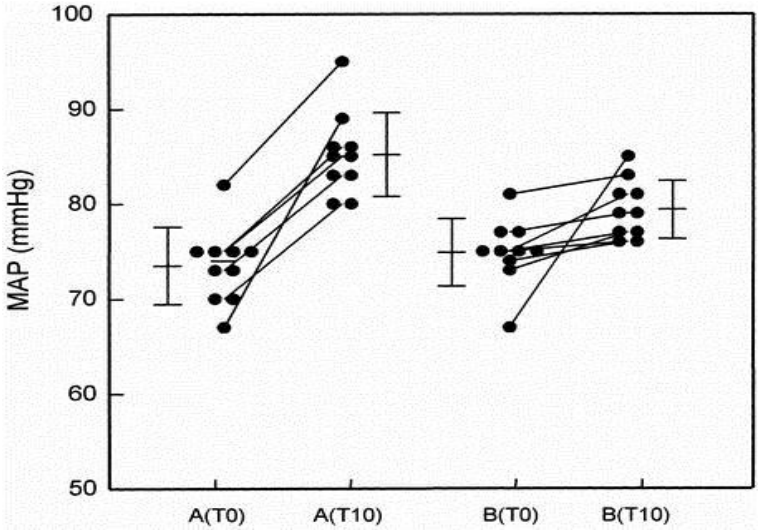
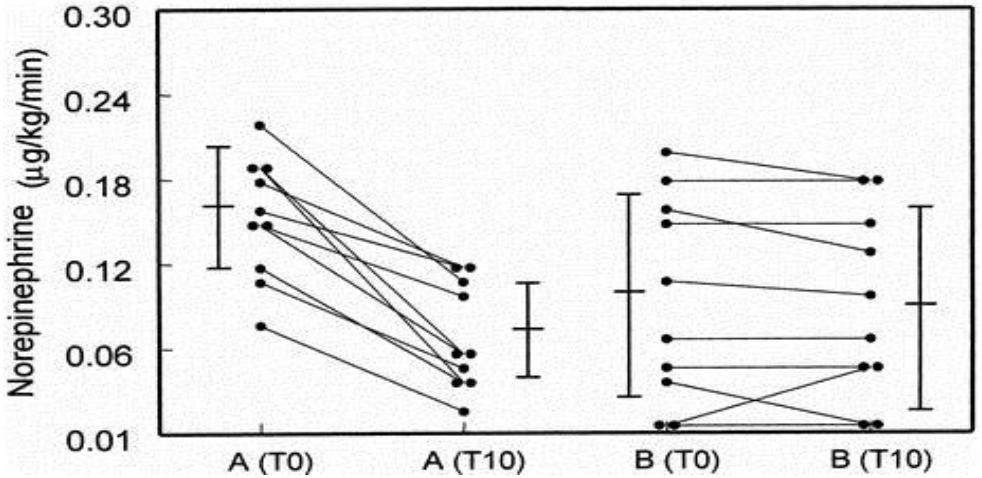


Table 1. Main characteristics of treated patients

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

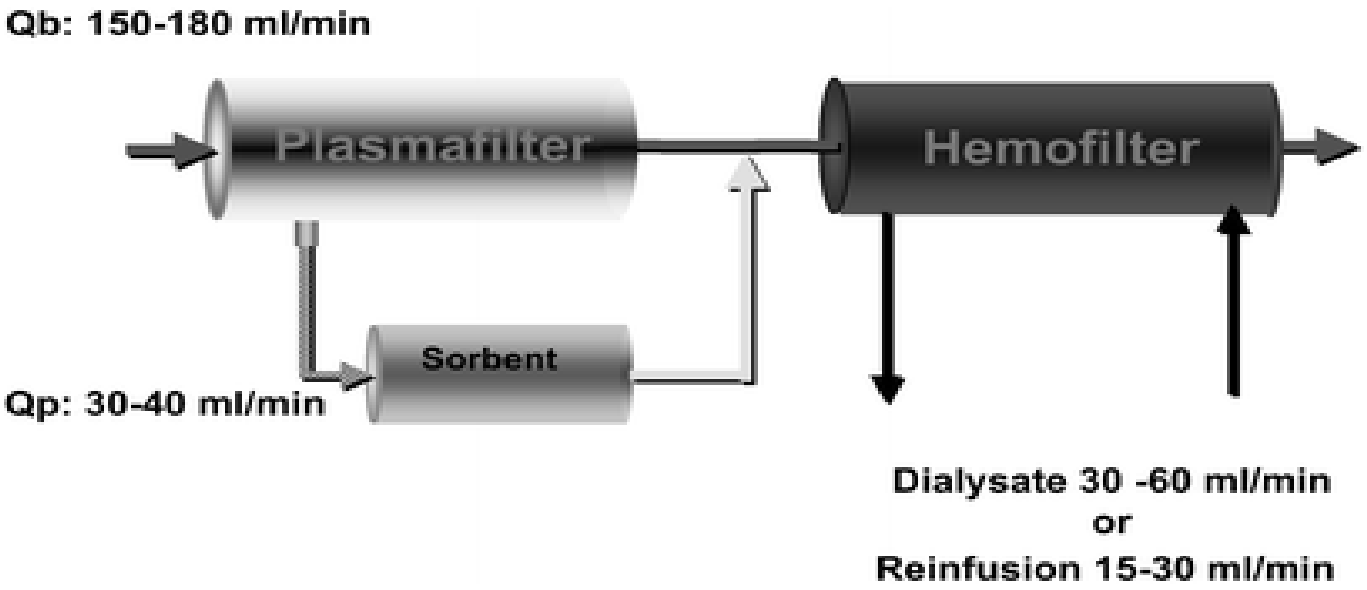
APACHE, Acute Physiology and Chronic Health Evaluation; Tx, treatment; NE, norepinephrine; AB, treatment sequence of coupled plasma filtration adsorption plus hemodialysis, then continuous venovenous hemodiafiltration; BA, treatment sequence of continuous venovenous hemodiafiltration, then coupled plasma filtration adsorption plus hemodialysis.





Hemodynamic response to coupled plasmafiltration-adsorption in human septic shock

Formica M et al, Intensive Care Med, 2003

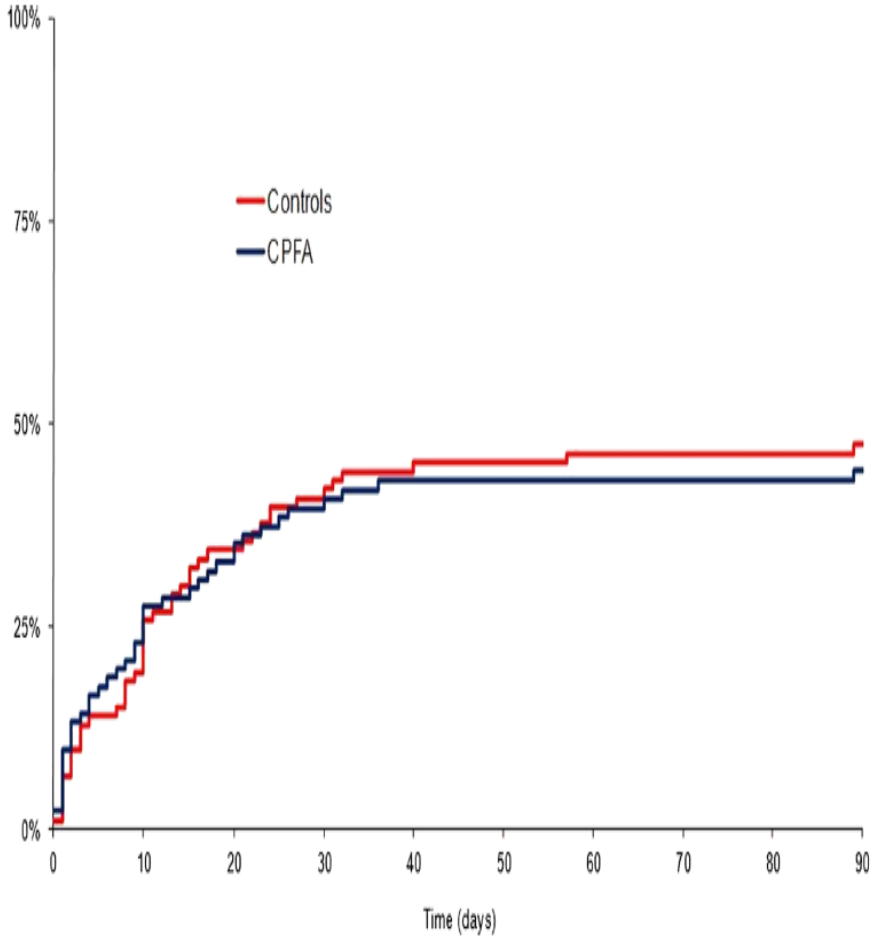


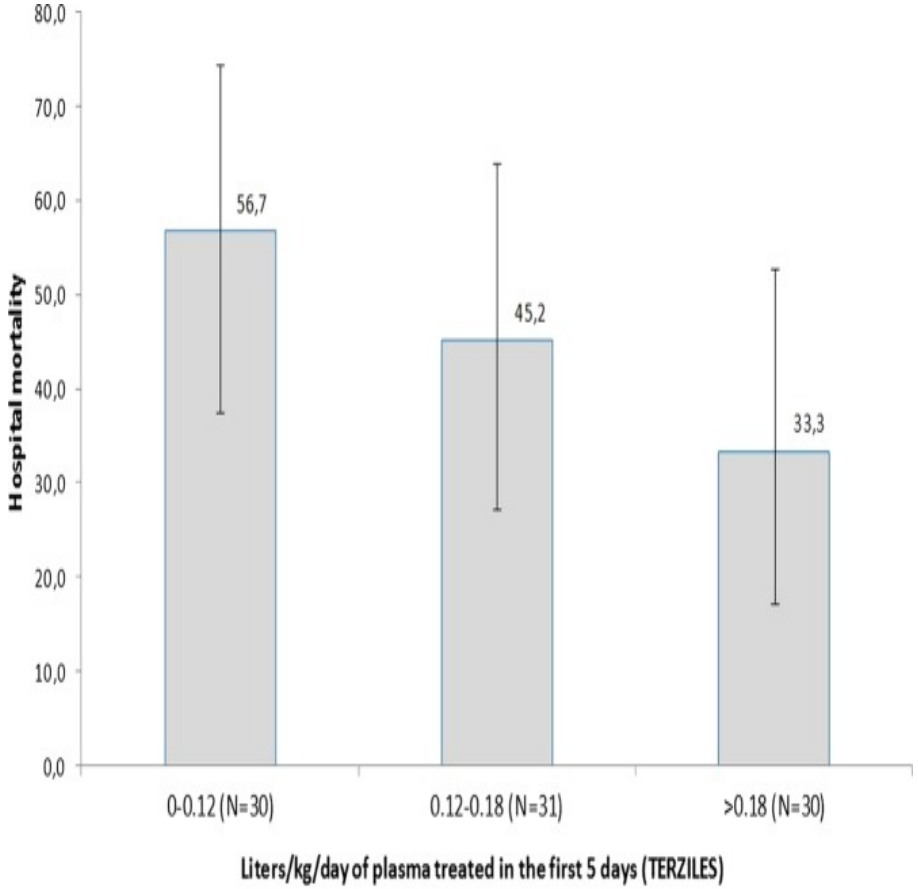
Safe use of CPFA in ICU-hospitalized patients with septic shock independently of the presence of concomitant ARF. In this long-term study, we showed CPFA to be a safe and feasible treatment with significant improvement in hemodynamic stability, vasopressor requirement, pulmonary function, and 28- and 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

BMJ Open

Sergio Livigni,[1] Guido Bertolini,[2] Carlotta Rossi,[2] Fiorenza Ferrari,[1] Michele Giardino,[2] Marco Pozzato,[3] Giuseppe Remuzzi,[2] 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





χ^2 test for general association, 3.26; $p = 0.20$
Cochran-Armitage test for trend, 1.82; $p = 0.069$

