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5th Journées Réanimation et Urgences Respiratoires

“Epuración extra-renalé et sepsis...”

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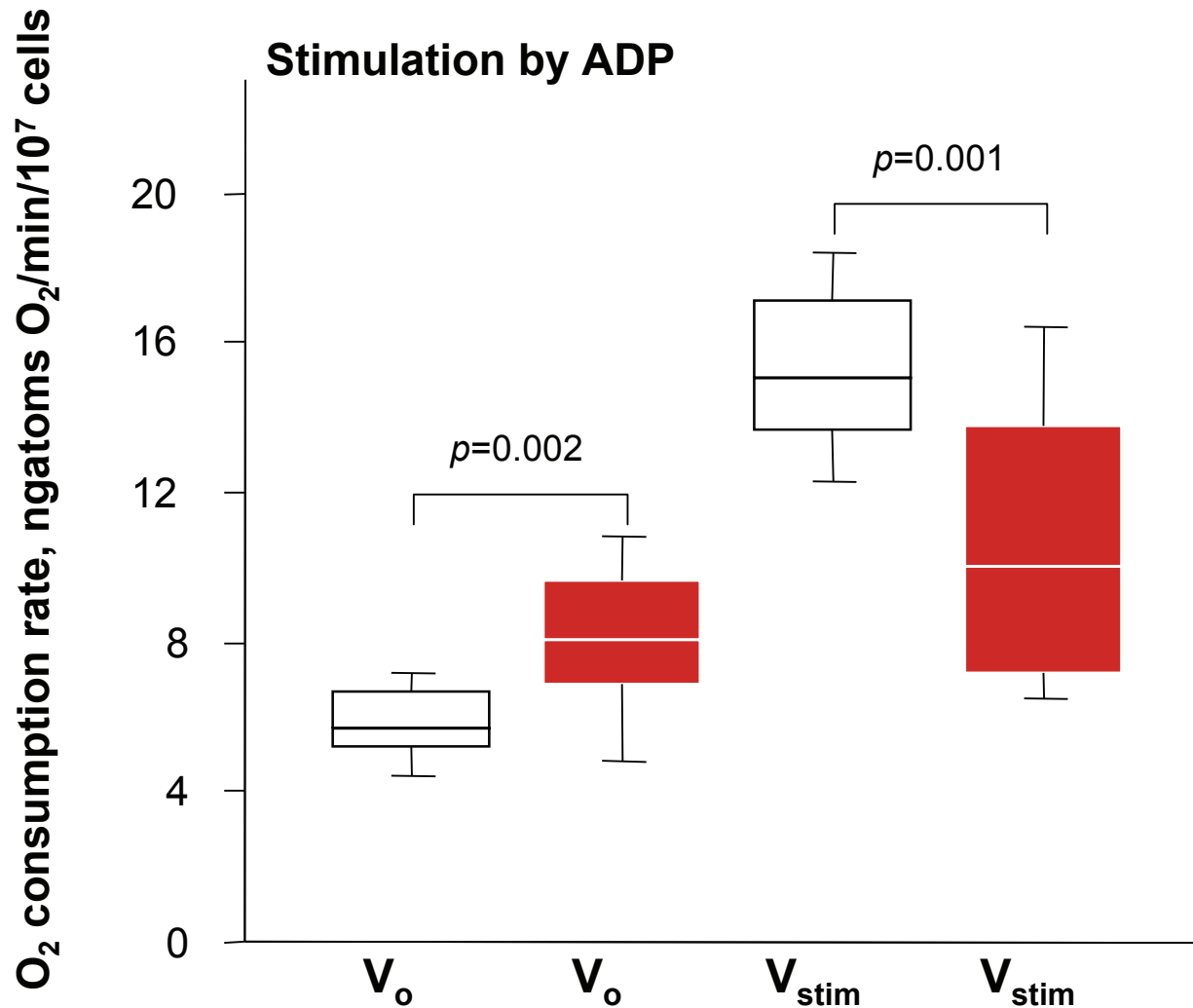
Content

- **The concept**
- The mediator removal in sepsis
- High volume HF
- Experimental studies
- Clinical studies
- Conclusion

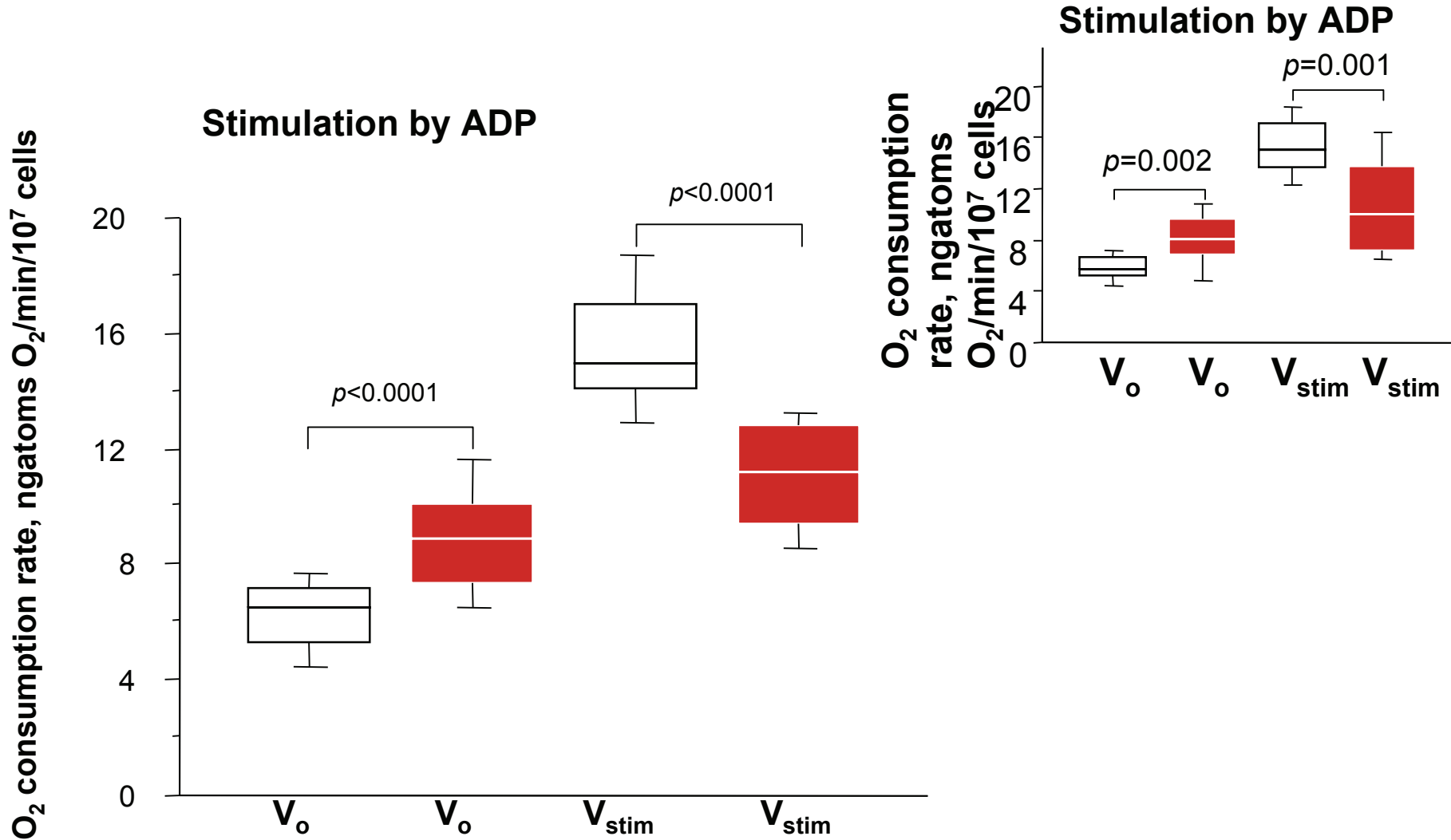
Introduction

- Sepsis or septic shock: “tsunami” changing rapidly with a predominant anti-inflammatory phenotype
- Sepsis → cell dysfunctions → immune cells →
 - LPS tolerance; immunoparalysis; bio-energetic failure...
- The plasma: source of the cell dysfunction
 - Immune cells oxymetry: an example

PBMC ex vivo O_2 consumption



HCells + Septic plasma



➔ Plasma induces immune cells bioenergy

- Septic plasma contains “bad humors”
 - Types? Bacterial products; Mediators...
- Plasma environment changes cellular functions
- QS could be:
 - Should we purified the plasma?
 - When? TIME IS CRUCIAL
 - What type of molecules has to be removed?
 - what is(are) the good technique(s)?
 - HVOLUME?
 - High permeability?
 - Others: apheresis; cartridges...

