

Hemofiltration in sepsis

Rinaldo Bellomo
Austin Hospital
Melbourne, Australia

Middle molecules

- The “humoral theory of sepsis” is supported by much evidence that “mediators” have a strong association with organ failure and mortality
- Most inflammatory mediators are middle molecules (cytokines, chemokines, complement anaphylatoxins etc.)
- Thus, middle molecules >600 but <50,000 kD appear important in the pathogenesis of severe sepsis

Some of the humoral mediators of sepsis

- TNF (MW 17 kD but trimer and bound)
- IL-1 (17kD); IL-8 (MW 9 kD); IL-6 (MW 22kD), IL-10 (17 kD)
- Complement: Factor D (MW< 25kD), C3a, C5a (MW < 11.5 kD)
- Eicosanoids: TxB₂, PGE₂ (MW 500)
- PAF: MW < 600
- Others: endothelin, myocardial depressant factors (MW 4-5kD)

Targeting one or all?

- Studies targeting single inflammatory mediators: unsuccessful
- Imbalance might be more important
- First too much inflammation
- Later too much immunosuppression
- Restoring homeostasis by attenuating excesses more important

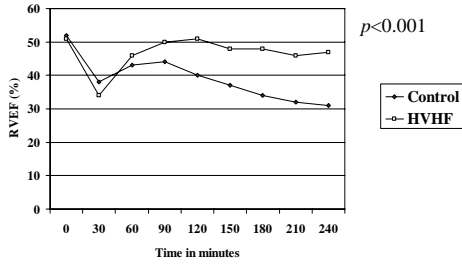
Middle molecular clearance

- Cellulose membranes = none
- Synthetic membranes (high-flux) = some
- Mechanisms: adsorption and little convection
- Nominal pore size (high flux): 20-30 kD
- Functional pore size: mostly < 15 kD
- Standard hemofiltration shows limited adsorption or removal: sufficient "renal" dose but insufficient "immunological" dose
- **We need something more effective**

High-volume hemofiltration

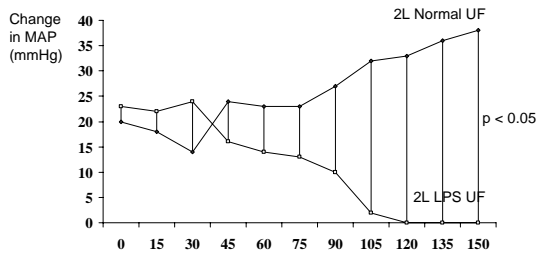
- The term was first used by Grootendorst in 1992
- Animal experiments in pigs (weight 36-39 kg)
- Blood flow 300 ml/min
- UF flow 6000 ml/min
- Replacement fluid given pre-filter
- Polysulfone filters (Amicon, USA)
- IV endotoxin over 30 minutes

HVHF and RVEF



Grootendorst et al, Intensive Care Med 1992

Effect of septic UF on MAP



Grootendorst et al, J Crit Care 1993

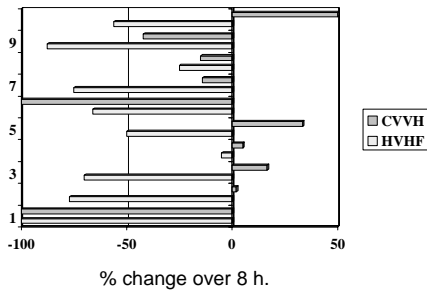
HVHF

- Higher levels of filtration appear safe
- Animal studies show improved BP and EF with HVHF
- No human studies
- Phase I study needed
- Cross-over design

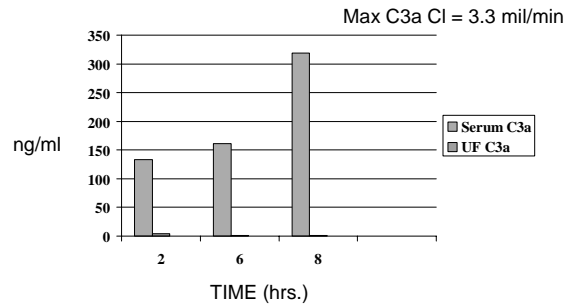
HVHF vs. CVVH

- 10 patients with septic shock and ARF
- Noradrenaline dependent
- Randomized to 8 hrs of HVHF (6L/hr) or CVVH (1L/hr) in random order
- Physiological outcome: hemodynamic response
- Biological outcome: Complement and cytokines