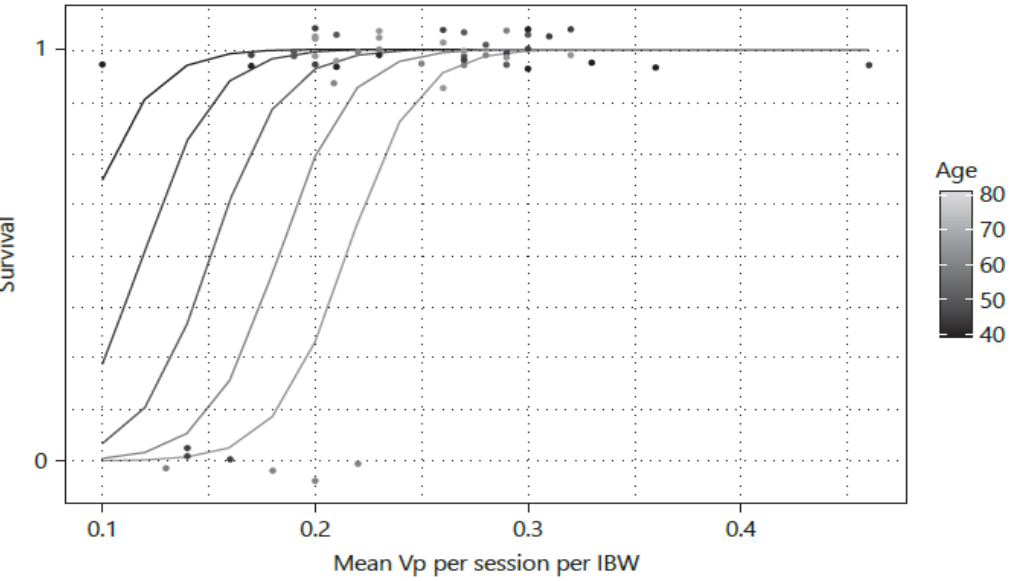
Influence of Timing of Initiation and Volume of Processed Plasma on the Outcome of Septic Shock Patients Treated with Coupled Plasma Filtration and Adsorption

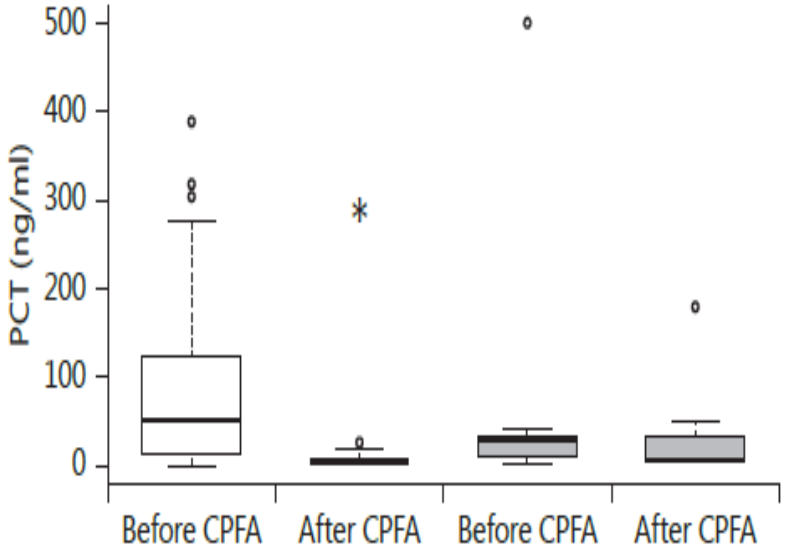
Giorgio Berlot[a] Stefano Falini[a] Virginia Negro[a] Antoinette Agbedjro[a] Ariella Tomasini[a] Fulvio Iscra[a] Francesco Bianco[b] Ugo Gerini[b] Giuliano Boscutti[b]

Blood Purification

	Survivors	Non-survivors	Significance, *p* value	Bonferroni, *p* value
Age, years, median (IQR)	63 (55–71)	66 (64–69)	0.369	1.000
IBW, kg, mean ± SD	67±13	74±9	0.164	1.000
SAPS II, median (IQR)	47 (43–54)	44 (41–58)	0.591	1.000
Charlson Comorbidity Index, median (IQR)	1 (0–3)	2 (1–3)	0.699	1.000
Timing of CPFA initiation, h, median (IQR)	25 (18–31)	27 (22–32)	0.573	1.000
Number of CPFA sessions, median (IQR)	5 (4–5)	4 (4–5)	0.271	1.000
Total Vp, L, median (IQR)	85 (60–98)	54 (43–68)	0.007	0.102
Total Vp/IBW, L/kg, mean ± SD	1.23±0.37	0.76±0.29	0.002	0.032
Vp/IBW, L/session/kg, mean ± SD	0.25±0.06	0.17±0.03	<0.001	0.009
SOFA before CPFA, median (IQR)	11 (9–13)	12 (10–15)	0.617	1.000
MAP before CPFA, mm Hg, mean ± SD	61±7	57±10	0.205	1.000
Norepinephrine dose before CPFA, μg/kg/min, median (IQR)	1.09 (0.76–1.51)	1.62 (1.22–2.03)	0.137	1.000
CI before CPFA, μg/kg/min, median (IQR)	109 (76–151)	162 (122–213)	0.123	1.000
PACI before CPFA, μg/kg/min/mm Hg, median (IQR)	1.83 (1.16–2.81)	2.36 (2.05–4.14)	0.123	1.000

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.





CPFA, citrate and outcome

Regional Citrate Anticoagulation During Coupled Plasma Filtration and Adsorption May Increase Survival in Septic Shock

Michele Claudio Vassallo[a] Fabiana Tartamella[a] Pradipta Bhakta[b]

Blood Purification

Regional Citrate Anticoagulation During Coupled Plasma Filtration and Adsorption May Increase Survival in Septic Shock

Giorgio Berlot[a] Stefano Falini[a] Virginia Negro[a] Antoinette Agbedjro[a] Ariella Tomasini[a] Fulvio Iscra[a] Francesco Bianco[b] Ugo Gerini[b] Giuliano Boscutti[b]

Blood Purification

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 .

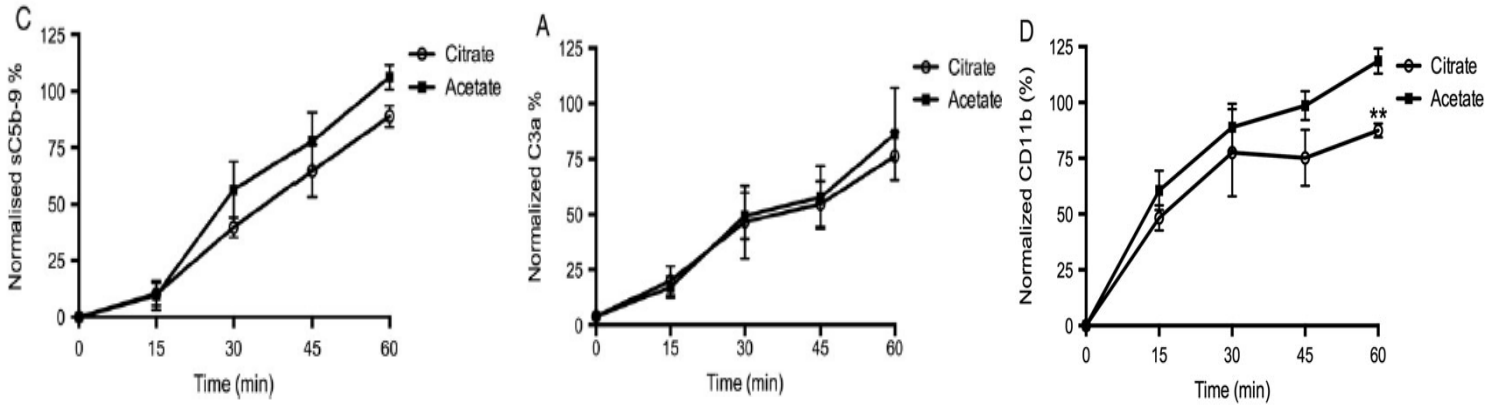
The recent COMPACT II study, which has been prematurely suspended due to an excess mortality rate in the treatment group, required the use of RCA instead of heparin during the CPFA

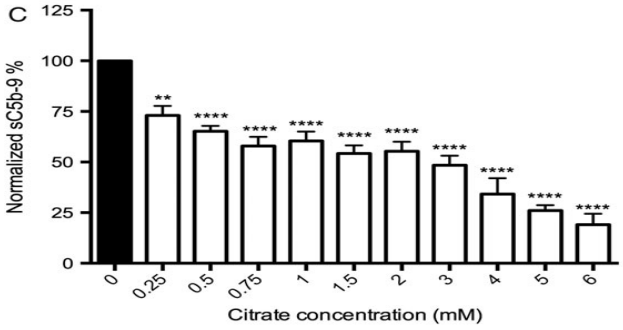
Low concentrations of citrate reduce complement and granulocyte activation *in vitro* in human blood

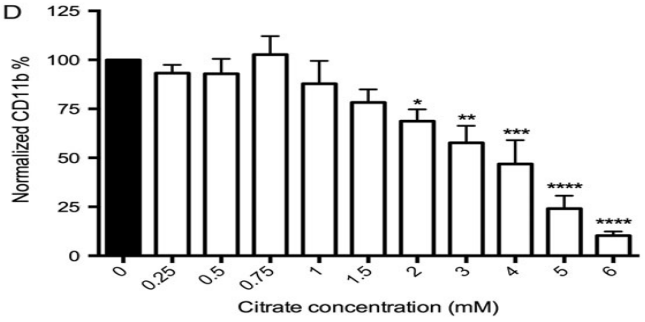
Shan Huang[1], Kerstin Sandholm[1], Nina Jonsson[1,2], Anders Nilsson[3], Anders Wieslander[3], Gunilla Grundström[3], Viktoria Hancock[3] and Kristina N. Ekdahl[1,2]

ckj

Effects of citrate and acetate on complement and granulocyte activation at concentrations relevant in haemodialysis and effect of different citrate concentrations on complement and granulocyte activation in whole blood





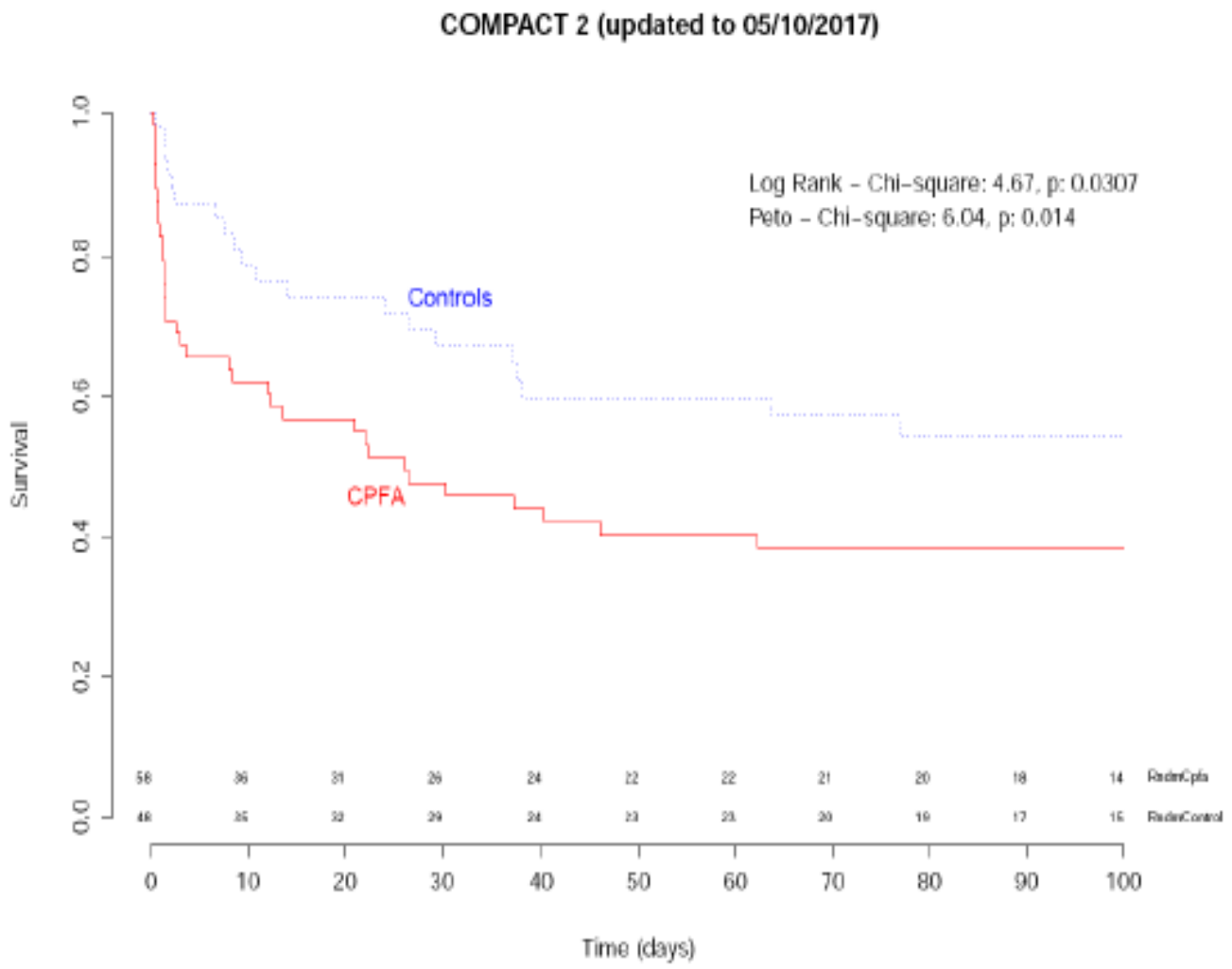


Low concentrations of citrate can reduce complement and granulocyte activation in human whole blood in vitro.