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Removing mediators:

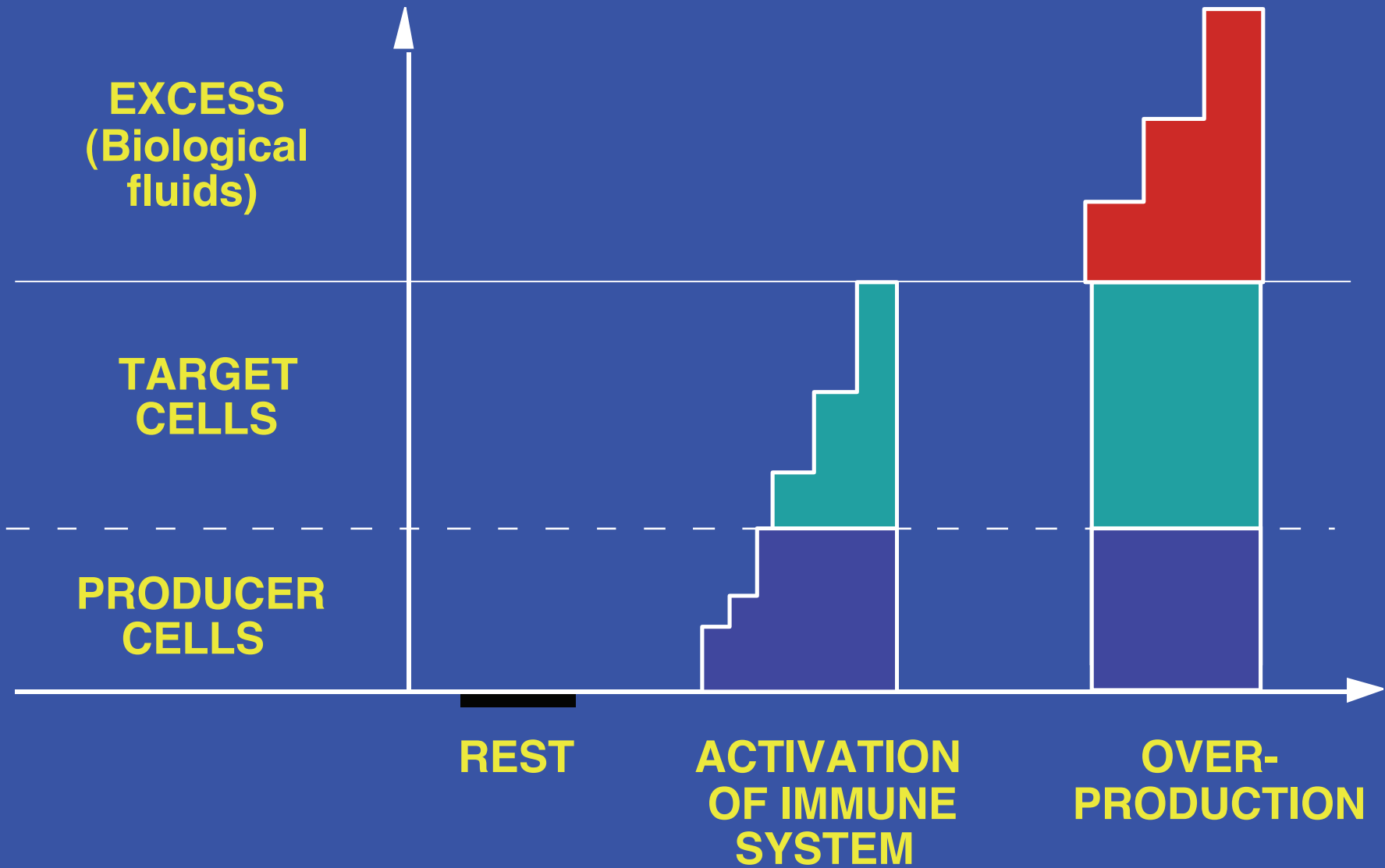
- The goals:
 - Elimination >> to the production
 - Elimination enough to < tissue level
 - Elimination has to be selective for "toxic" but not for "protective: mediators!!!
- Last point is lacking → remove all?
 - To "reset" the system → "reboot" the cells
- HVHF: plasmapheresis: cartridges ...

Removing mediators:

- HF → removes plasma molecules having adequate electrical charge and size → limitations come from mbne characteristics
- The “tip of the iceberg”: a low plasma level may correspond to a high tissue level of mediators
- Do we know the tissue production ? → fixing the mediators elimination rate
- Knowing time evolution of mediators release → best time to perform HVHF
 - Along time, phenotype moves from pro to anti-inflammatory balance

The "tip of the iceberg" from JM Cavillon

Detection of cytokines



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HVHF

- **Definition:**
 - Unclear: HV \leftrightarrow higher V than 1 or 2 L/Hr
 - **Dose**: is defined for RRT (35ml/kg/hr)
- **HVHF from 4 l/hr to 11l/hr**
- **Middle term: 0.15L/kg/hr \leftrightarrow 11l/hr for 70 kg**
 - \rightarrow very **specific device + trained team**
- **RCT is warranted**

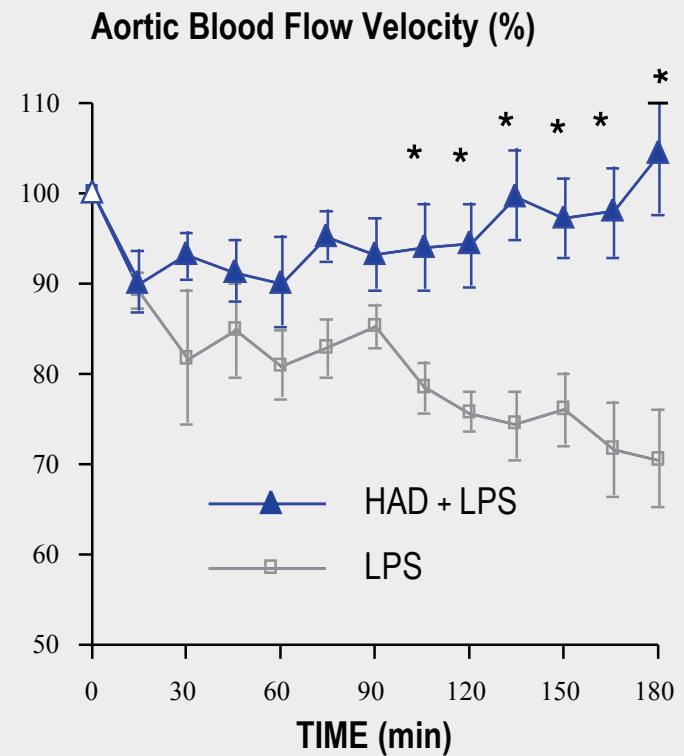
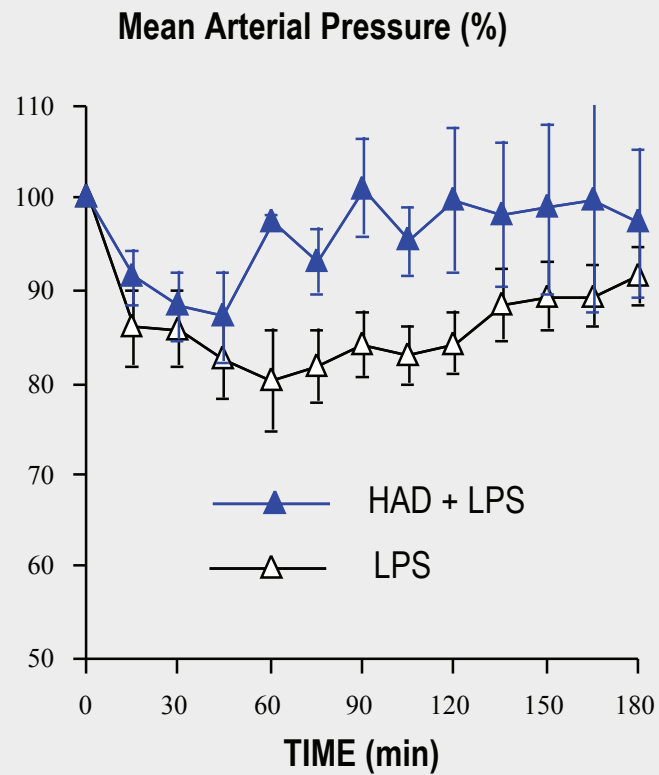
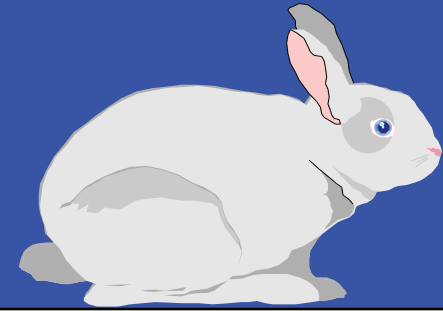
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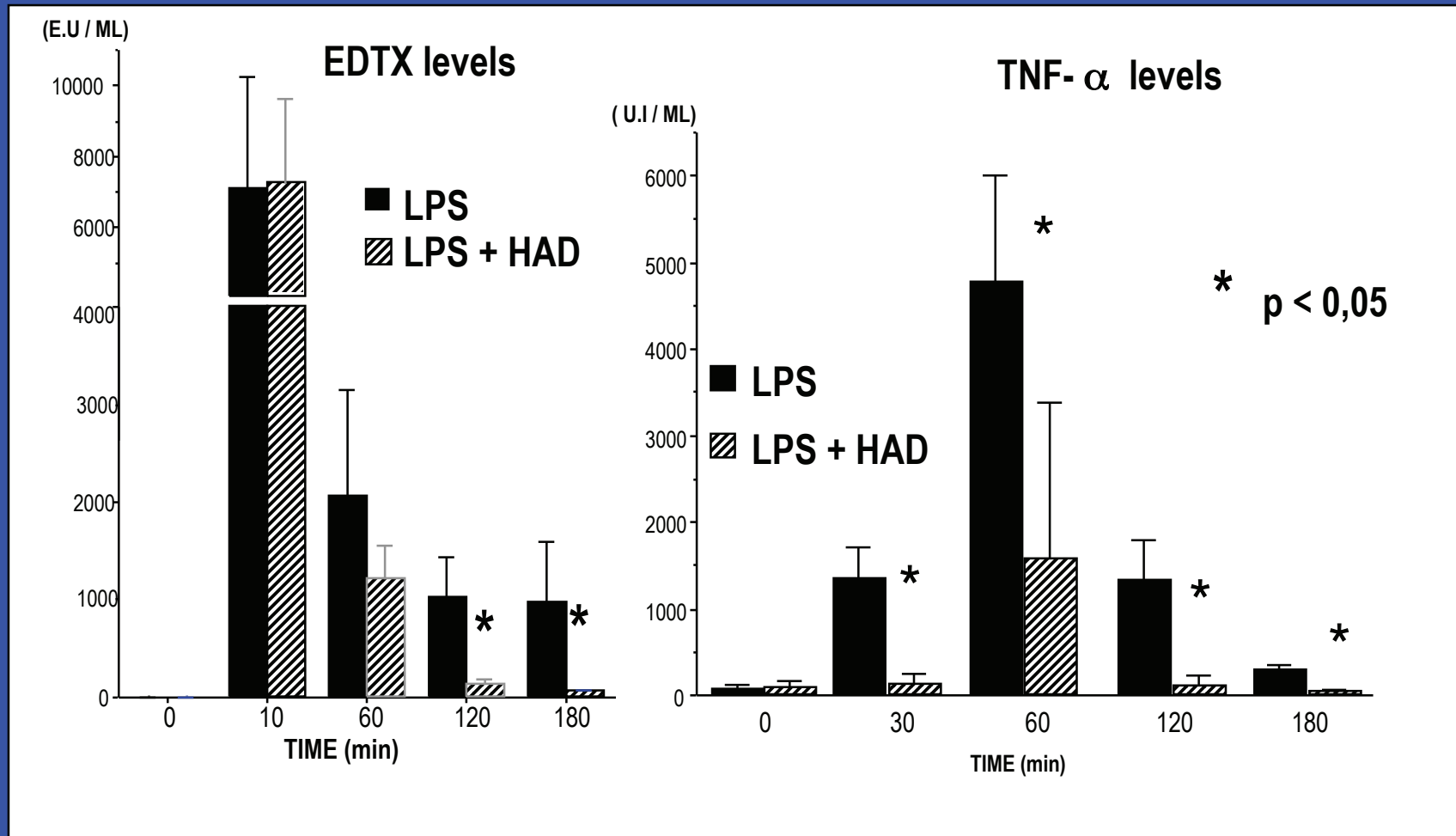
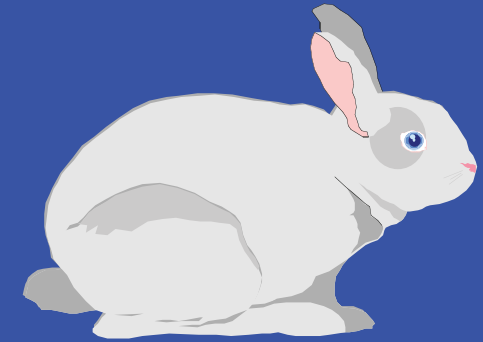
The landmark paper: *Grootendorst et al ICM 1992*