% Change in Norepinephrine Dose: HVHF vs. CVVH



**HVHF:
C3a: Serum vs. UF concentration**



Conclusions

- HVHF has beneficial short term effects in human septic shock similar to those in animals
- With AN69 and molecules >8-9 kD it results in adsorptive removal, not filtration
- There is now a rationale for phase II studies

Short Term-HVHF

- Patrick Honore et al. (CCM 2000; 28: 3581-3587)
- 20 patients in severe refractory septic shock
- 4 hours of HVHF (blood flow 450 ml/min, 1.6 m² Fresenius polysulfone filter, bicarbonate buffer, post-dilution, UF rate 8750 ml/hr)
- Approx. small solute clearance: 116ml/kg/hr

Results

- 11 responders (rapid increase in CI, MVS_{O2}, pH>7.3 and 50% reduction in adrenaline dose)
- 9 of 11 responders survived
- Responders weighed less : 66 vs. 83 kg
- Responders got more UF: 132 ml/kg/min vs. 107 ml/kg/min
- Responders were treated earlier: 6.5 vs. 13.8 hrs

Comments

- No controls
- No randomization
- No predefined criteria of response
- However.....
- Provocative study
- Findings consistent with expectations

HVHF: large series

- Oudemans-van Straaten et al, Intensive Care Med 1999; 25: 814-821)
- 306 patients with SIRS ± oliguria
- UF rate 63 ml/min
- Approx. small solute CI = 56ml/kg/hr
- APACHE II predicted mortality: 67% but actual mortality: 40%
- HVHF safe and feasible

Comments

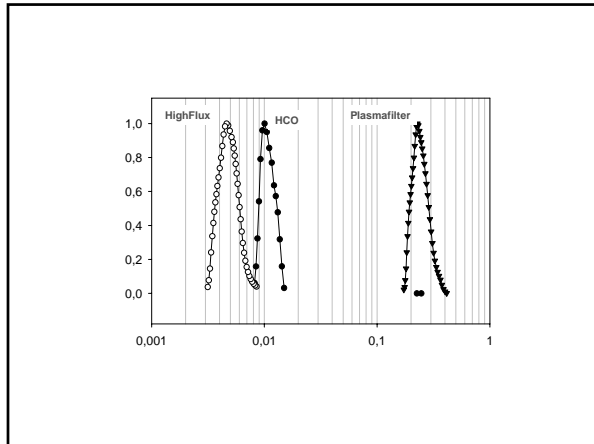
- We have no consensus definition for the term “HVHF” but we have several phase I studies and observational data suggesting that “more” UF might be useful sepsis.
- We have limited understanding of mechanisms, dose and duration, however, and no markers like urea
- Still...the data look promising

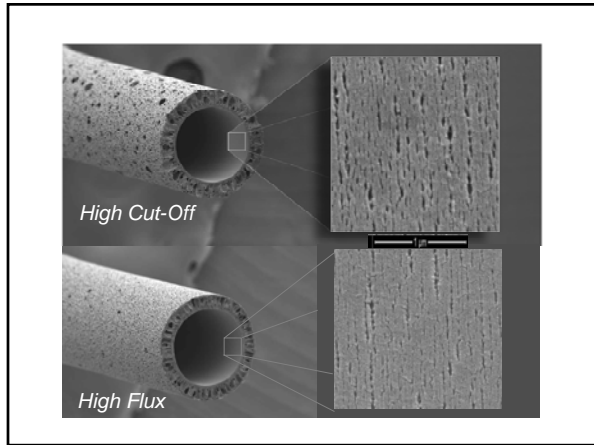
Comments: So...why isn't everyone using HVHF?

- Technically demanding and labour intensive
- Fluids are expensive – may need to generate them on line (limited data on safety)
- Needs trained nurses and doctors
- It is not an injection or a tablet – this makes trials difficult
- Very few centres can do it reliably 24 hrs/day
- Hemofiltration companies are small – can't fund phase III trials
- What else can we do?