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.

EARLY STOP FOR COMPACT-2



Increased mortality in CPFA group vs control, expecially during the first days of treatment.

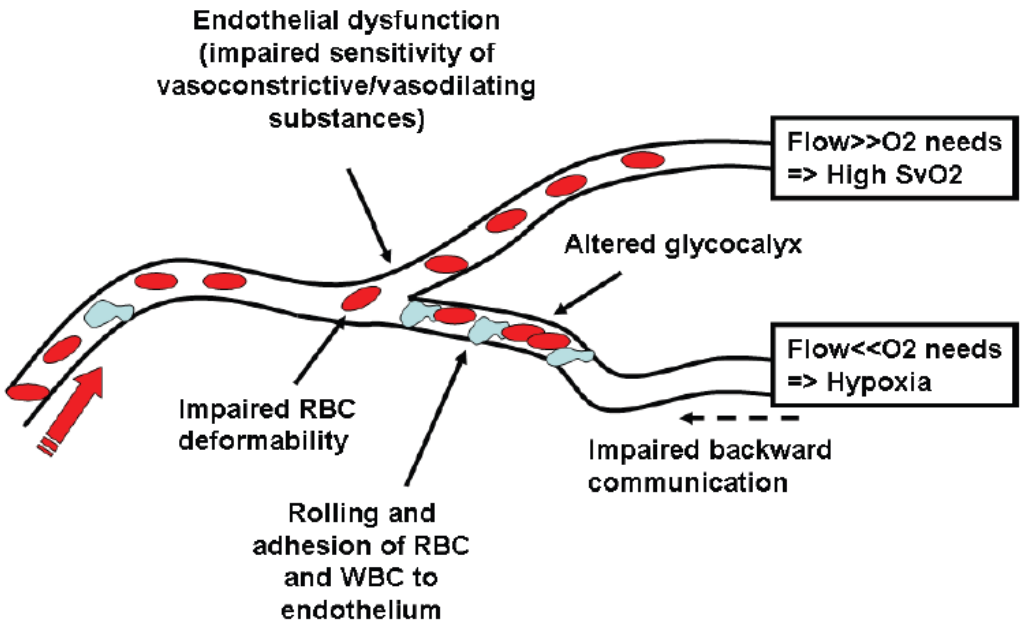
In septic shock patients enrolled in the study, a clinical poor outcome in the CPFA group was observed.

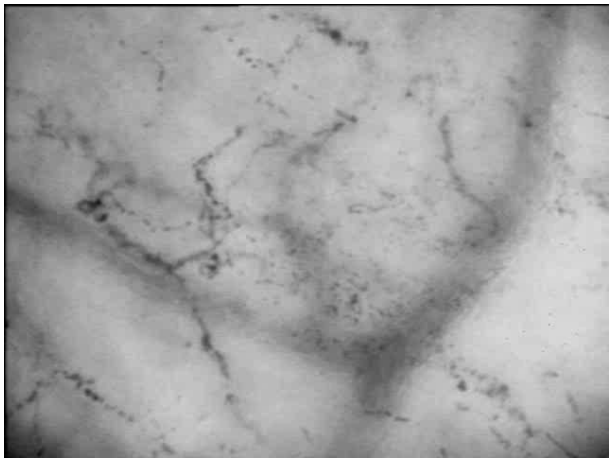
COMPACT-2 was prematurely interrupted and GiViTI did not reccomend the use of CPFA for septic shock patients.

Sepsis and alteration of microvascular flow

De Backer et al. Annals of Intensive Care 2011

Principal mechanisms implicated in the development of microcirculatory alterations





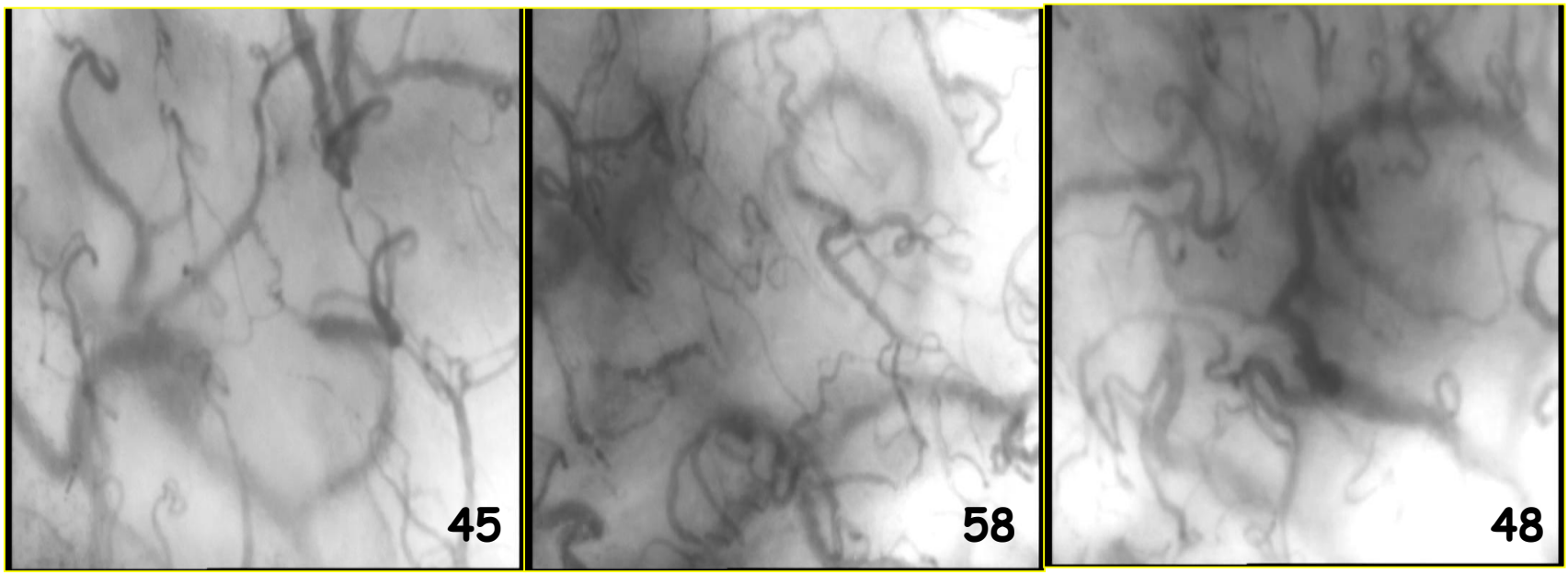
↓ Capillary density

↑ 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

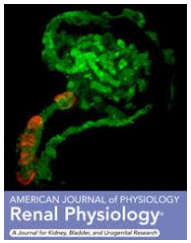
2 h after
CPFA initiation

1 after
Stop CPFA

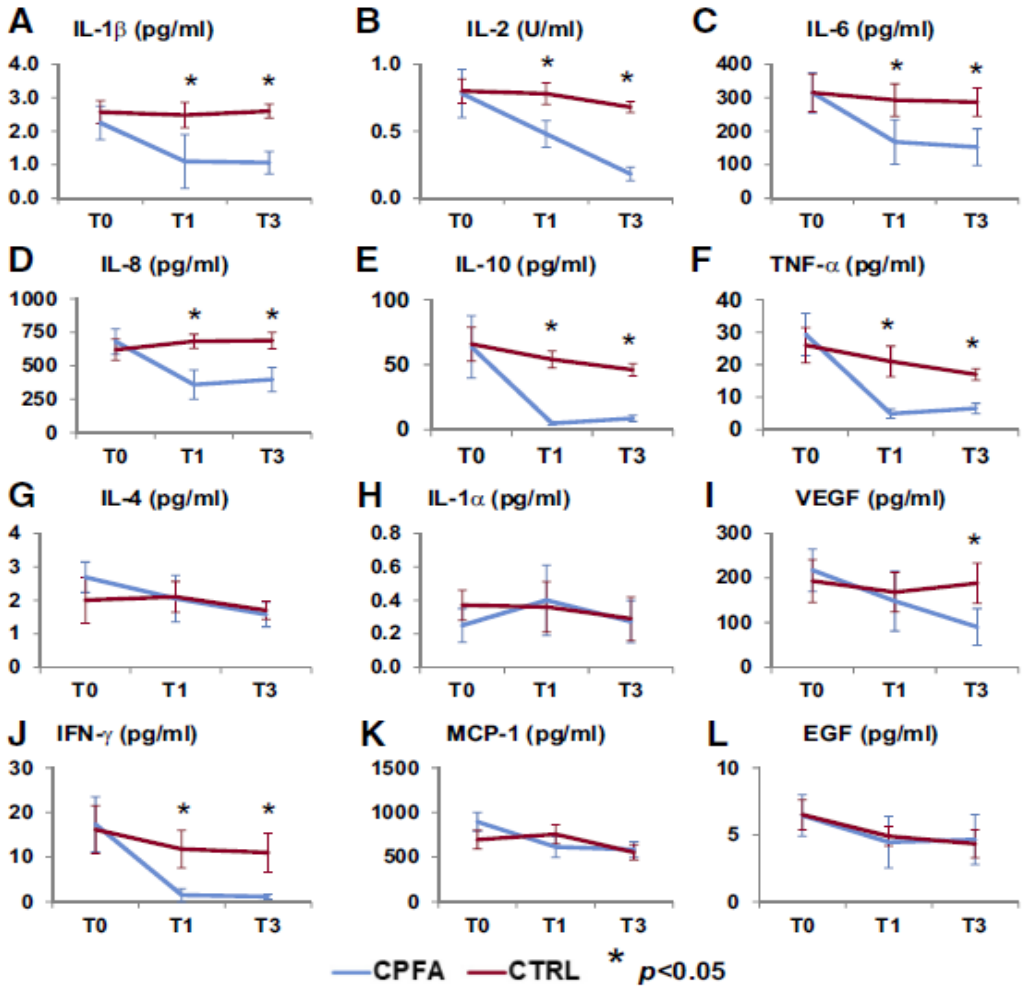
Berlot G. et al Anaesth Intensive Care 2011; 39: 687-689

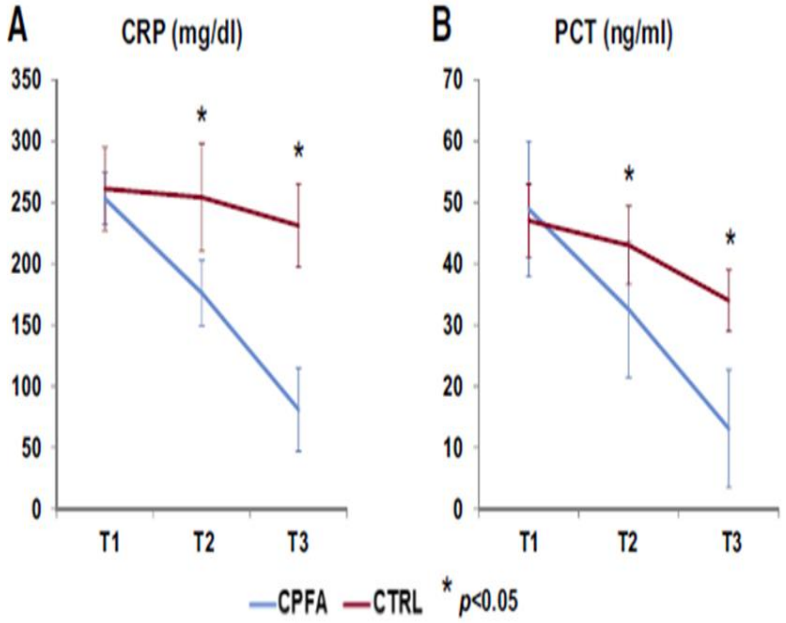
LPS removal reduces CD80-mediated albuminuria in critically ill patients with Gram-negative sepsis

Giuseppe Stefano Netti,[1] Fabio Sangregorio,[2] Federica Spadaccino,[1] Francesco Staffieri,[3] Antonio Crovace,[3] Barbara Infante,[2] Annamaria Maiorano,[2] Giulia Godeas,[2] Giuseppe Castellano,[4] Anna Maria Di Palma,[4] Clelia Prattichizzo,[1] Antonella Cotoia,[5] Lucia Mirabella,[5] Loreto Gesualdo,[4] Gilda Cinnella,[5] Giovanni Stallone,[2] Elena Ranieri,[1]* and Giuseppe Grandaliano[2]*



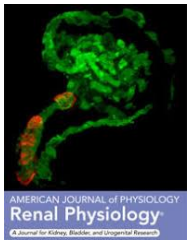
Effects of extracorporeal treatments CPFA on cytokine removal.