- Pig LPS model
- After 4hrs of sepsis → HD unstability + signs of OF
- application of zero balance HVHF (6l/hr; 200 ml/kg/hr) →
 - Better RVFunction
 - Better CO and BP
 - Outcome effect: uncertain...

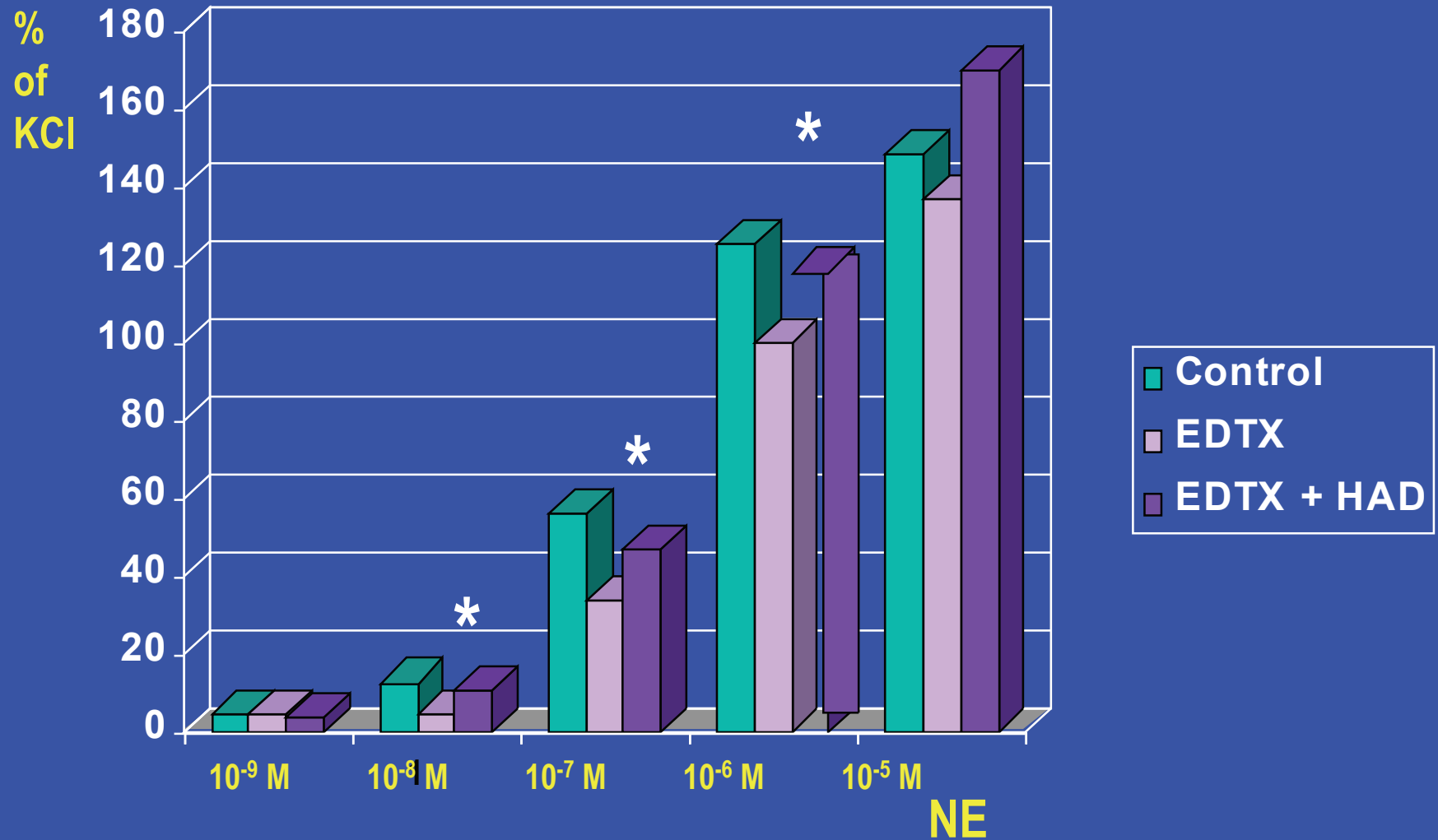
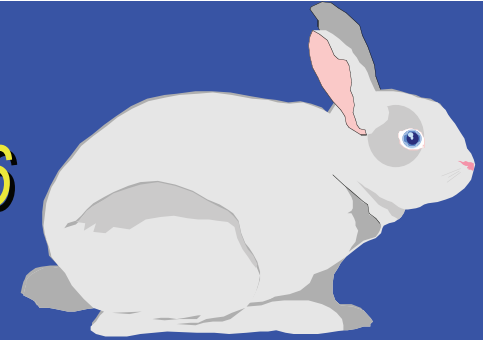
From Mateo et al *AJRCCM* 1996



From Mateo et al *AJRCCM* 1996



From Mateo et al AJ R&CCM 1996



Minipigs pancreatogenic sepsis model *Yekebas et al CCM 2001*

- After 12 hrs, during 60 hrs; 4 gps
 - G1 control
 - G2 + G 3 regular CVVH (20ml/kg) ± change the mbne
- The G4 (HV: 100ml/kg)
 - → higher survival rate (67% vs 33% in Gpe 3)
 - → best MAP & nl body temp
 - The MHC class II +CD14 were preserved in G 4 → improved innate immunity.
- The highest dose of HF was the most efficient

Discussion/conclusion

- Difficult to transpose exp data to clinical field, because:
 - Delay for HVHF is always shorter than in clinic
 - The dose used is always > than used in human studies
- But, filtrated fluid from septic animals
→ ex vivo induces sickness
- Direct proof for a benefit to remove "toxic compounds" is controversial for

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Literature...

Comparison of polyacrylonitrile (AN69) and polysulphone membrane during hemofiltration in canine endotoxic shock

Rinaldo Bellomo, John A. Kellum, Stephen R. Wisniewski, and Michael R. Pinsky

Attenuation of sepsis-related immunoparalysis by continuous veno-

The Effect of Intensive Plasma Water Exchange by Hemofiltration on Hemodynamics and Soluble Mediators in Canine Endotoxemia

RIN

Tec

Dep

Effects of Norepinephrine on the Renal Vasculature in Normal and Endotoxemic Dogs

RINALDO BELLOMO, JOHN A. KELLUM, STEPHEN R. WISNIEWSKI, and MICHAEL R. PINSKY
with the Technical Assistance of Brian Ondulik

Cardiopulmonary Research Laboratory, Division of Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh Medical Center; and Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania

Adjunctive therapies in sepsis: An evidence-based review

Alain Cariou, MD; Christophe Vinsonneau, MD; Jean-François Dhainaut, MD, PhD

Effect of filtration volume of continuous venovenous hemofiltration in the treatment of patients with acute renal failure in intensive care units

A phase II randomized, controlled trial of continuous hemofiltration in sepsis

Louise Cole, MBBS, FFICANZCA; Rinaldo Bellomo, MBBS, MD, FRACP; Graeme Hart, MD, FFICANZCA; Didier Journois, MD, PhD; Piers Davenport, BSc; Peter Tipping, MBBS, PhD; Claudio Ronco, MD

Demir A. Özyürekçi, MD, PhD, Navjet Dalgıç, Lale Özyürekçi, Gül Nurda, Alioğlu Nyuvallı, Tulin Özyürekçi

Takumi Taniguchi
Akihide Kurita
Chisui Mukawa
Ken Yamamoto
Hideo Inaba

Dose-related effects of direct hemoperfusion using a cytokine adsorbent column for the treatment of experimental endotoxemia