High Cut-Off Membranes

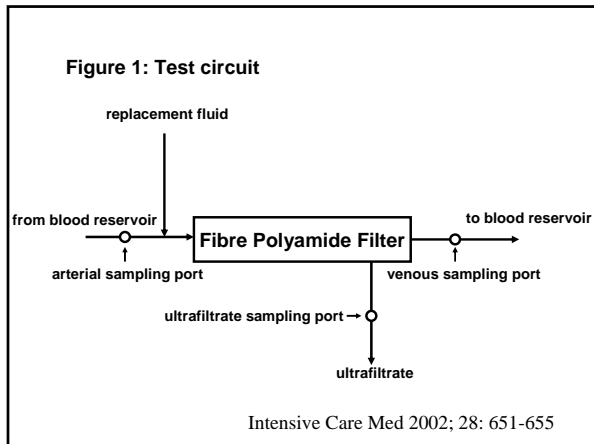
- Potential to increase middle molecular clearance
- Might achieve cytokine clearances as high as current urea clearances
- Should be of biocompatible material
- Should not lead to albumin loss
- **Prototype produced by Gambro for research purposes**

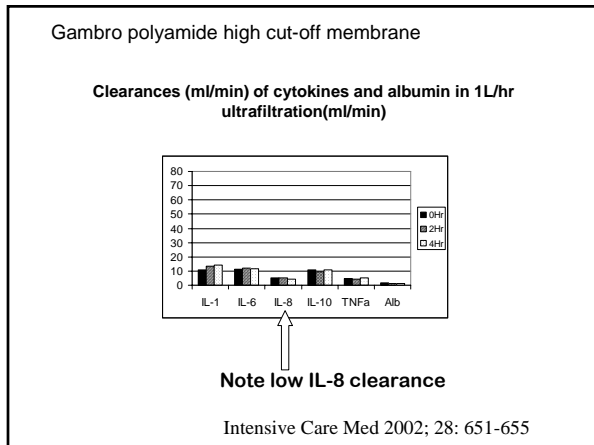


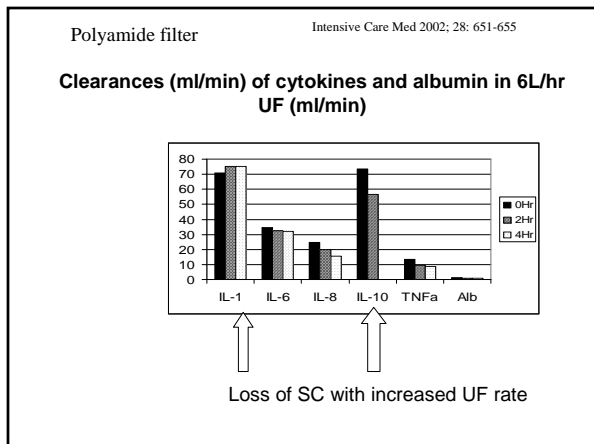


Ex-vivo testing

- 300 ml of fresh blood from volunteer
- Spike with endotoxin
- Incubate at 39 degrees for >4 hours
- Circulate through closed CRRT circuit
- Study membrane properties at different times and under different conditions







Observations

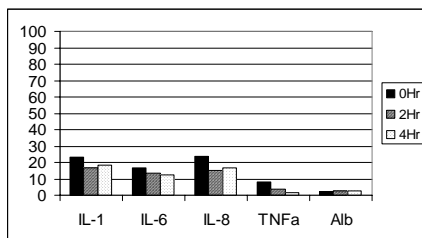
- Increasing UF rate increases clearance but decreases SC
- Time effect small
- Albumin losses sustainable
- Highest cytokine removal ever reported
- There is potential for a biological effect
- However higher volumes are technically demanding and potentially expensive

Can we dialyze cytokines?

- Hemofiltration requires high blood flows
- Without high blood flows, no high UF flow rates
- High UF flows increase TMP and decrease functional pore size
- Replacement fluid expensive
- How about **diffusing** middle molecules?