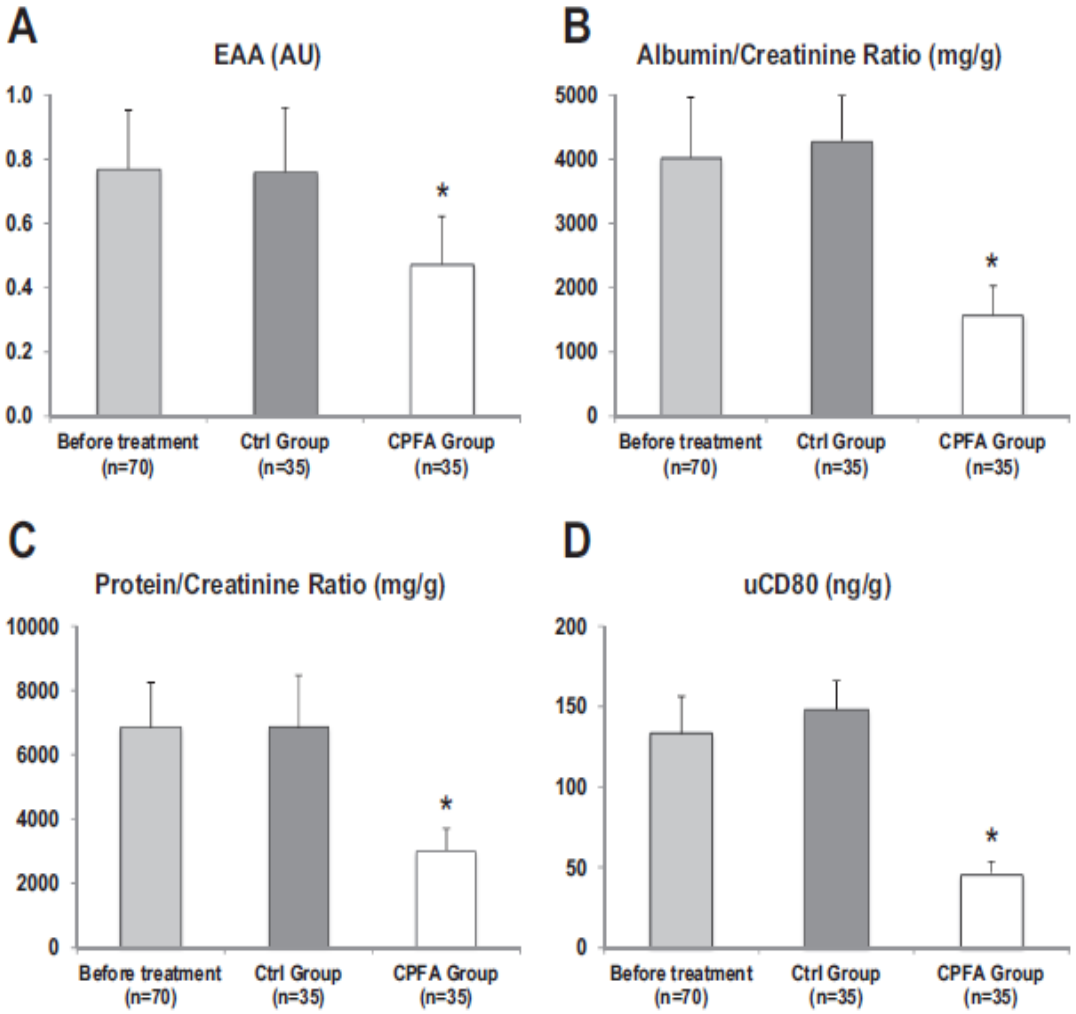


LPS removal reduces CD80-mediated albuminuria in critically ill patients with Gram-negative sepsis

Giuseppe Stefano Netti,[1] Fabio Sangregorio,[2] Federica Spadaccino,[1] Francesco Staffieri,[3] Antonio Crovace,[3] Barbara Infante,[2] Annamaria Maiorano,[2] Giulia Godeas,[2] Giuseppe Castellano,[4] Anna Maria Di Palma,[4] Clelia Prattichizzo,[1] Antonella Cotoia,[5] Lucia Mirabella,[5] Loreto Gesualdo,[4] Gilda Cinnella,[5] Giovanni Stallone,[2] Elena Ranieri,[1]* and Giuseppe Grandaliano[2]*



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

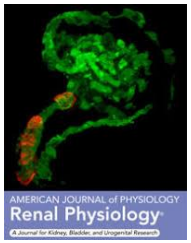
Baseline proteinuria and albuminuria were significantly high in Gram-negative septic patients, but the reduction in circulating LPS levels by CPFA induced a reduction in glomerular permeability to plasma proteins, as demonstrated by the reduction of proteinuria and albuminuria levels

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

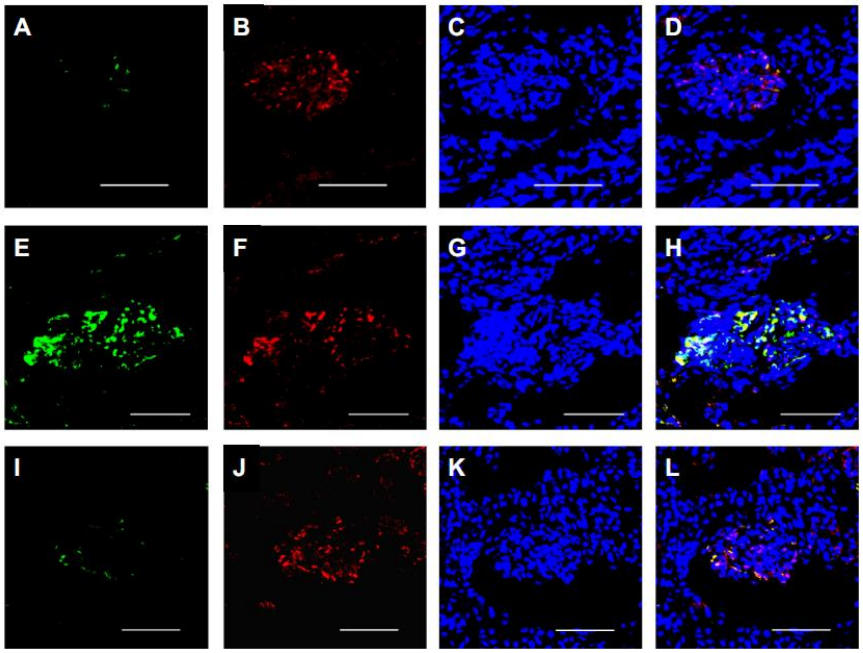
Removal of LPS by CPFA induced a statistically significant reduction in urinary CD80 excretion as compared with control group

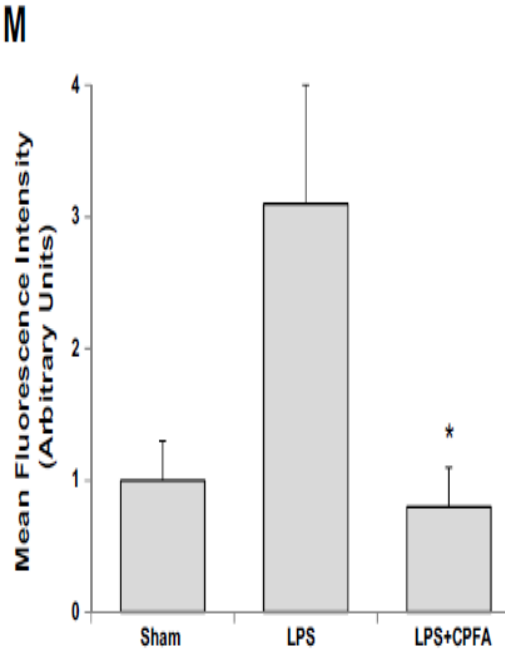
LPS removal reduces CD80-mediated albuminuria in critically ill patients with Gram-negative sepsis

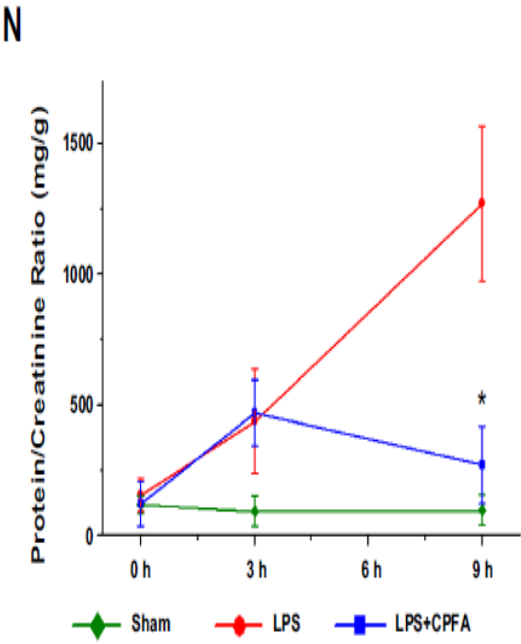
Giuseppe Stefano Netti,[1] Fabio Sangregorio,[2] Federica Spadaccino,[1] Francesco Staffieri,[3] Antonio Crovace,[3] Barbara Infante,[2] Annamaria Maiorano,[2] Giulia Godeas,[2] Giuseppe Castellano,[4] Anna Maria Di Palma,[4] Clelia Prattichizzo,[1] Antonella Cotoia,[5] Lucia Mirabella,[5] Loreto Gesualdo,[4] Gilda Cinnella,[5] Giovanni Stallone,[2] Elena Ranieri,[1]* and Giuseppe Grandaliano[2]*



CPFA treatment reduces podocyte expression of CD80 and urinary protein excretion after LPS exposure in a pig model of acute renal damage







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

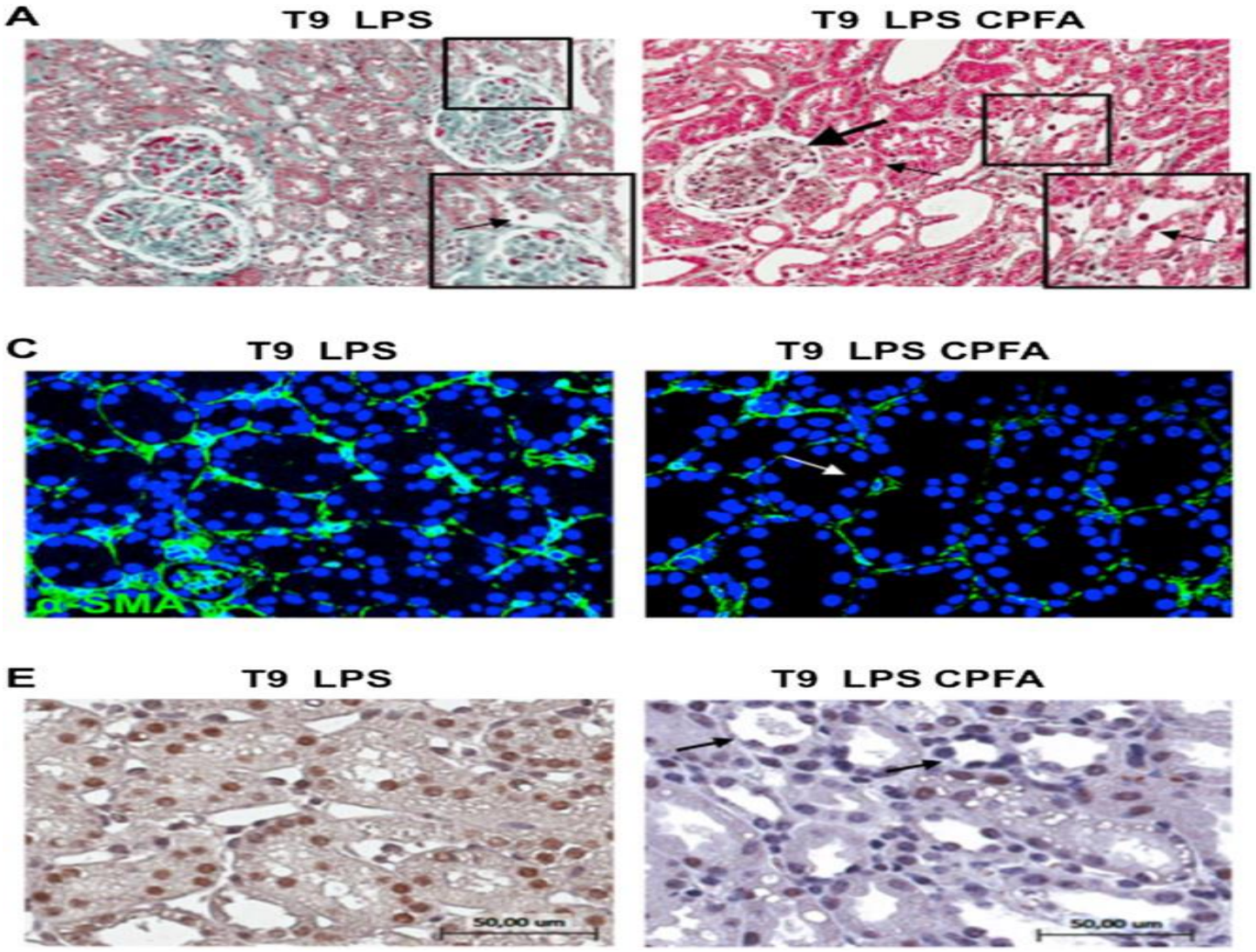
CPFA treatment, while reducing LPS levels and inhibiting CD80 induction at the podocyte level, was also able to reduce glomerular permeability to proteins

Endothelial dysfunction and renal fibrosis in endotoxemia-induced oliguric kidney injury: possible role of LPS-binding protein

Giuseppe Castellano[1†], Alessandra Stasi[1†], Angelica Intini[1], Margherita Gigante[1], Anna Maria Di Palma[1], Chiara Divella[1], Giuseppe Stefano Netti[2], Clelia Prattichizzo[2], Paola Pontrelli[1], Antonio Crovace[3], Francesco Staffieri[3], Enrico Fiaccadori[4], Nicola Brienza[5], Giuseppe Grandaliano[2], Giovanni Pertosa[1] and Loreto Gesualdo[1*]

CRITICAL CARE

Prevention of LPS-induced renal fibrosis by CPFA treatment.