Clinical studies

- Review only data with zero fluid balance
- Most of the studies are uncontrolled studies with small number of patients
- Heterogeneous trial for:
 - Patients enrolled
 - Technique used (mbne; surface; sieving coeff...)
 - Time for application

A positive fluid balance is associated with a worse outcome in patients with acute renal failure

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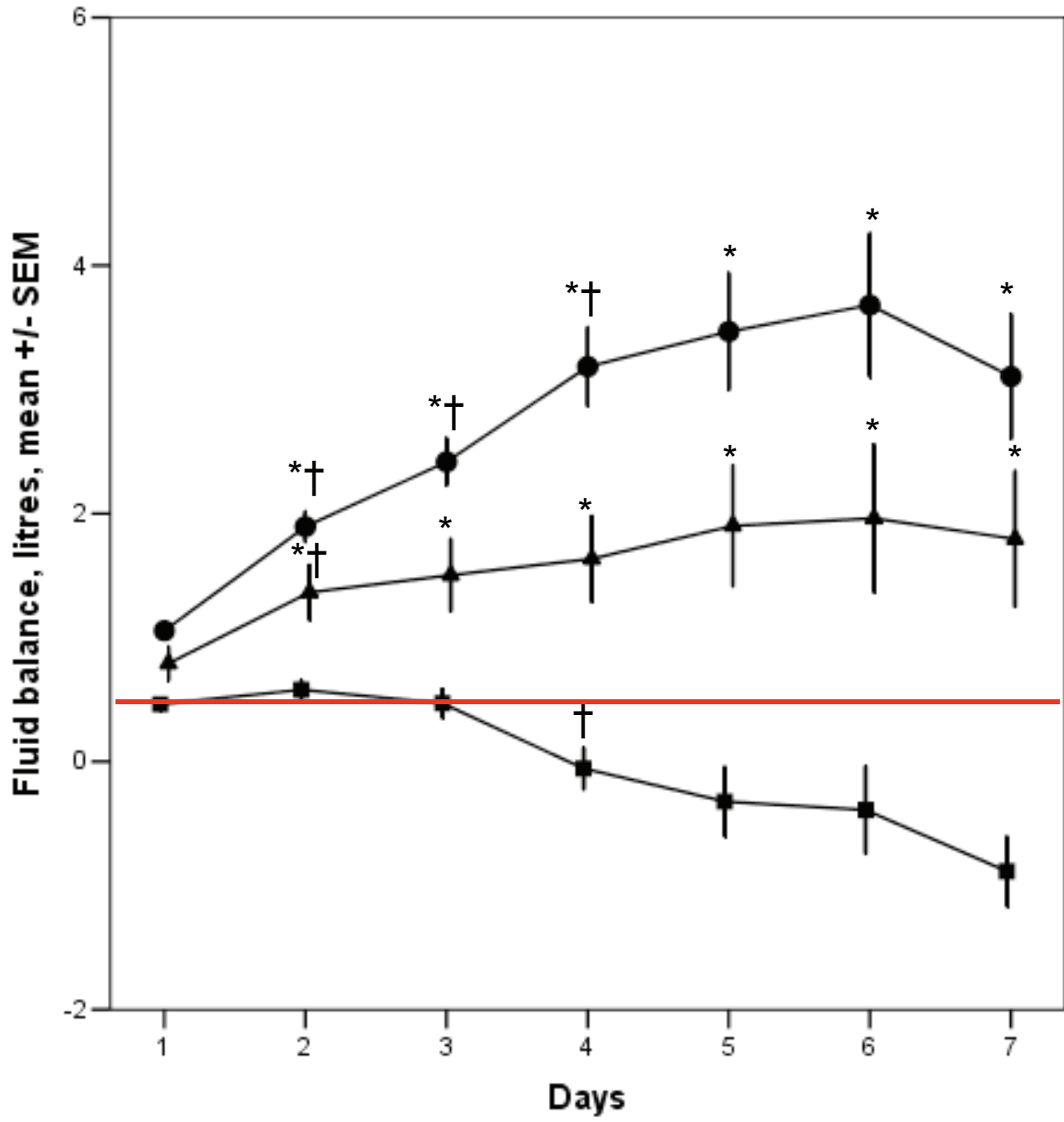
Konrad Reinhart MD PhD

Dept of Anesthesiology and Intensive Care, Friedrich-Schiller-University Jena, Germany

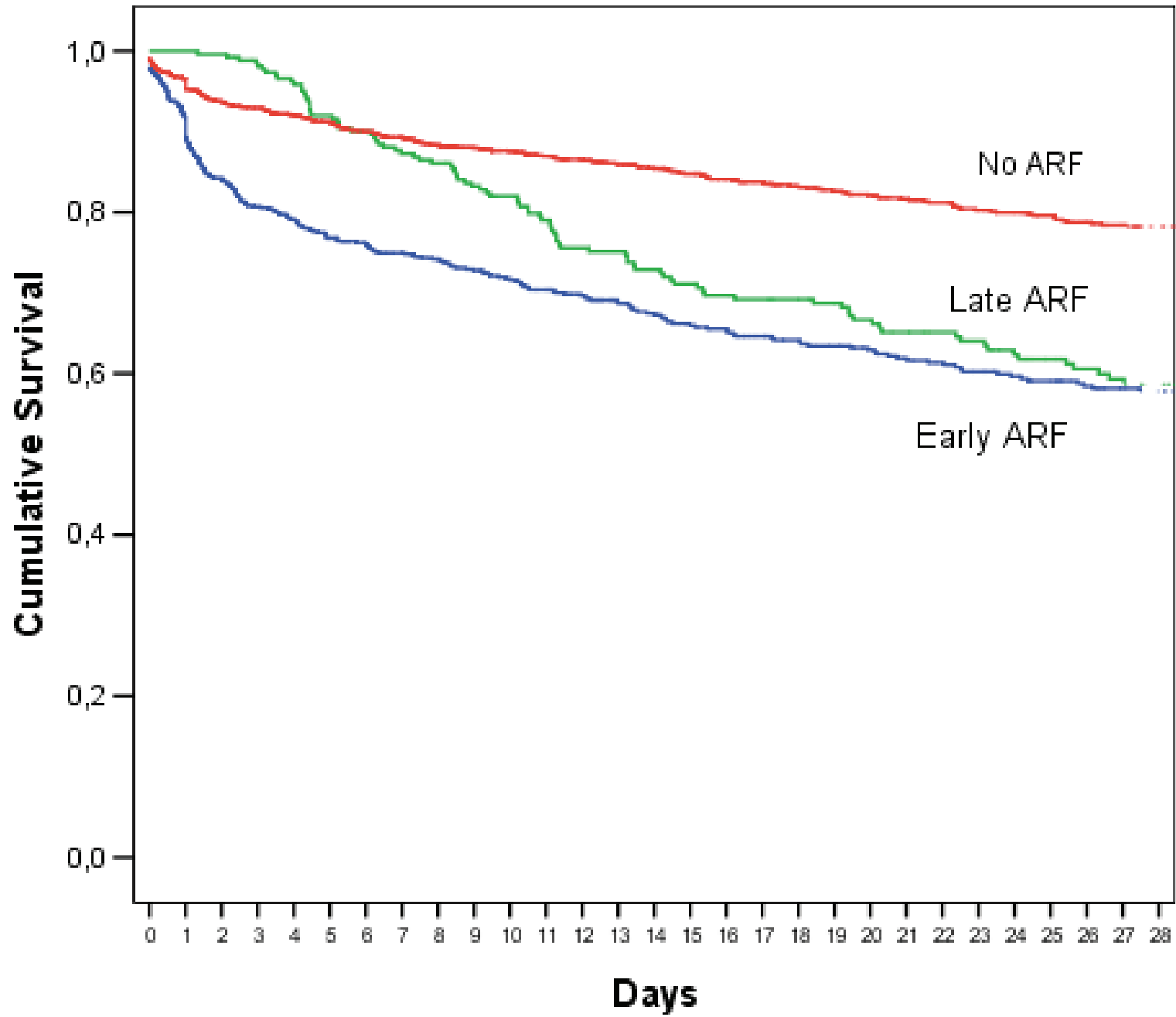
Jean-Louis Vincent MD PhD FCCM

Department of Intensive Care, Erasme Hospital, Free University of Brussels, Belgium
on behalf of the Sepsis Occurrence in Acutely Ill Patients (**SOAP**) Investigators

2nd submission to Crit Care 2008



? Late ARF
? Early ARF
? No ARF



Outcome among patients with acute renal failure,
stratified by time of initiation of renal
replacement therapy (RRT).

Characteristic	Early RRT n=213	Late RRT n=65	p value
ICU mortality	84 (39.4)	40 (61.5)	0.002
ICU stay	6.1 (2.5 - 14.8)	12.2 (8.0 - 26.5)	< 0.001
Hospital mortality	102 (48.6)	44 (67.7)	<0.007
Hospital stay	25.0 (8.0 - 46.0)	27.0 (17.0 - 45.0)	0.105

Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis. A Randomized Controlled Trial.