Polyamide filter

Clearances of cytokines and albumin in 1L/hr dialysis (ml/min)

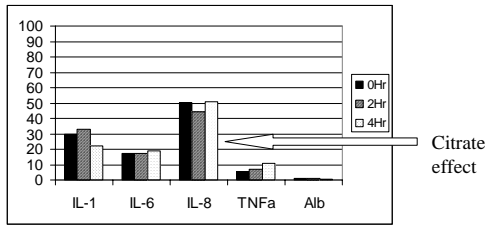


ASAIO J 2002; 48: 650-653

Polyamide filter

ASAIO J 2002; 48: 650-653

Clearances (ml/min) of cytokines and albumin in 9L/hr (150 ml/min) dialysis



Diffusive clearance is clearly possible

High Cut-Off Membranes (Super High Flux)

- Easy to use
- Do not need complex circuit
- Cheap
- Can be used by anyone
- Better middle molecular clearance
- Ideal for treatment of sepsis
- **Does all of this matter clinically?**

Pilot study on the effects of high cutoff hemofiltration on the need for norepinephrine in septic patients with acute renal failure*

Stanislao Morgera, MD; Michael Haase, MD; Thomas Kuss, MD; Ortrud Vargas-Hein, MD; Heidrun Zuckermann-Becker, MD; Christoph Melzer, MD; Hanno Krieg, MD; Brigitte Wegner, PhD; Rinaldo Bellomo, MD; Hans-H. Neumayer, MD

Objective: High cutoff hemofilters are characterized by an increased effective pore size designed to facilitate the elimination of inflammatory mediators in sepsis. Clinical data on this new renal replacement modality are lacking.

Design: Prospective, randomized clinical trial.

Setting: University hospital, intensive care units.

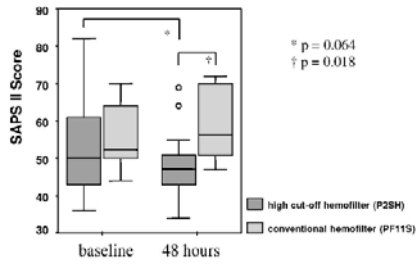
Patients: Thirty patients with sepsis-induced acute renal failure.

Intervention: Patients were allocated to high cutoff (n = 20) or conventional (n = 10) hemofiltration in a 2:1 ratio. Median renal replacement dose was 31 mL/kg/hr. For high cutoff hemofiltration, a high-flux hemofilter with an *in vivo* cutoff point of approximately 60 kilodaltons was used. Conventional hemofiltration was performed with a standard high-flux hemofilter (PF1S). The impacts of high cutoff hemofiltration on the need for norepinephrine and on plasma levels and clearance rates for interleukin (IL)-6 and IL-1 receptor antagonist (IL-1ra) were analyzed. Absolute values, but also adjusted values (expressed as proportion of

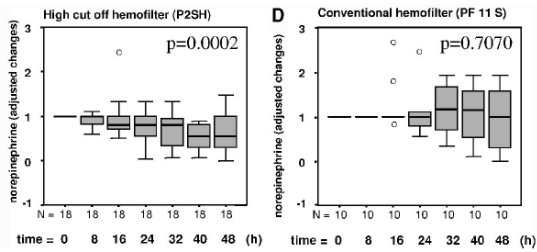
Main Results: Apart from higher antithrombin III levels at entry into the study, main clinical and laboratory parameters were comparable between both groups. The median norepinephrine dose at entry into the study was 0.30 µg/kg/min in the high cutoff group and 0.21 µg/kg/min in the conventional hemofiltration group (p = .446). Only the high cutoff group showed a significant decline (p = .0002) in "adjusted" norepinephrine dose over time. Clearance rates for IL-6 and IL-1ra were significantly higher in the high cutoff hemofiltration group (p < .0001), which translated into a significant decline of the corresponding plasma levels (p = .0465 for IL-6; p = .0293 for IL-1ra).