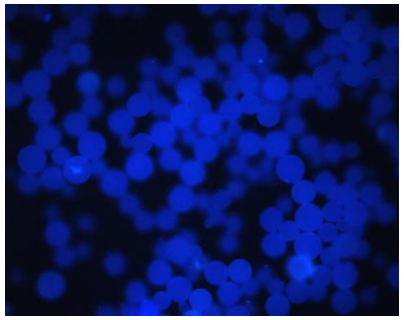
CRITICAL CARE

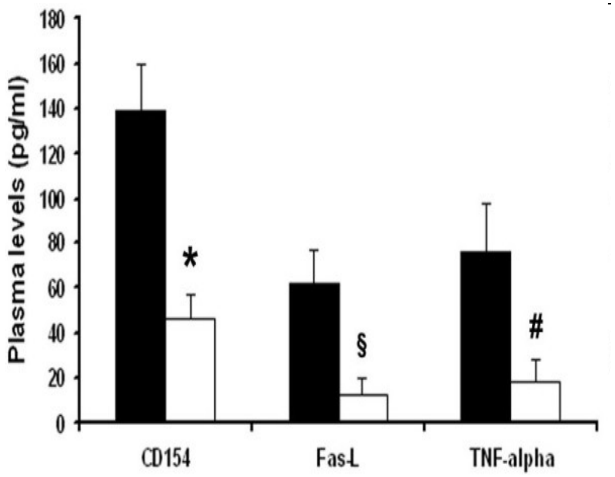
Protective effect of resin adsorption on septic plasma-induced tubular injury.

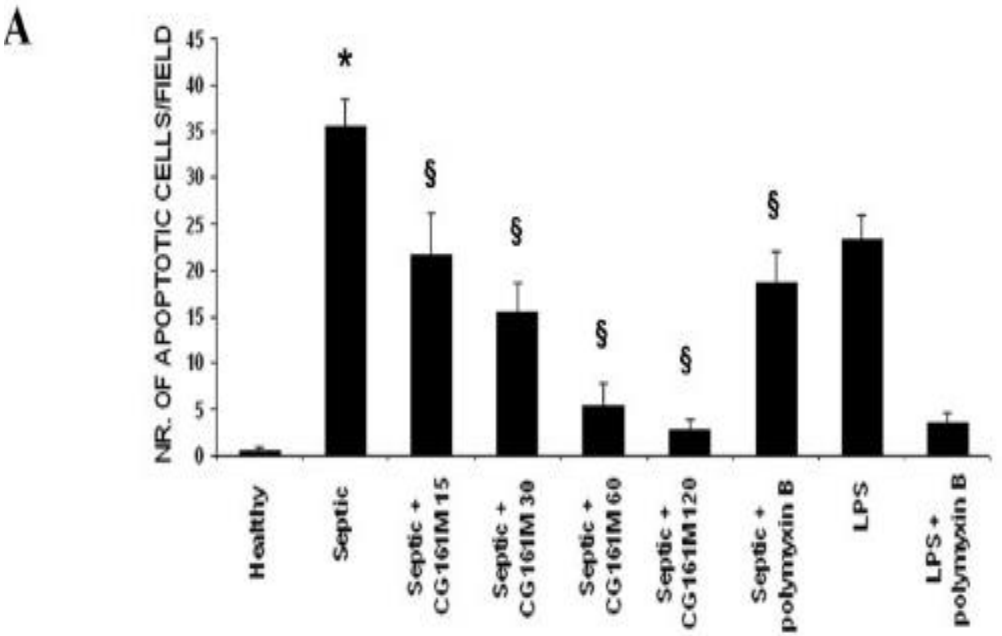
Cantaluppi V, Weber V, Lauritano C, Figliolini F, Beltramo S, Biancone L, De Cal M, Cruz D, Ronco C, Segoloni GP, Tetta C, Camussi G

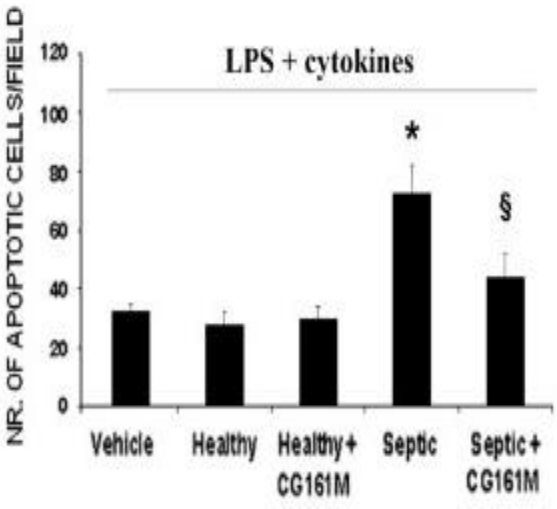
Crit Care 2010

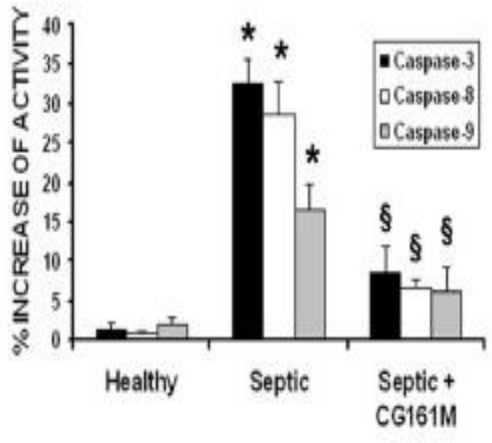
Amberchrom CG161M resin (Rohm and Haas Co. Philadelphia, PA)









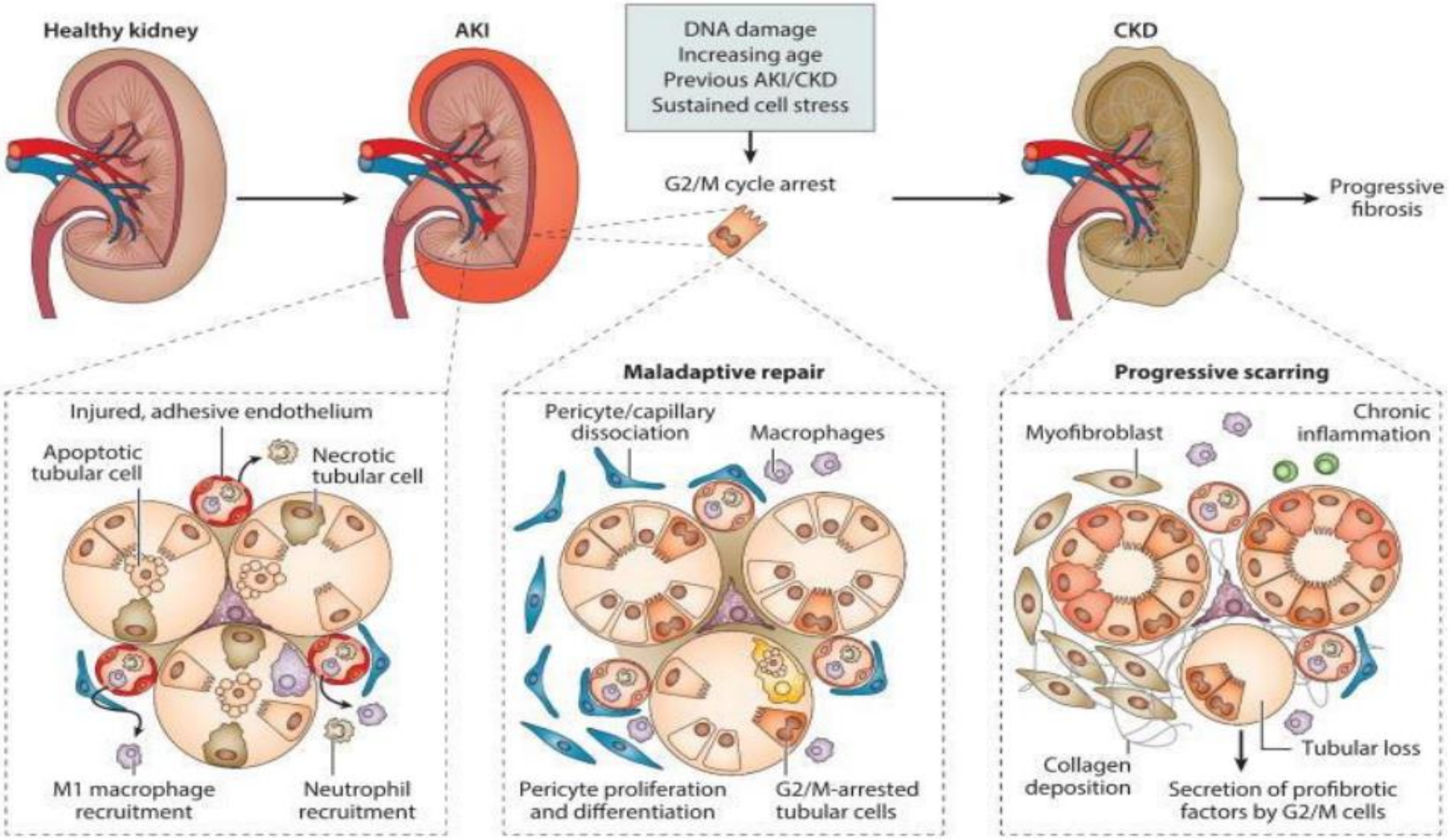


Acute Kidney Injury

Anna Zuk[1] and **Joseph V. Bonventre**[1,2]

Annals of IM

Maladaptative repair following AKI



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;