Didier Payen, MD, PhD

Joaquim Mateo, MD

Jean Marc Cavillon, PhD

François Fraisse, MD

Christian Floriot, MD

Eric Vicaut, MD, PhD

*for the Hemofiltration & Sepsis Group of the **Collège National de Réanimation et de Médecine d'Urgence des Hôpitaux extra-Universitaires***.*

Trial design (4th Submission to CCM)

- comparison conventional therapy vs conventional therapy + CVVH

Inclusion within 24 hours after meeting the inclusion criteria

- *Conventional treatment*: treatment decided by the physician in charge
- *HF treatment*: conventional treatment + CVVH started within 24 hrs for at least 96 hrs
- Primary end point: the reduction of number and duration of sepsis-induced organ failure at day 14
- Secondary end point: mortality at day 14; withdrawal of catecholamines infusion and length of mechanical

Primary end point

Figure 1: evolution of SOFA score in the 2 groups:

SOFA was compared to Day 0. A positive value indicates a maintenance or a deterioration

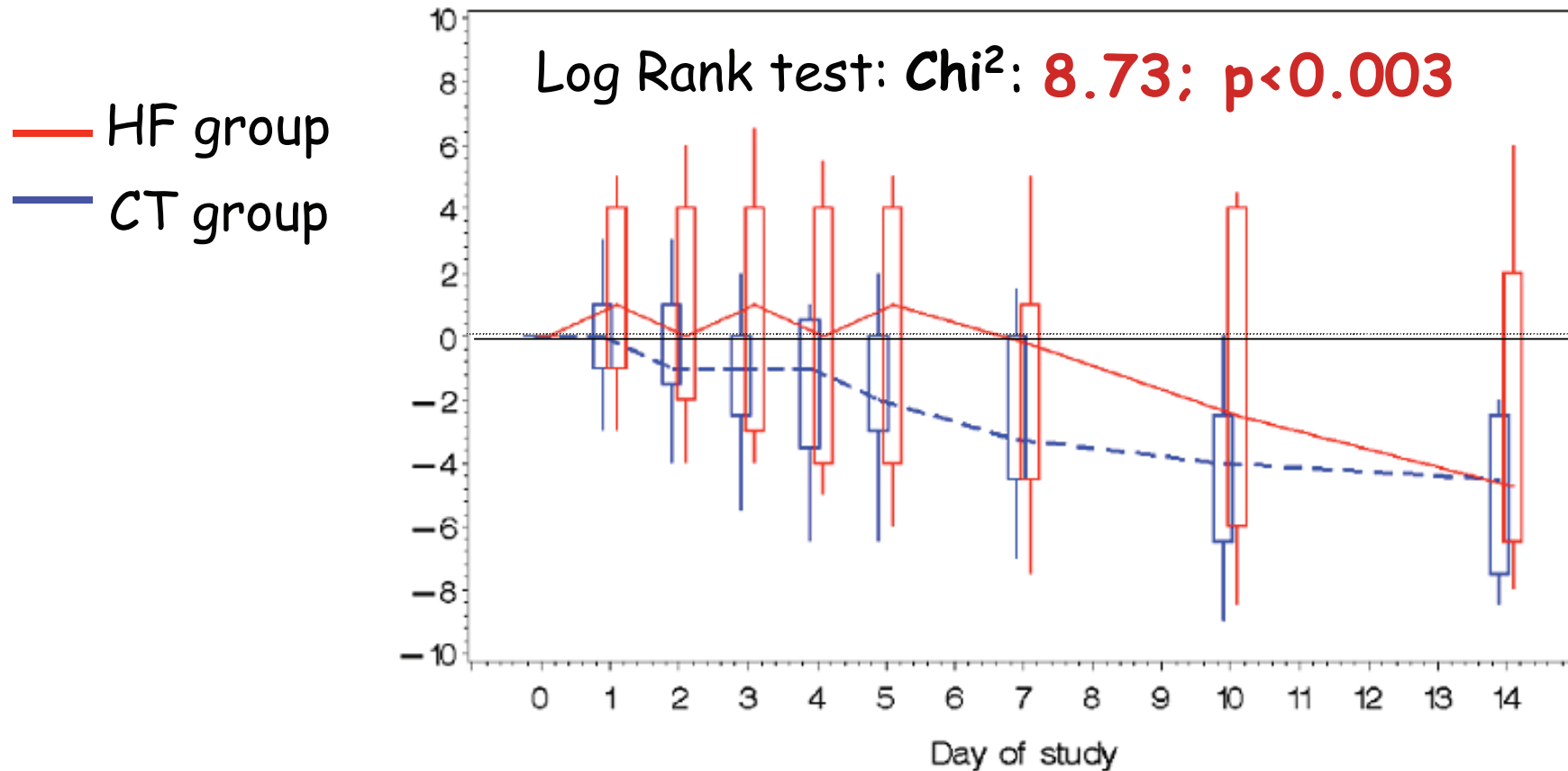
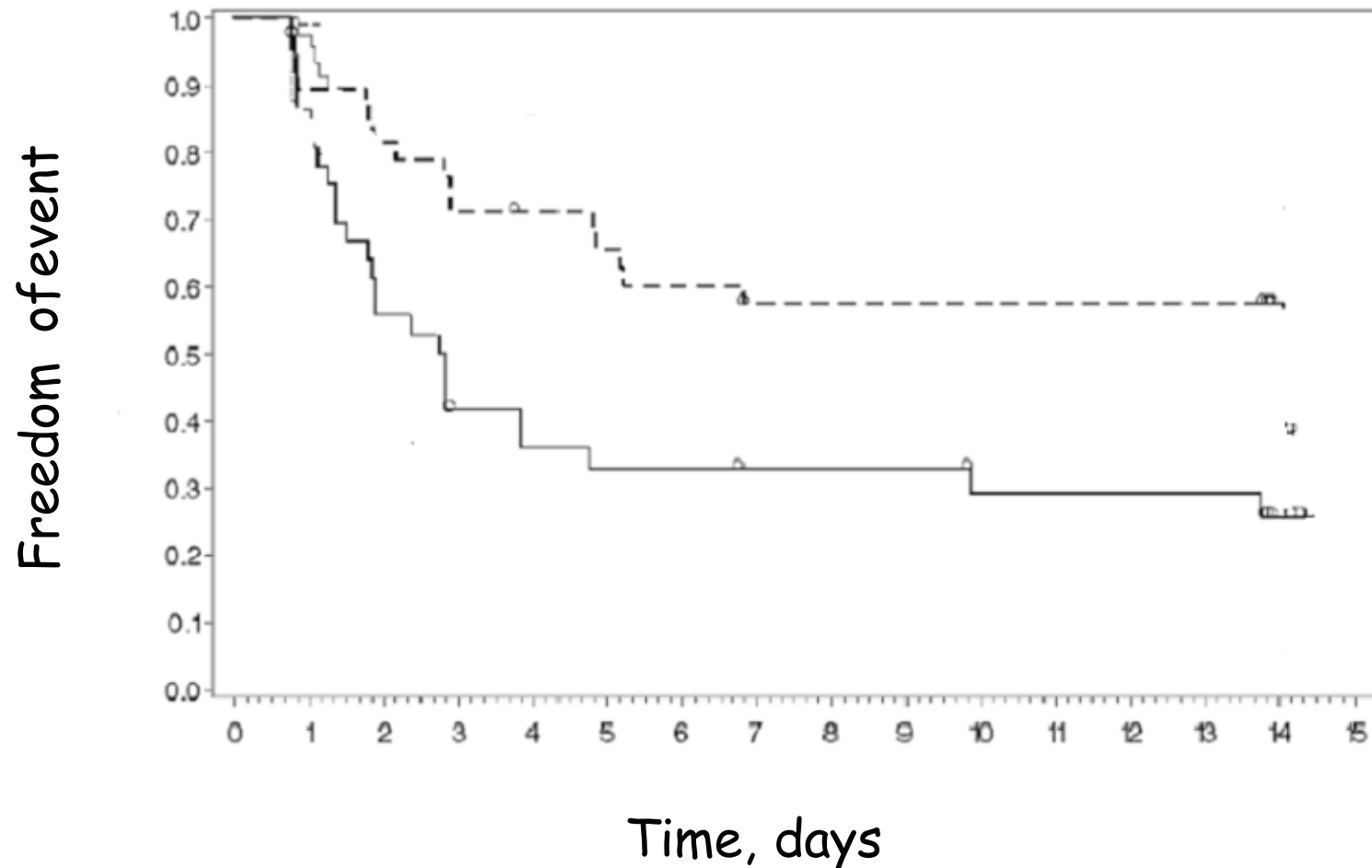


Figure 2 Time to multiple organ worsening SOFA
(worsening corresponded to **at least one point** of SOFA score).



--- CT group
— HF group

Log Rank test: Chi^2 : 8.73; $p < 0.003$



« The St Pierre Hemodynamical Study »

Short Term HVHF

- * **35 liters in 4 hours**
- * **Neutral balance**
- * **Polysulfone membranes (1.6 m²)**
- * **Post-dilution technique**
- * **Bicarbonate as buffer (40 mMoles/l)**

LVHF

- * **1 L/hr (24 liters per day)**
- * **Polyacrylonitrile membranes (1 m²)**
- * **Pre-dilution technique**
- * **Bicarbonate as buffer (40 mMoles/l)**



« The St Pierre Hemodynamical Study »

- But, it is an uncontrolled study
- It concerned a limited number of patients



The « Amsterdam II » Study.

Randomized controlled « Two Centers » Study

Discussion:

- But what about septic population ?
- Great proportion of « cardio-surgical ptns ».
- « to high » Survival rate to detect a signal?



The « Bordeaux study » (Sepsis & MOF):

The design

24 Septic Shock > 2 Organ Failures

Post-op abdominal surgery

60 ml/kg/hr for 96 hrs of HVHF

Predicted mortality at 28 days: 70 %



Observed mortality at 28 days 46% (P<0,075)



RCT is still warranted !!!



« The « Vicenza - Piccinni Study »

(80 pts SShock

HF

It is a retrospective Study!

APACHE II	05
NE Dose	05
Ventilator we	01
28 days survi	05
Lenght of sta	002

Commentary

Pro/con clinical debate: Is high-volume hemofiltration beneficial in the treatment of septic shock?