Conclusion: In this pilot study, high cutoff hemofiltration has been shown to exert a beneficial effect on the need for norepinephrine in septic patients with acute renal failure. In addition, we demonstrate that high cutoff hemofiltration is superior to conventional hemofiltration in the elimination of IL-6 and IL-1ra from the circulating blood of septic patients. (Crit Care Med 2000; 34:2099-2104)

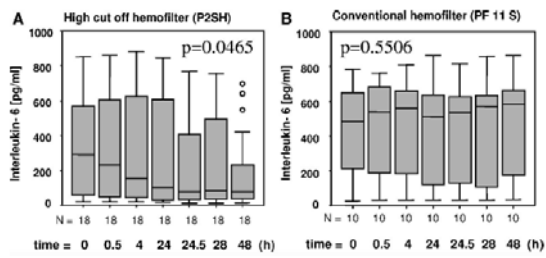
Effect of HCO-HF on SAPS II score



Effect of HCO-HF on norepinephrine dose



Effect of HCO-HF on interleukin-6 levels



Clearances and SC for IL-6 and IL-1ra with HCO-HF

Table 4. Sieving coefficients and clearance rates for interleukin-1 receptor antagonists (ra) and interleukin-6

| | Sieving Coefficient | | | Clearance, mL/min | | |
|------------------------|---------------------|------------------|---------|-------------------|---------------|---------|
| | P2SH | PF11 | p Value | P2SH | PF11 | p Value |
| Interleukin-6 | | | | | | |
| 0.5 | 0.93 (0.89-1.06) | 0.01 (0-0.3) | <.001 | 40 (37-44) | 0.4 (0.1-1.3) | <.001 |
| 4 | 0.93 (0.69-1.00) | 0.01 (0-0.3) | <.001 | 39 (27-41) | 0.1 (0-0.4) | <.001 |
| 24 | 0.84 (6.30-1.03) | 0.00 (0-0.2) | <.001 | 36 (27-45) | 0.1 (0-0.5) | <.001 |
| Interleukin-1ra | | | | | | |
| 0.5 | 0.92 (0.71-1.16) | 0.14 (0.07-0.18) | <.001 | 39 (28-45) | 6.2 (3.1-7.2) | <.001 |
| 4 | 0.92 (0.85-1.02) | 0.08 (0.05-0.20) | <.001 | 39 (30-44) | 3.6 (2.8-8.3) | <.001 |
| 24 | 0.92 (0.81-1.05) | 0.08 (0.05-0.18) | <.001 | 39 (33-43) | 3.5 (2.1-7.6) | <.001 |

Median and quartiles. Clearances are expressed as mL/min.

Preliminary conclusions

- Standard HF with HCO membranes achieves clearances of middle molecules in man consistent with ex-vivo data and expectations
- Such clearances tend to lower middle molecular substances blood levels compared to standard HF
- This decrease is associated with a decrease in norepinephrine requirements
- **Still no data on diffusive clearance in man**
- **One could use B2-MG as a marker**

β_2 -microglobulin removal and plasma albumin levels with high cut-off hemodialysis

M. HAASE^{1,2}, R. BELLOMO³, I. BALDIWIN⁴, A. HAASE-FIELTZ^{1,2}, N. FEALY², S. MORGERA², H. GOEHL¹, M. STORP², N. BOYCE², H.-H. NEUMAYER²

¹Intensive Care Research, Austin Hospital, University of Melbourne - Australia

²Department of Nephrology, Charité University Medicine, Berlin - Germany

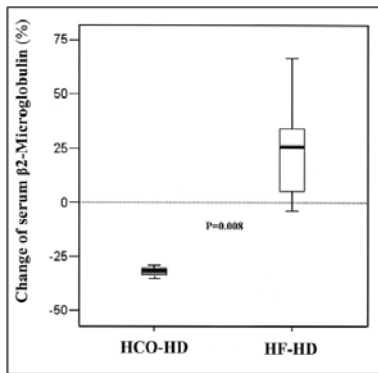
³Gambro Dialysatoren GmbH, Hechingen - Germany

⁴Australian Red Cross Blood Service, University of Melbourne, Melbourne - Australia

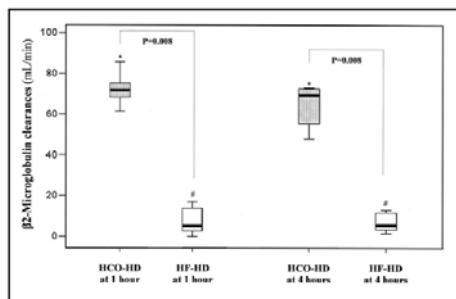
Double-blind cross over design

- Four hours of treatment (A or B)
- One hour wash out
- Four hours of treatment (A or B)
- Random allocation of first treatment
- Blood flow 200 ml/min; Dialysate 300 ml/min
- A = HCO membrane; B = standard membrane (indistinguishable)

Big effect!