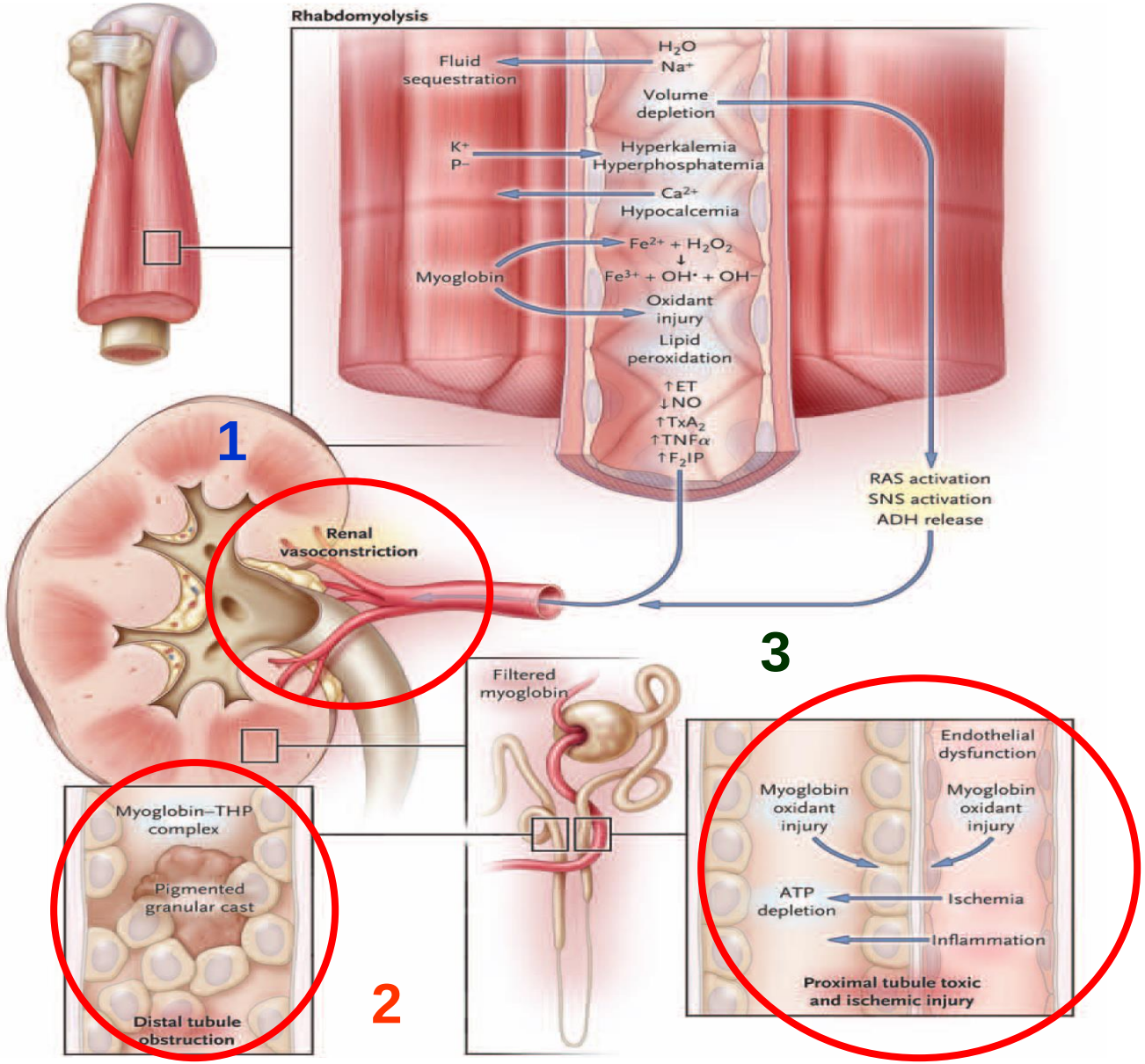
Other clinical applications and potential protective role of CPFA in septic and nephrotoxic AKI.

The question……

Rhabdomyolysis and Acute Kidney Injury

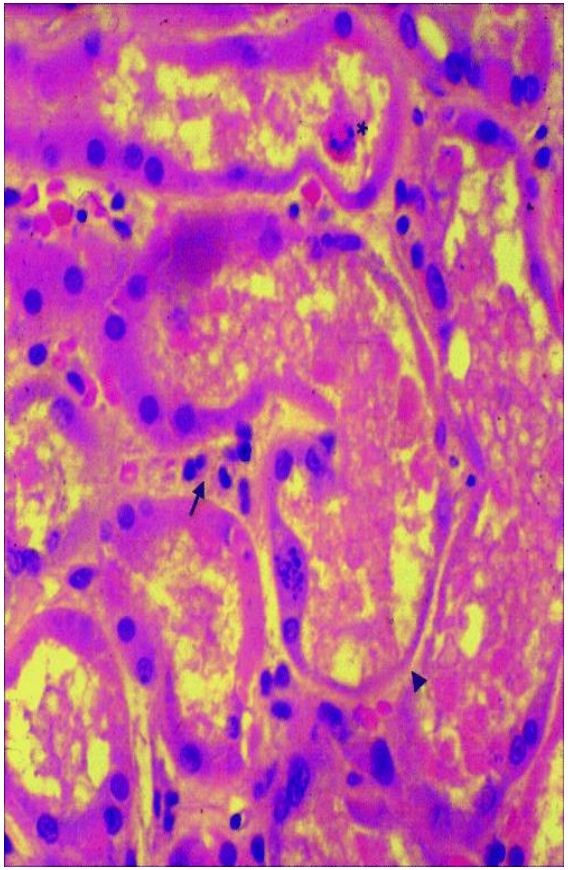
Xavier Bosch, M.D., Ph.D., Esteban Poch, M.D., Ph.D.,
and Josep M. Grau, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE



Renal injury related with Myoglobin:

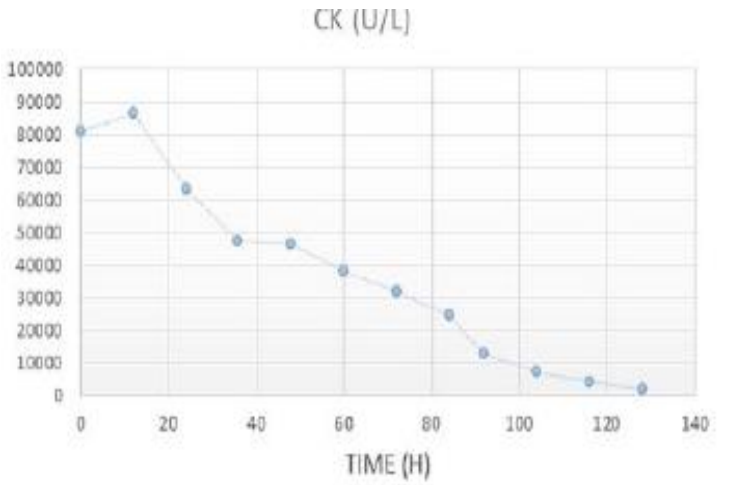
1) ISCHEMIA
2) CAST NEPHROPATHY
3) OXIDATIVE INJURY

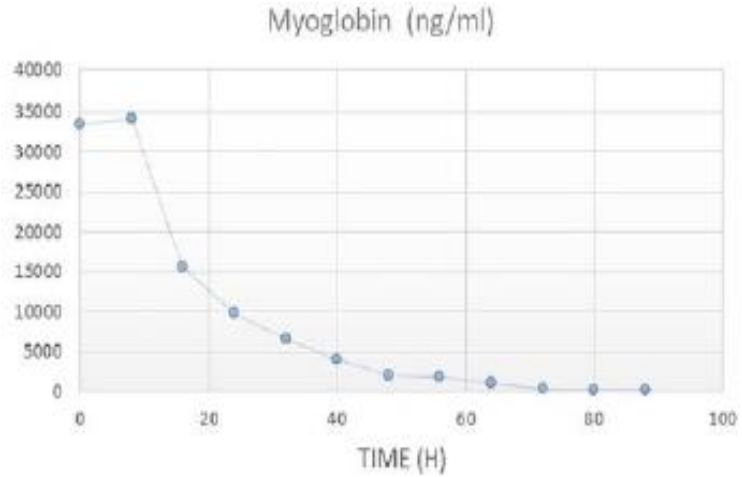


Early intensive treatment to prevent kidney failure in post-traumatic rhabdomyolysis: Case report

Mario Pezzi, Anna Maria Giglio, Annamaria Scozzafava, Giuseppe Serafino, Pietro Maglio and Mario Verre

SAGE Open Medical Case Reports





The experience of CPFA in rhabdomyolysis is limited. The use of CPFA in rhabdomyolysis resulting in kidney transplantation has been described.23 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.

The Use of Coupled Plasma Filtration Adsorption in Traumatic Rhabdomyolysis

Mario Pezzi,[1] Silvia Renda,[1] Anna Maria Giglio,[1] Anna Maria Scozzafava,[1] Simona Paola Tiburzi,[1] Patrizia Casella,[1] Fabrizio Iannelli,[2] and Mario Verre[1]

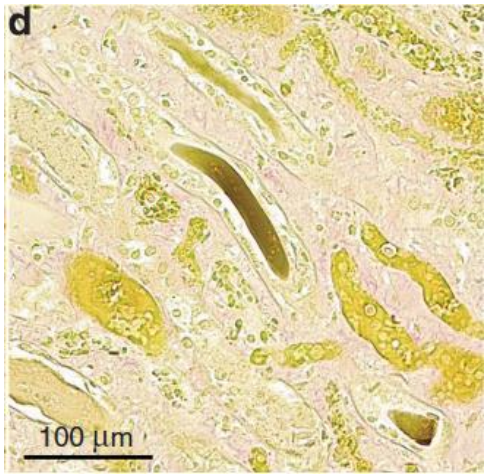
Case Reports in Critical Care

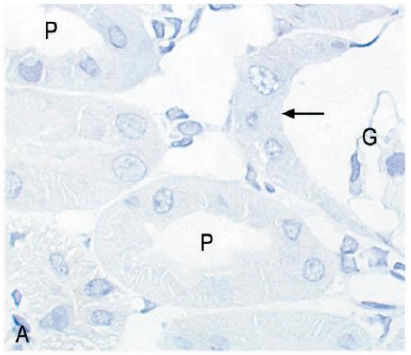
Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction

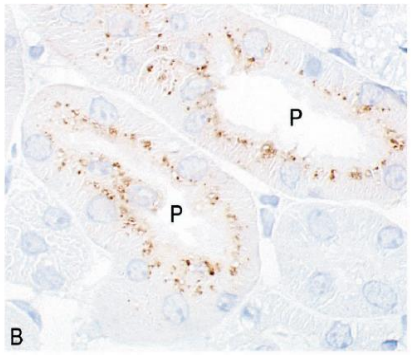
Charles M. van Slambrouck[1], Fadi Salem[2], Shane M. Meehan[1] and Anthony Chang[1]

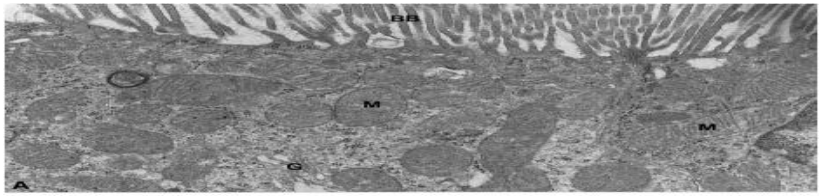
Megalin Knockout Mice as an Animal Model of Low Molecular Weight Proteinuria

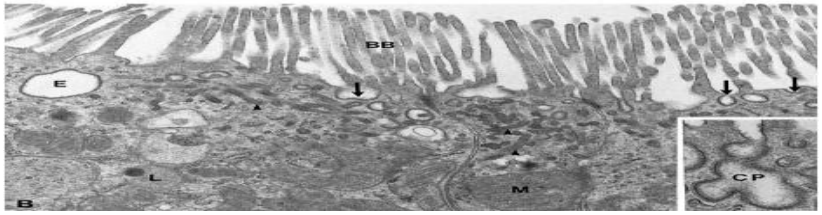
Jörg-Robert Leheste,* Boris Rolinski,† Henrik Vorum,‡ Jan Hilpert,* Anders Nykjaer,* Christian Jacobsen,‖ Pierre Aucouturier,§ Jan Øivind Moskaug,¶ Albrecht Otto,* Erik Ilsø Christensen,‖ and Thomas E. Willnow*











Bile-cast nephropathy: proximal tubular injury due to bile cast formation.

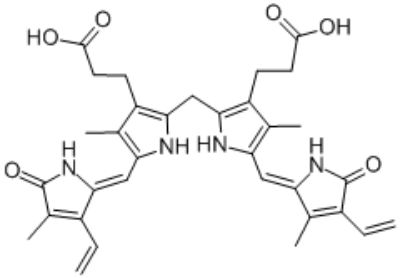
Bilirubin may contribute to AKI in patients with severe liver dysfunction for a direct toxic and pro-apoptotic effect on tubular epithelial cells

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.

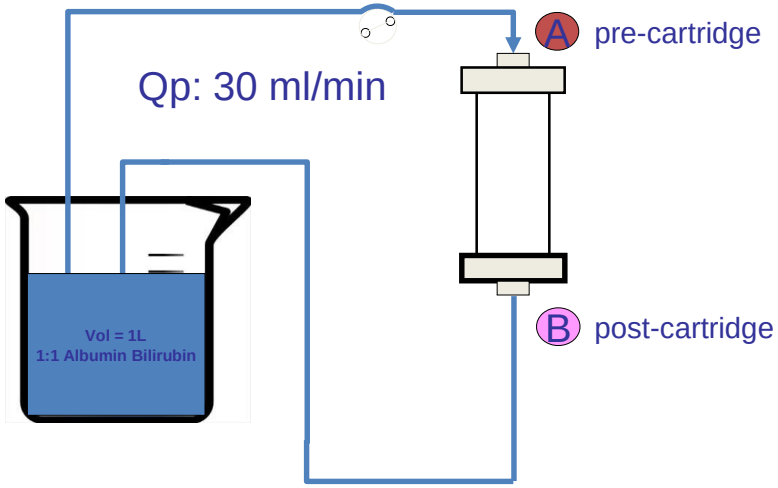
Megalin is an endocytic receptor expressed on the luminal surface of the renal proximal tubules.