Karl Reiter^{*}, Rinaldo Bellomo[†], Claudio Ronco[‡] and John A Kellum[§]

Critical Care 2002, **6**:18-21

^{*}Professor of Pediatric Intensive Care, University Children's Hospital, Muenchen, Germany

[†]Director of Intensive Care Research, Austin & Repatriation Medical Center, Heidelberg, Victoria, Australia

[‡]Professor of Nephrology, S. Bortolo Hospital, Vicenza, Italy

[§]Associate Professor of Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

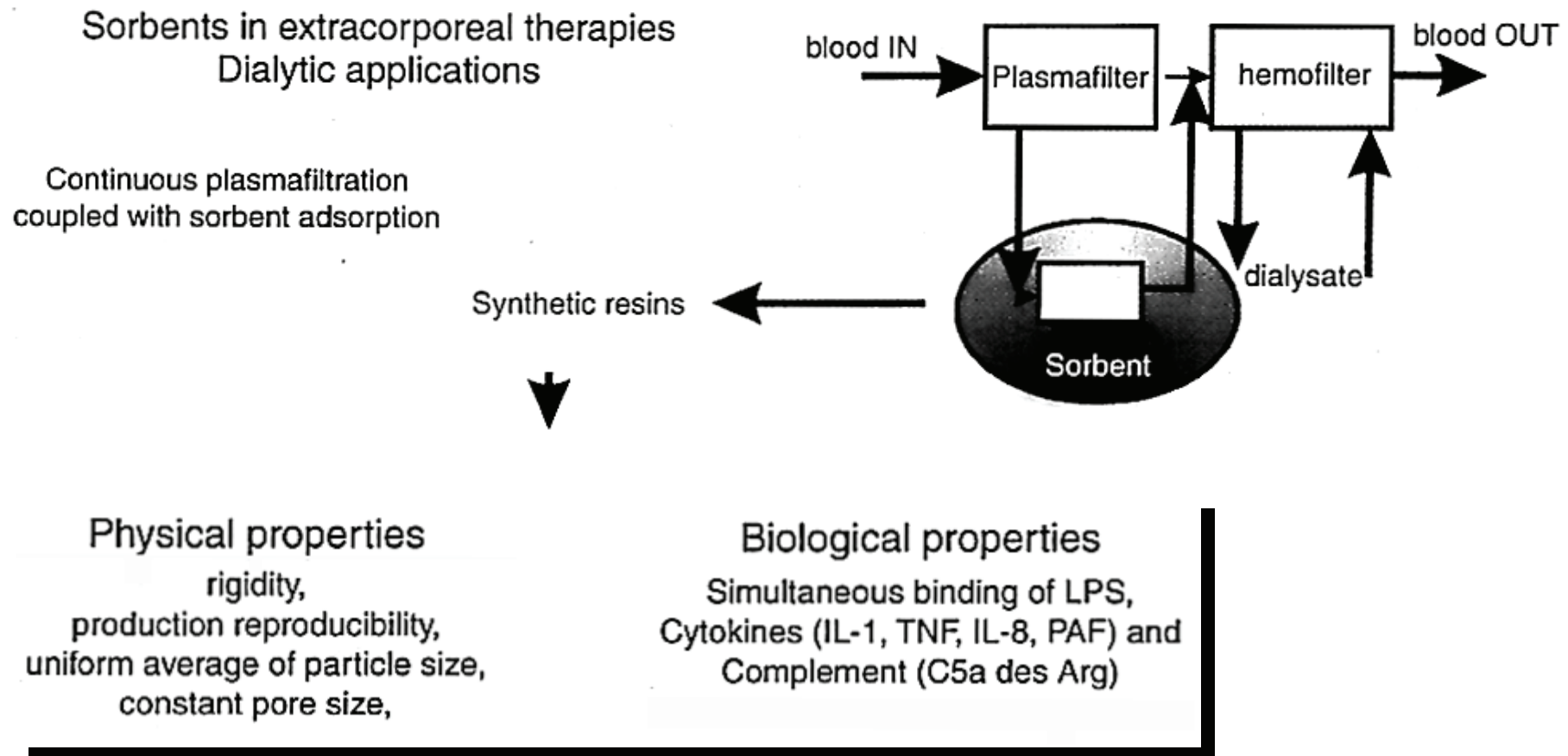
Abstract

Although there have been exciting advances in the management of sepsis and septic shock, mortality still remains high. Recent data suggest that high-volume hemofiltration (HVHF) may play a role in these patients. In contrast to the usual rate of hemofiltration, HVHF is felt to be better able to remove the inflammatory mediators associated with sepsis and septic shock. Such an approach is currently incapable of selectively removing specific mediators. This may be a problem when one considers that several mediators may in fact be beneficial. When determining whether HVHF should be instituted in a patient with septic shock, one need remember that its role is far from clear and its usefulness remains the subject of much debate. Although early data is encouraging, it is clear that additional data is required before HVHF becomes standard management. The authors of this pro/con debate, which is based on a clinical scenario, first describe their own position and then respond to their opponent's position.

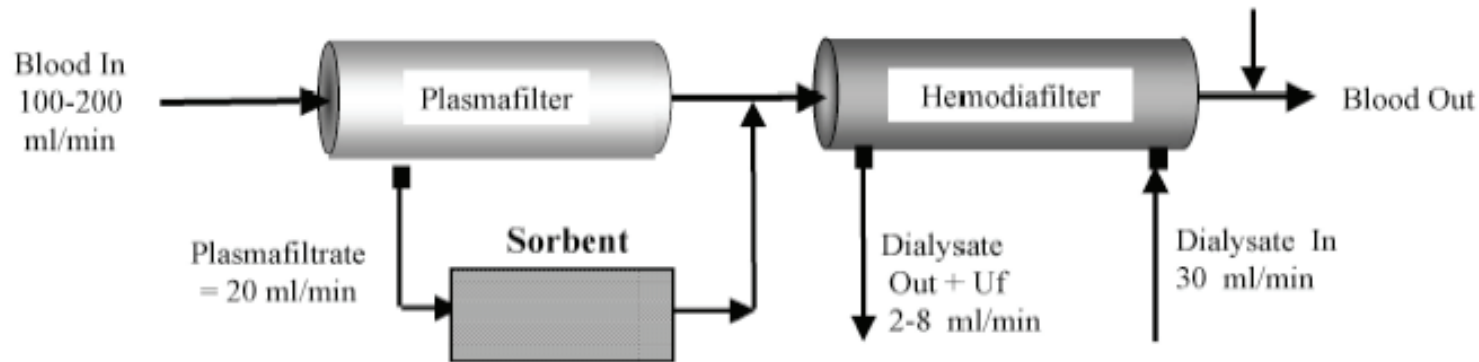
Little as changed from this 2002 Pro/Con viewpoint, but it will do....

Content

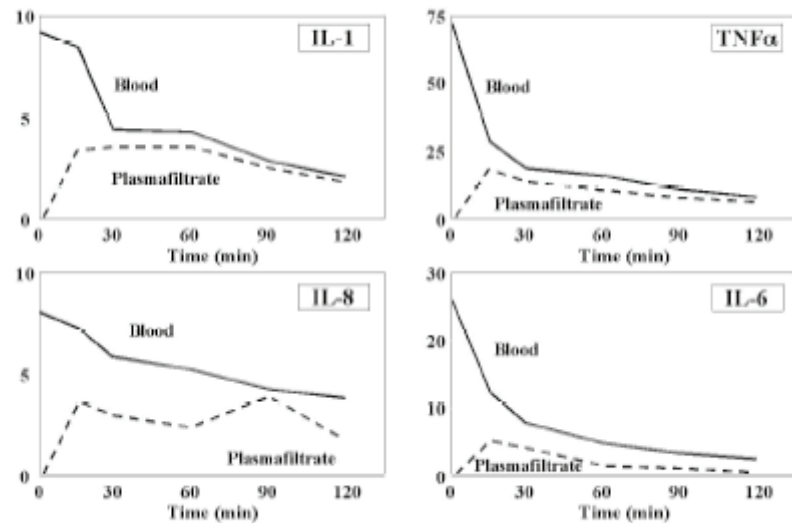
- The concept
- The mediator removal in sepsis
- High volume HF
- Experimental studies
- Clinical studies
- **Other EC techniques**
- Conclusion



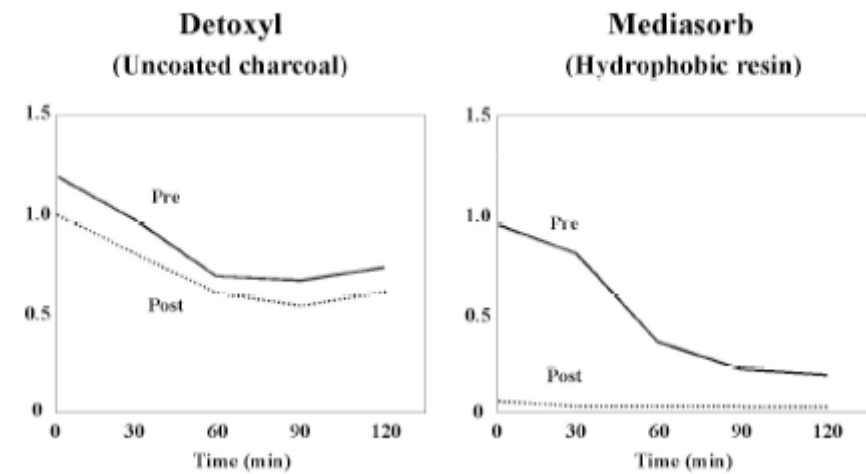
C.Tetta et al. Continuous plasma filtration coupled with sorbents.
Critical Care Nephrology 1998; 66(sup): S186-S189



CYTOKINES CONCENTRATION IN BLOOD AND UF



Adsorption capacity for TNF α of two sorbent materials



Extracorporeal Endotoxin Removal For The Treatment of Sepsis: Endotoxin Adsorption Cartridge (Toraymyxin)