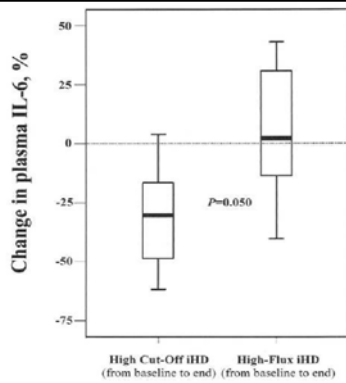
High clearances for a middle molecules
Greater than creatinine clearance for CRRT



Only modest albumin losses – no change in blood levels

Preliminary conclusions

- Can perform HCO hemodialysis in septic man safely
- Albumin losses acceptable
- Striking clearance of marker for middle molecular substances
- **What about cytokines?**



Haase M. Am J Kidney Dis 2007;50:296-304

Effect on four different cytokines

Plasma cytokine clearances at start and end of high cut-off intermittent hemodialysis and high-flux intermittent hemodialysis.

| Cytokine | Clearance at start, mL/min | | <i>P</i> | Clearance at end, mL/min | | <i>P</i> |
|----------|----------------------------|-----------------|----------|--------------------------|-----------------|----------|
| | HCO-IHD | HF-IHD | | HCO-IHD | HF-IHD | |
| IL-6 | 14.1 (5.0-26.9) | 6.6 (0-34.8) | 0.024 | 9.6 (8.2-11.7) | 1.6 (0-11.1) | 0.028 |
| IL-8 | 75.2 (51.4-131.2) | 0 (0-0) | 0.008 | 68.3 (46.9-102.3) | 0 (0-0) | 0.018 |
| IL-10 | 25.5 (12.2-35.4) | 0 (0-0) | 0.015 | 10.5 (4.2-16.3) | 0 (0-0) | 0.018 |
| IL-18 | 11.5 (7.5-30.4) | 0 (0-0) | 0.008 | 6.5 (3.2-18.7) | 0 (0-0) | 0.018 |

Cytokine clearances presented as median (25th - 75th percentiles)

Effect over 4 hours

| Plasma cytokine | HCO-IHD | HF-IHD | <i>P</i> |
|-----------------|-----------------------------|------------------------|----------|
| IL-6 | -13.5 (-22.1-[-0.7]) | 0.9 (-5.6-12.9) | 0.023 |
| IL-8 | -7.2 (-10.9-1.8) | 2.2 (-1.1-7.9) | 0.012 |
| IL-10 | -17.5 (-24.3-7.6) | 0.8 (-8.8-6.5) | 0.006 |
| IL-18 | -17.1 (-25.0-8.2) | 1.8 (-8.3-6.2) | 0.184 |

Relative changes (%) changes presented as median (25th - 75th percentiles);

Preliminary conclusion

- We can perform cytokine dialysis safely and remove a wide array of cytokines
- The clearance is sufficient to lower blood levels over 4 hours by 15-20%
- These phase I data justify further Phase IIa studies in man

Conclusions

- High-cut off membranes represent a logical “next step” in blood purification technology
- The ex-vivo, animal and preliminary human data are internally consistent
- A phase IIa study is now under way for CRRT and one is planned for IHD
- By 2011 we should know whether there is a case for multicentre phase IIb studies
- **This is an exciting development in Critical Care Nephrology**

Conclusions

- The hemofiltration in sepsis story is a complex story to tell – We have only written a few chapters
- Although almost 20 years old, it has not made it into “mainstream” medicine
- Standard hemofiltration clearly “doesn’t do it”
- Because of the technical demands of more advanced techniques, more background work is needed before it can be taken further
- I remain uncertain whether I will ever see a large phase III RCT in my lifetime