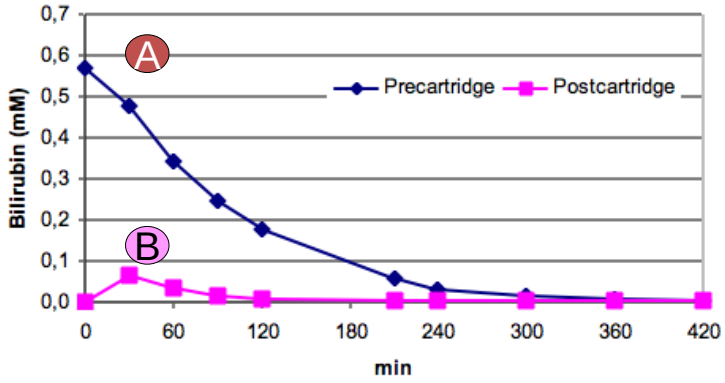
Megalin plays a crucial role together with cubilin in re-adsorption of filtered vitamin/carrier complexes.

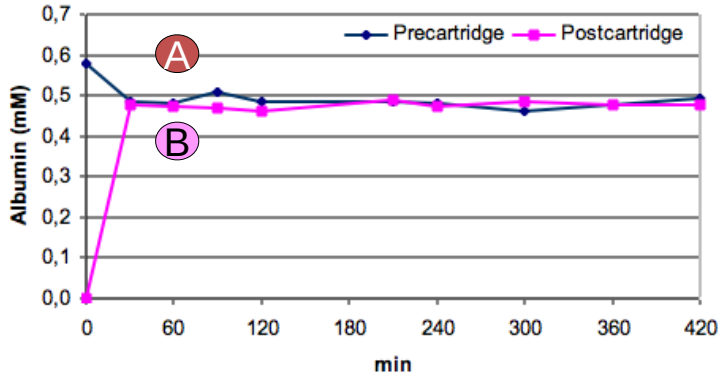
In vitro data: kinetics of bilirubin and albumin adsorption during CPFA



Experimental set-up



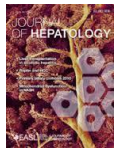




Courtesy by Wratten ML,

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

Santo Caroleo[1], Antonino S. Rubino[2], Francesco Tropea[1], Orlando Bruno[1], Domenico Vuoto[1], Bruno Amantea[1], Attilio Renzulli[2]



ELSEVIER

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

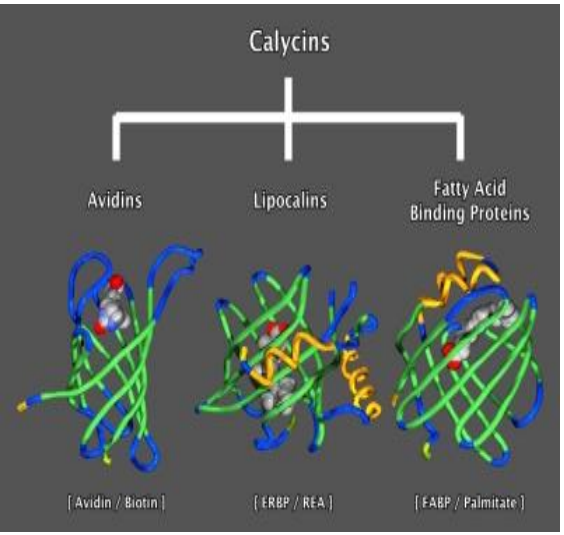
U. Maggi, G. Nita, S. Gatti, B. Antonelli, R. Paolo, G. Corno, P. Messa, and G. Rossi

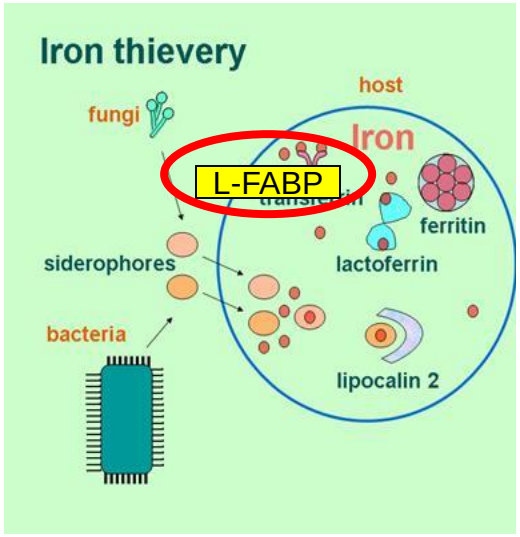
Evidence for megalin-mediated proximal tubular uptake of L-FABP, a carrier of potentially nephrotoxic molecules

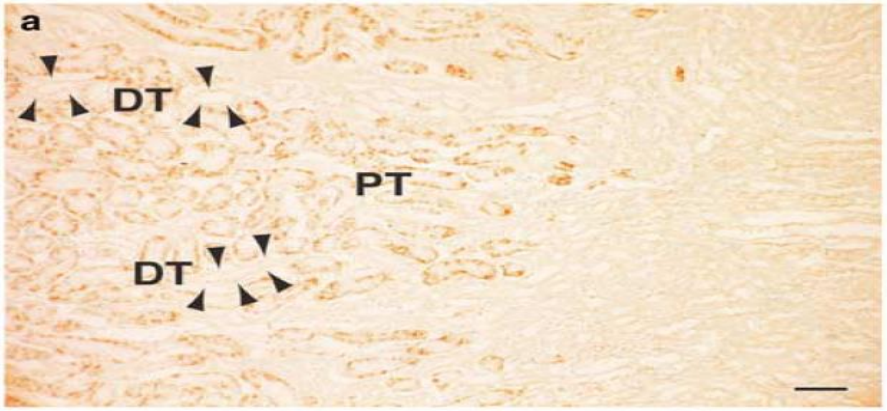
Yuko Oyama[1], Tetsuro Takeda[1,2], Hitomi Hama[1], Atsuhito Tanuma[1], Noriaki Iino[1], Kiyoko Sato[1], Ryohei Kaseda[1], Meilei Ma[3], Tadashi Yamamoto[3], Hiroshi Fujii[4], Junichiro J Kazama[5], Shoji Odani[6], Yoshio Terada[7], Kunihiro Mizuta[8], Fumitake Gejyo[1] and Akihiko Saito[1,2]

Laboratory Investigation
An official journal of the United States & Canadian Academy of Pathology, Inc

LIVER TYPE FATTY ACID BINDING PROTEIN (L-FABP)







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.

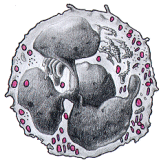
L-FABP is released into the bloodstream and patients with liver damage have elevated plasma L-FABP levels.

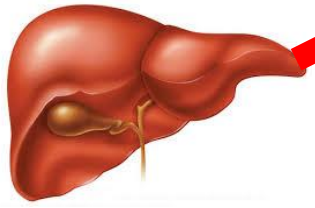
L-FABP is also present in kidney tubular epithelial cells and its expression is increased during ischemic and nephrotoxic AKI.

Evidence for megalin-mediated proximal tubular uptake of L-FABP, a carrier of potentially nephrotoxic molecules

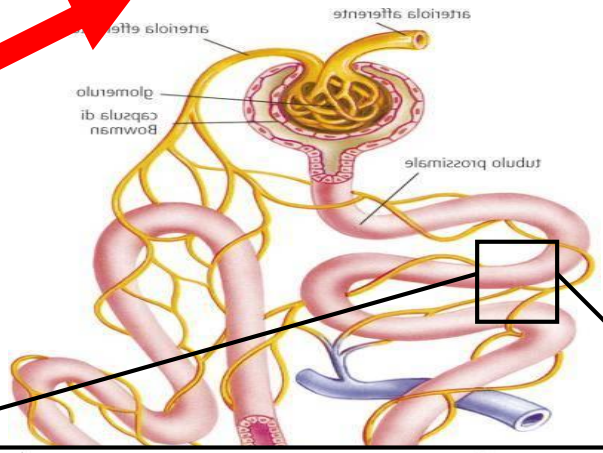
Yuko Oyama[1], Tetsuro Takeda[1,2], Hitomi Hama[1], Atsuhito Tanuma[1], Noriaki Iino[1], Kiyoko Sato[1], Ryohei Kaseda[1], Meilei Ma[3], Tadashi Yamamoto[3], Hiroshi Fujii[4], Junichiro J Kazama[5], Shoji Odani[6], Yoshio Terada[7], Kunihiro Mizuta[8], Fumitake Gejyo[1] and Akihiko Saito[1,2]

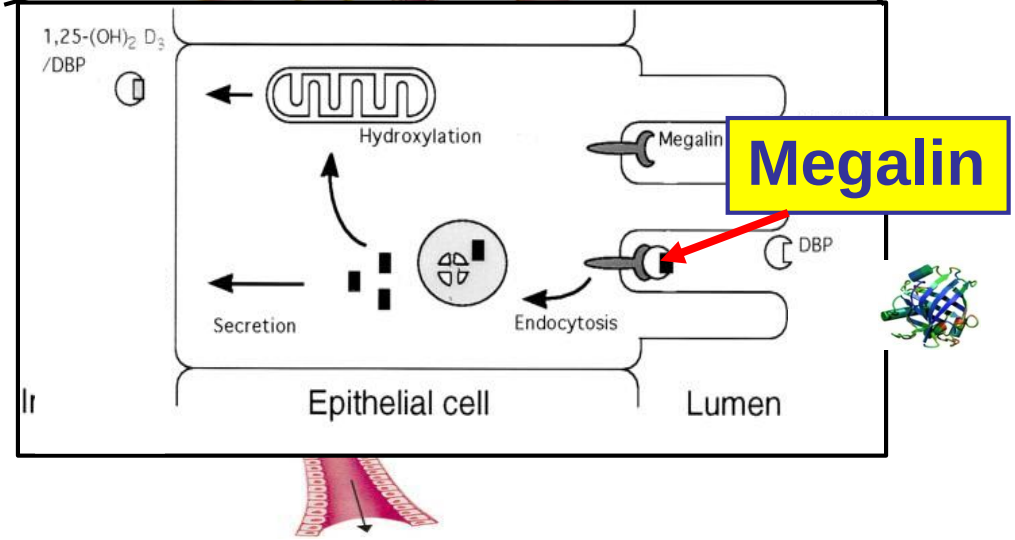
Laboratory Investigation
An official journal of the United States & Canadian Academy of Pathology, Inc





L-FABP





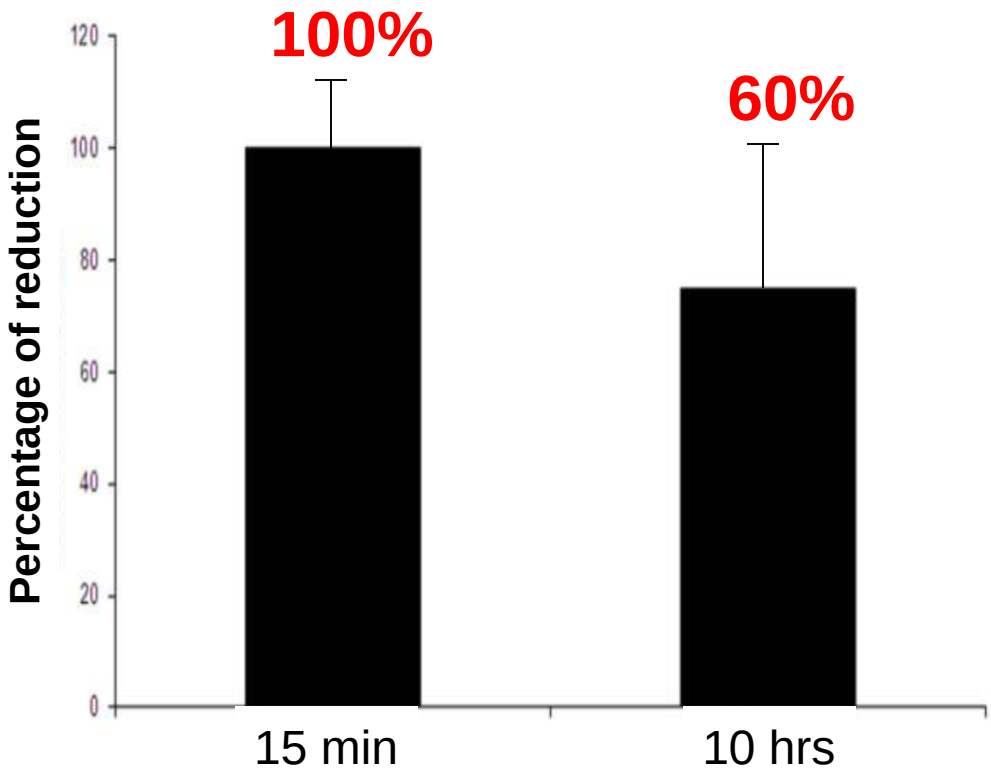
Megalin

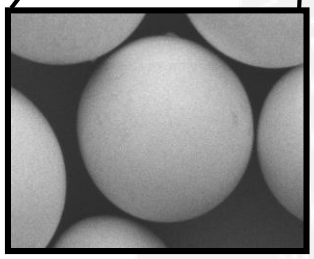
L-FABP is uptaken by kidney proximal tubular epithelial cells by the endocytic receptor megalin