Hisataka Shoji

Therapeutic Apheresis and Dialysis

Outlet

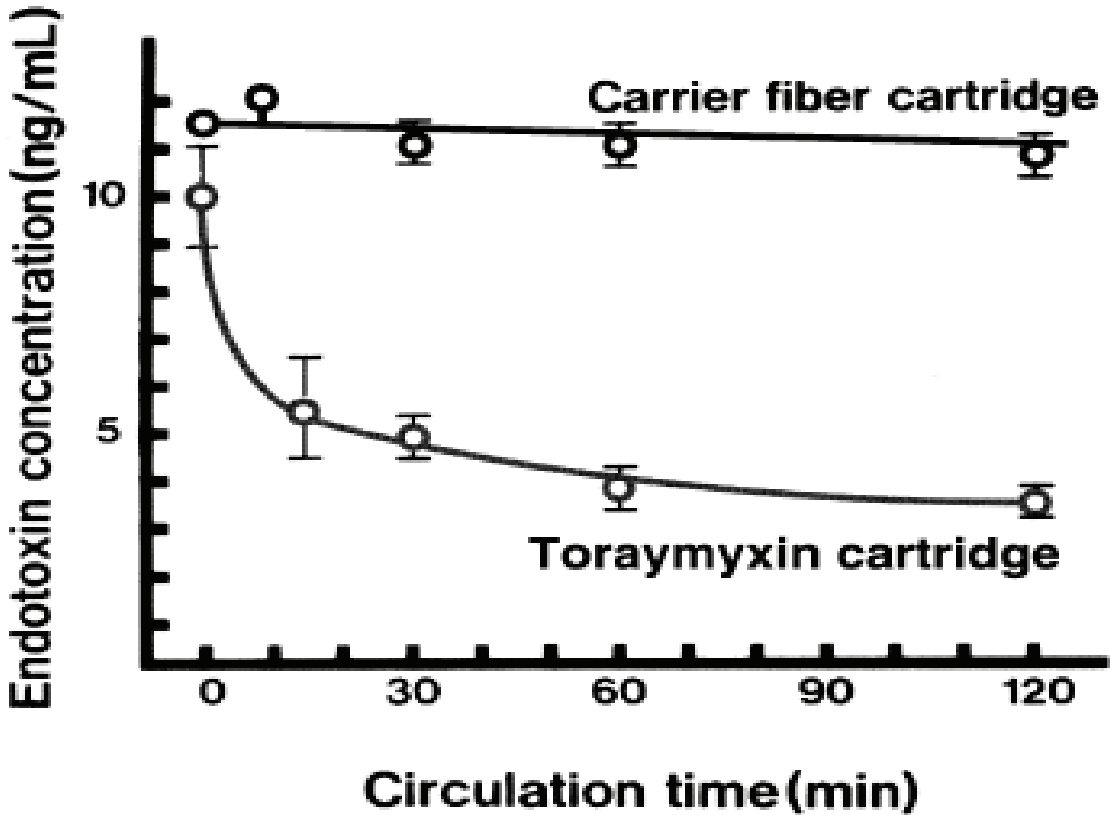


FIG.3. Adsorb

ow within a Toraymyxin

FIG.7. Graph to show the changes in endotoxin concentration with a carrier fiber cartridge and a PMX cartridge over 2 h.

A PILOT-CONTROLLED STUDY OF A POLYMYXIN B-IMMOBILIZED HEMOPERFUSION CARTRIDGE IN PATIENTS WITH SEVERE SEPSIS SECONDARY TO INTRA-ABDOMINAL INFECTION

Jean-Louis Vincent,* Pierre-François Laterre,[†] Jonathan Cohen,[‡] Hilmar Burchardi,[§] Hajo Bruining,^{||} Francisco Alvarez Lerma,[¶] Xavier Wittebole,[†] Daniel De Backer,* Stephen Brett,** Dolores Marzo,[¶] Haruji Nakamura,^{††} and Stephanie John^{‡‡}

6 Academic centers; 36 pts
Severe sepsis or SShock from
abdominal infection; PMX ttmt 2 hrs;

RESULTS:

- No diff in LPS level; in IL-6; SOFA
- Significant increase in LVSWI and DO₂
- Significant reduction in CRRT need in PMX treated group

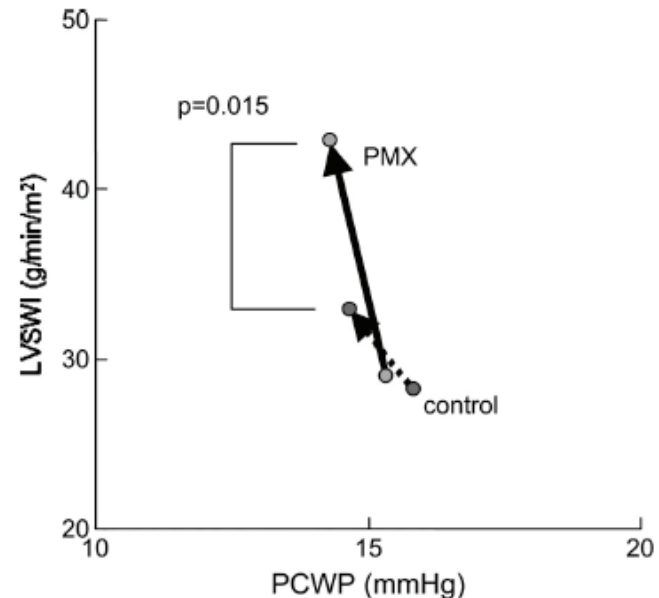


FIG. 1. Effects of PMX on left ventricular function. Arrows show the direction of the changes of LVSWI and PCWP from baseline to day 2.

→ RCTrial to prove the benefit of the technique; what type of patients?

CLINICAL APPLICATIONS: THE JAPANESE EXPERIENCE

1. Endotoxemia or suspected gram-negative infection
2. Two or more of the following conditions from a total of 11: (a) Fever with oral temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; (b) tachycardia >90 beats/min; (c) tachypnea >24 breaths/min; (d) leukocytosis $>12\,000/\text{mm}^3$; or leukopenia: $>4000/\text{mm}^3$ or 10% bands form.
3. Septic shock which necessitates vasopressor therapy.

The Japanese clinical experience
2 trials

first multicenter clinical study:

- blood LPS detected in 37 out of 42 pts
- endotoxin level reduced significantly (83 ± 26 pg/mL to 56 ± 27 pg/mL after 2 h hemoperfusion).
- 20 patients survived more than 14 days
17 patients died.

Retrospective study;

- 37 patients treated with Toraymyxin compared with 33 pts treated with conventional therapy.
- severity scores and OF $>$ in PMX group

•RESULTS:

survival rate after 14 days $>$ significantly higher in the Toraymyxin group than in the control group

2nd multicenter clinical study,

88 patients; positive effect on HD

→ A major role of LPS in sepsis induced OF and poor outcome

Foot print at day 0 of sepsis for ARF

occurrence

SOFA 3-4 vs SOFA 0

P<0,01

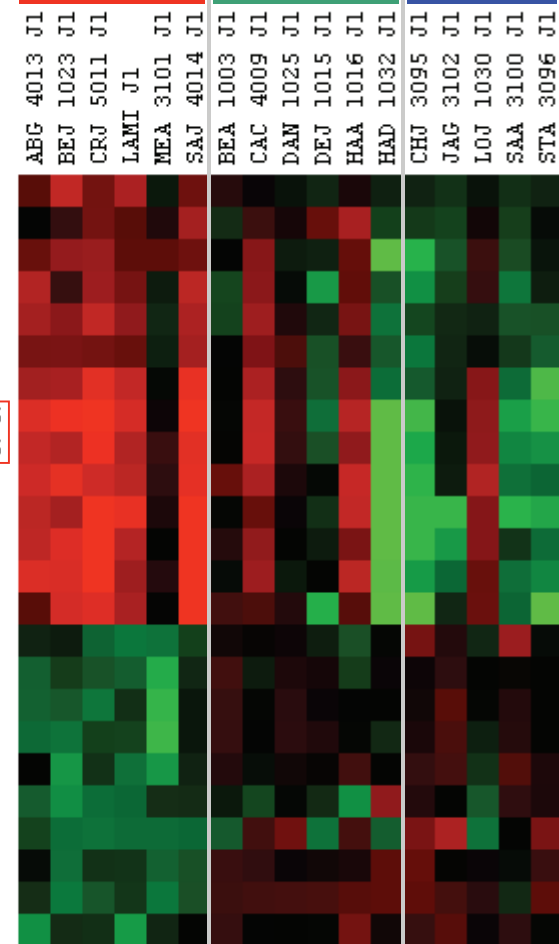
FC>3

24 probesets

SOFA = 0

SOFA = 2

SOFA = 3-4



Genes of interest are related to the ROS metabolism

-Both for synthesis and detoxification

-And for maintenance of cell structure

Hyper-expression
Under-expression

10 genes were potential predictor for 82.3 %
Using the "Leave One Out" technique

Conclusion

- The good technique for the good goal!
- How to define the good goal?
 - What molecules to target?
 - The cell function; the organ function
 - Should the plasma be "normalized" ?
- What would be the consequences of a **huge fluid replacement** by an artificial fluid on long term follow up
- What are the consequences of ECC on

Conclusion

- Is HVHF preferable to apheresis or specific cartridges?
- Should we remove LPS? Cytokines? Others? All?
- When? Early use or later?
- Different RCTrials have to be performed on AKI:
 - in a context with systemic inflammation

ARF Epidemiology SOAP Study Results

- ICU Mortality rate in Renal failure: **30.2%** vs 12.1%; $p < 0.05$
- **Higher (33.2) in late** than in early (29.2) RF
 - Older pts **62.8** vs 59.3; $p < 0.05$
 - Higher rate of heart failure: **12%** vs 8.6; $p < 0.05$
 - Lower BP: **68.9** vs 72.4; $p < 0.05$
 - Higher incidence of Severe Sepsis: **42.5** vs 22.4%;
 $p < 0.05$, or septic shock **22.8** vs 10.2%; $p < 0.05$

2nd Submitted to CCM

Mean fluid balance and outcome among survivors and non-survivors with acute renal failure (ARF), stratified by time of onset

fluid balance L/24 h	Survivors	N-Surv	p value
ARF	0.17 (-0.44 - 0.70)	0.95 (0.31 - 1.97)	<0.01
Early ARF	0.18 (-0.41 - 0.73)	1.11 (0.40 - 2.21)	<0.01
Late ARF	0.13 (-0.52 - 0.62)	0.71 (-0.13 - 1.34)	<0.01

Mean and cumulative fluid balances and outcome among patients with acute renal failure (ARF), stratified by urine output and treatment.

Characteristic	Non-oliguric n=572	Oliguric n=548	p value	No RRT n=842	RRT n=278	p value
fluid balance L/24h	0.28 (-0.43 - 0.92)	0.51 (-0.06 - 1.19)	<0.001	0.27 (-0.28 - 0.97)	0.58 (-0.27 - 1.29)	0.006
Cumulative fluid balance, L	1.13 (-2.18 - 5.58)	1.75 (-0.21 - 6.00)	0.02	0.27 (-1.58 - 2.00)	3.90 (-1.91 - 11.82)	<0.001
ICU mortality	157 (27.4)	181 (33.0)	0.04	214 (25.4)	124 (44.6)	<0.01
Hosp mortality	190 (33.2)	223 (40.7)	0.01	267 (32.2)	146 (52.2)	<0.01
ICU stay	4.5 (2.0-11.1)	3 (1.4-8.6)	<0.01	2.9 (1.6-6.9)	8.4 (3.0-19.4)	<0.01
Hospital stay	12.7 (5.5-21.0)	10.3 (2.3-22.2)	<0.01	10.8 (3.8-24.1)	16 (6.8-34.9)	<0.01

Baseline characteristics of patients with acute renal failure (ARF), stratified by time of initiation of renal replacement therapy (RRT).

Characteristic	Early RRT n=213	Late RRT n=65	p value
Age	62.3 ± 15.5	64.6 ± 15.0	0.303
Male gender	126 (59.4)	44 (68.8)	0.179
SAPS II	49.7 ± 17.5	45.3 ± 18.0	0.035
SOFA score	9.2 ± 4.1	8.2 ± 3.5	0.041
Mechanical ventilation	166 (77.9)	61 (93.8)	0.004
Type of admission			
medical	87 (40.8)	38 (58.5)	0.012
surgical	126 (59.2)	27 (41.5)	0.013
Urine output, L	0.18 (0.03 – 0.50)	0.47 (0.09 – 1.74)	<0.001
Creatinine, mg/dL	3.99 (2.57 - 6.17)	3.29 (2.10 - 5.00)	0.058
Cumulative fluid balance, L	1.15 (-0.08 - 4.03)	6.34 (2.36 - 13.03)	<0.001

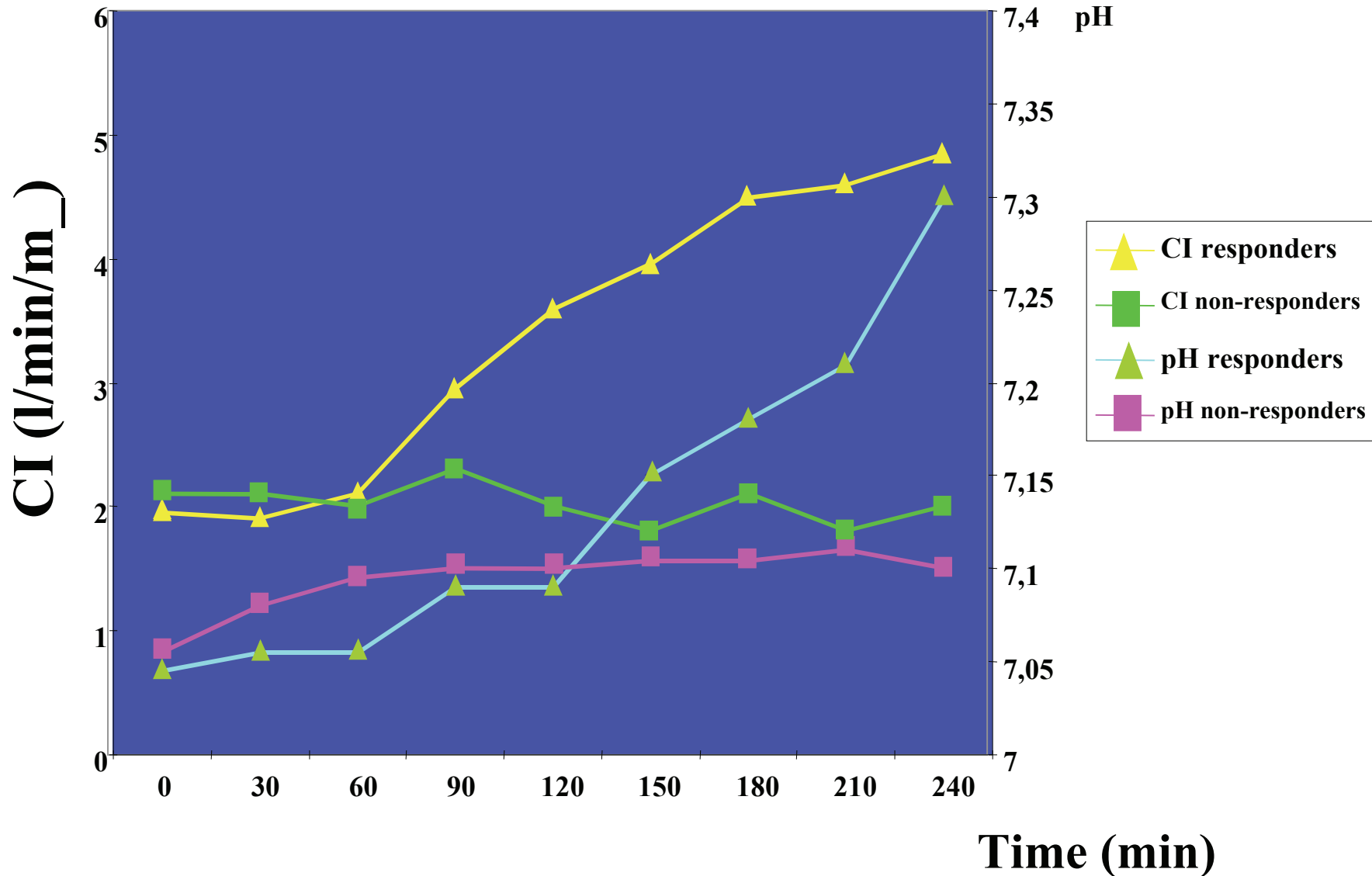
Removing mediators:

- Removal by convection:
 - Molecular size has to fit with mbne permeability
 - Transmbne forces
 - → HPerm Mbne were used + Adsorption
 - Blood flow and Mbne S have to be sufficient to maintain good convection
- There are still a lot of unclear aspects → hazardous therapy...



« The St Pierre Hemodynamical Study »

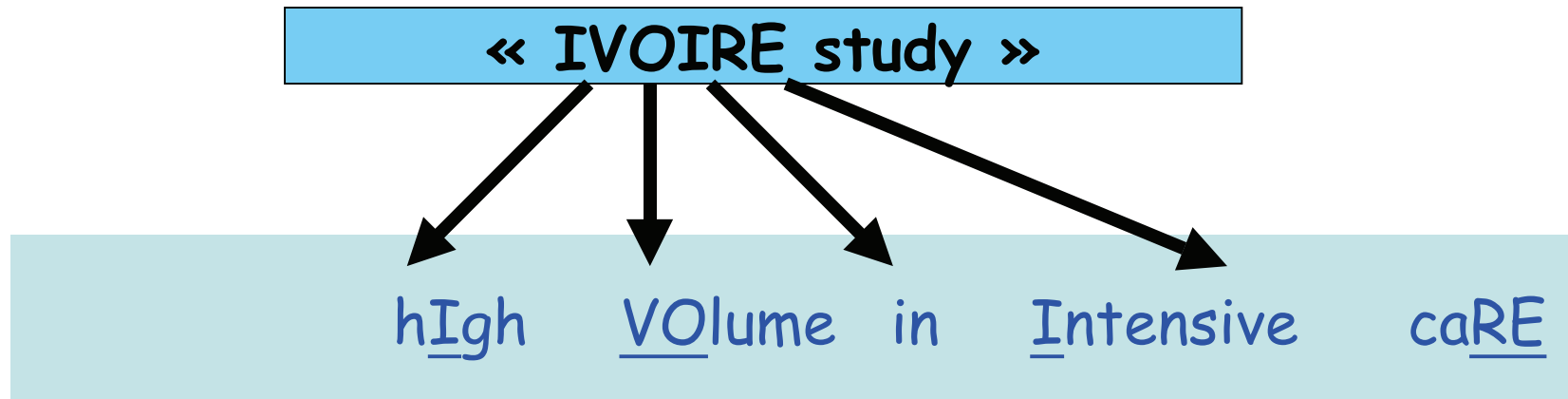
Evolution of pHa and the CI during HVHF





HV-CRRT in Septic AKI

The « IVOIRE Study »



Prospective **randomized multinational** single blind study **evaluating the adequate dose of CHVHF** in the **early** treatment of Septic Shock patients with Acute Kidney Injury.

→ defined the adequate « **Septic Dose** » of CRRT during Septic induced Acute Kidney Injury in ICU.

The « IVOIRE Study »: The design

it is a controlled study,

for efficacy...

HEMOFILTRATION :

In vivo experimental studies on myocardial depression

- Gomez et al, Anesthesiology, 1990
 - dog model, alive E coli ; in vitro study
 - Hfc with cuprophane membrane
 - **HFC reverses myocardial depression**
 - septic sera depress ex vivo rat myocardial contraction, an effect prevented by HFC → removing cardio-depressive