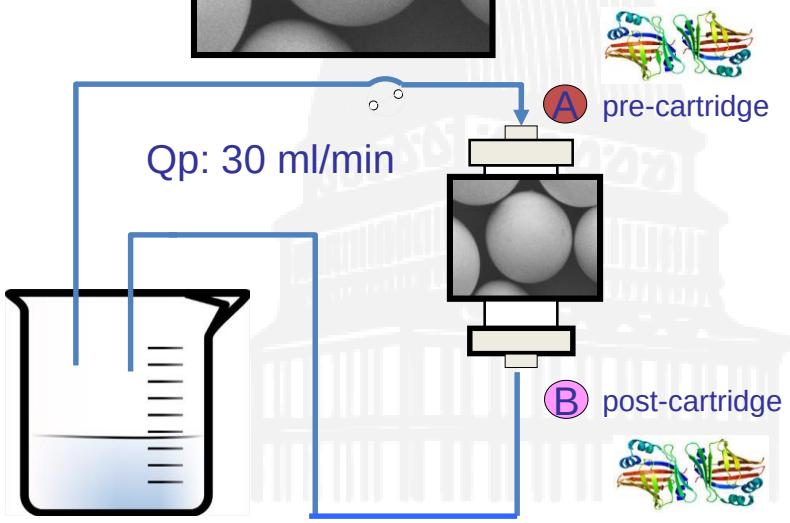
L-FABP may have a role as carrier of nephrotoxic molecules in tubular epithelial cells

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.**

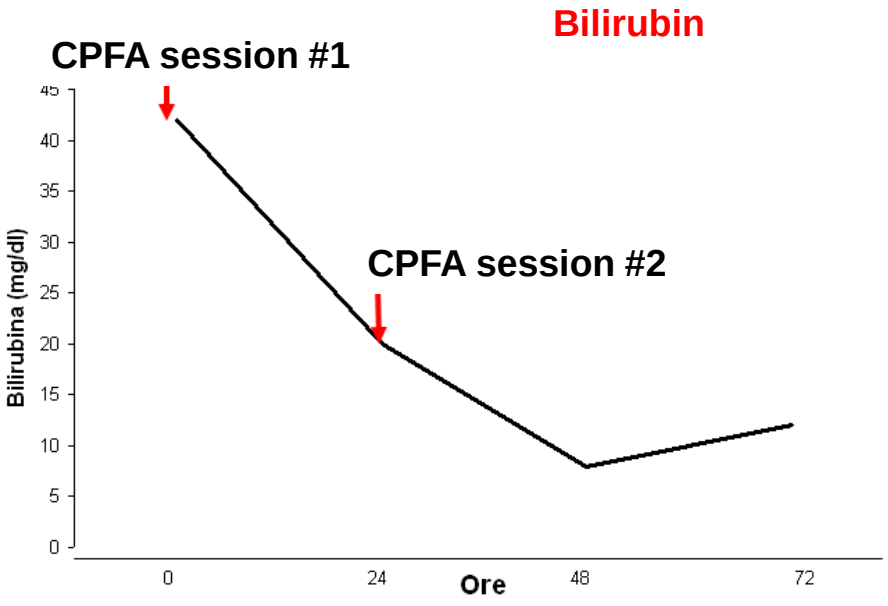




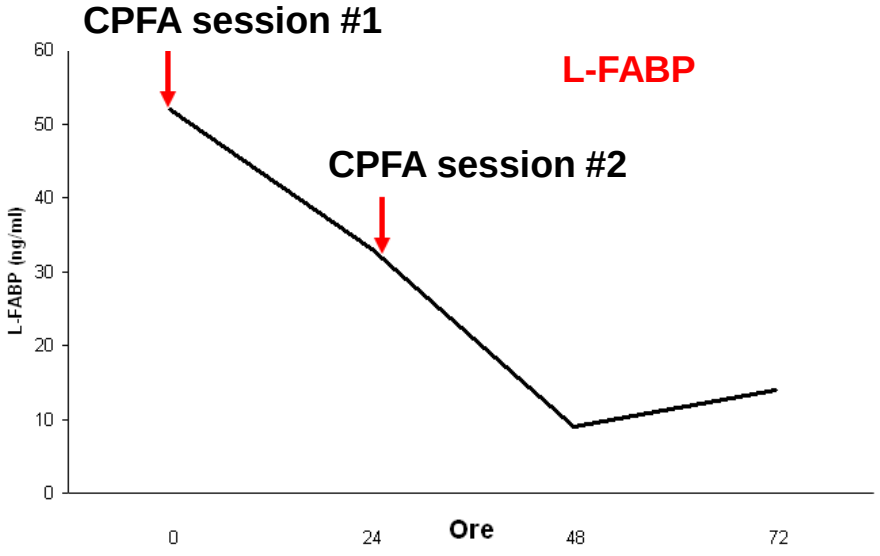


Data confirmed in vivo in septic patients

Effect of CPFA treatment on bilirubin and L-FABP levels

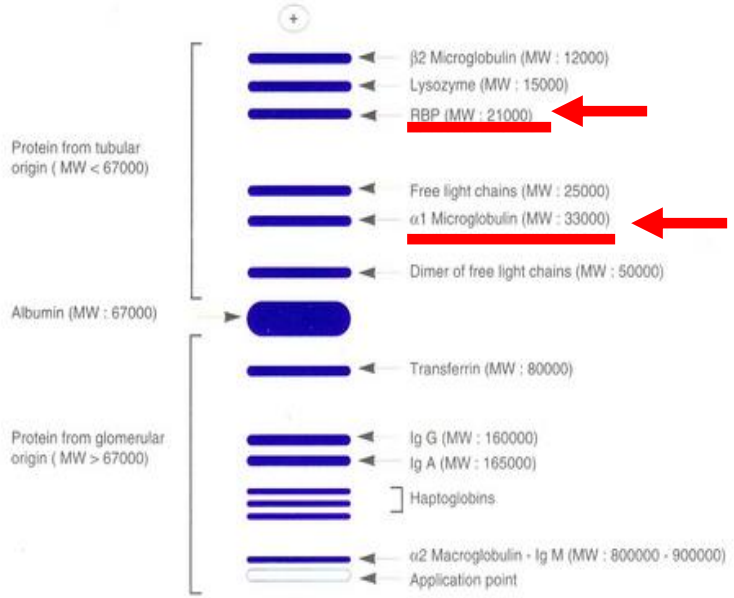


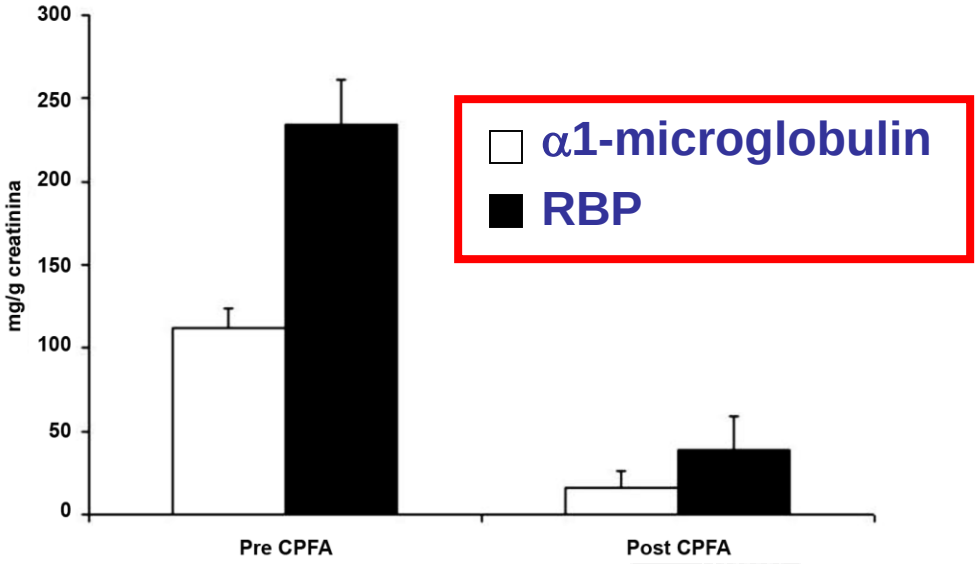
Bilirubin and L-FABP levels after CPFA treatment



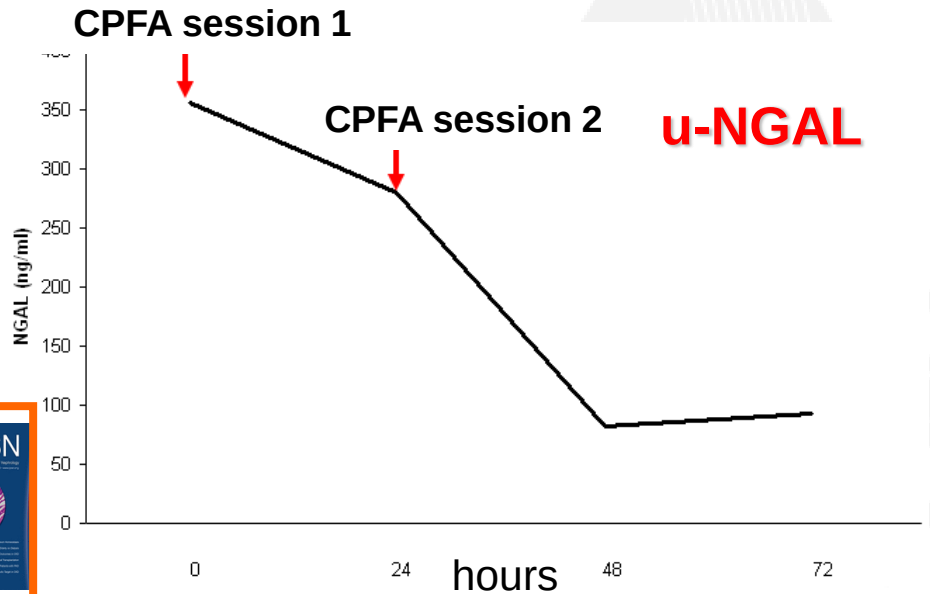
Bilirubin (< 15 mg/dl) and L-FABP (9 ng/ml) decrease was associated with an increase of urinary output.

Effect of CPFA on low molecular weight proteinuria and urinary NGAL levels





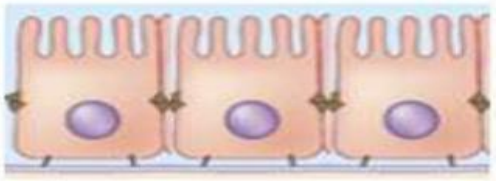
After CPFA treatment, we observed a reduction of urinary levels of low molecular wheight proteins (α1-microglobulin, Retinol Binding Protein), NGAL (uNGAL) and tubular cells (tubular score) at urine microscopy.

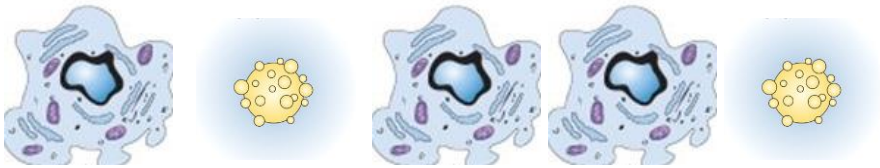


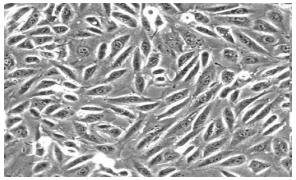
Diagnostic Value of Urine Microscopy for Differential Diagnosis of Acute Kidney Injury in Hospitalized Patients

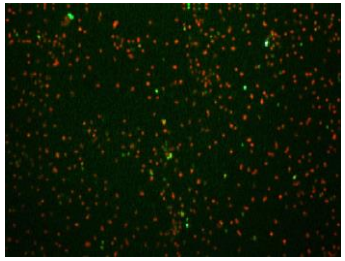
Mark A. Perazella, Steven G. Coca, Mehmet Kanbay, Ursula C. Brewster, and Chirag R. Parikh

Effect of septic plasma on kidney tubular epithelial cells (TEC): apoptosis









APOPTOSIS (TUNEL assay)

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 nephrotpathy and AKI are other potential clinical applications for CPFA.**

Coupled Plasma Filtration Adsorption

Thank you for the attention

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Società Italiana Nefrologia