Pro-Con Debate on High Volume Hemofiltration: Burial or Resurrection? The Pro Position

1. Why Moving From Dose To Membranes?

2. High Cut-Off Membranes in Sepsis (SepteX)

3. AN69-ST Highly Adsorptive Membrane in Sepsis

4. AN69 Oxiris LPS Adsorptive Membranes in Sepsis

5. Can AN69 ST and AN69 Oxiris Run Without Anticoagulation?

6. Conclusions-Perspectives

Prof Patrick Honoré, MD, PhD, FCCM Intensivist-Nephrologist
Prof of ICU Medicine, Senior Lecturer, VUB University, Bxl (Bel)
20th Annual CRRT Congress
Manchester Grand Hyatt, California, Feb 2015
Rational for believe that CVVH Post-dilution HFR RCA is the most appropriate therapeutic approach
CRRT is an extracorporeal blood purification therapy intended to substitute for impaired renal function over an extended period of time and applied for or aimed at being applied for 24 hours a day.

- A bridge to renal recovery
  - Restore and maintain homeostasis
  - Eliminate metabolic waste
  - Correcting any metabolic disorder
  - Providing conditions (TBD) to facilitate renal recovery
  - Qualitative and quantitative blood purification

- Hemodynamically unstable patients with the following diagnoses may be candidates for CRRT:
  - Fluid overload
  - Acute renal failure
  - Chronic renal failure
  - Life-threatening electrolyte imbalance
  - Major burns with compromised renal function
  - Drug overdose
  - Sepsis?
Technical background reminders

- Diffusion versus convection
- Dilution versus hemoconcentration
  - Predilution versus Postdilution
  - Filtration Fraction versus Filtration Ratio
- Gibbs-Donnan
- Citrate metabolism and anticoagulation procedure
- Steward approach
FR is looking for Haemoconcentration
Filtration ratio (FR) = (Post + Fluid loss) / Qs

Exemple

Qs : 250 ml/min = 15000 ml/h
Quf : 3000 ml/h (Post only)
FR = 0,2 (20%)

Qs : 200 ml/min = 12000 ml/h
Quf : 3000 ml/h (Post only)
FR = 0,25 (25%)
UF vs Qs : Filtration Ratio (FR)

FR = 33%

EVEN IF PRE-DILUTION IS USED

FR = HAEMOCONCENTRATION CONTROLLED VALUE
Filtration fraction (FF) = 
(Post + Pre + FL) / (Qs + 

Exemple

Qs : 250 ml/min = 15000 ml/h 
Quf : 3000 ml/h (Post (2000)+ Pre (1000)) 
FF = (3000 / 16000) 
FF = 0,18 (18%)  FR = 0,13 (13%) 

Qs : 250 ml/min = 15000 ml/h 
Quf : 2000 ml/h (Post only) 
FF = 0,13 (13%)  =FR
Some examples

<table>
<thead>
<tr>
<th>QS (ml/min)</th>
<th>QS (ml/h)</th>
<th>Post (ml/h)</th>
<th>Pre (ml/h)</th>
<th>FLR (ml/h)</th>
<th>FF</th>
<th>FR</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>12000</td>
<td>3000</td>
<td>0</td>
<td>0</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>200</td>
<td>12000</td>
<td>3000</td>
<td>2000</td>
<td>0</td>
<td>36%</td>
<td>25%</td>
</tr>
<tr>
<td>200</td>
<td>12000</td>
<td>1000</td>
<td>2000</td>
<td>0</td>
<td>21%</td>
<td>8%</td>
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<tr>
<td>200</td>
<td>12000</td>
<td>0</td>
<td>3000</td>
<td>0</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>200</td>
<td>12000</td>
<td>3000</td>
<td>500</td>
<td>2000</td>
<td>44%</td>
<td>42%</td>
</tr>
<tr>
<td>200</td>
<td>12000</td>
<td>4000</td>
<td>0</td>
<td>0</td>
<td>33%</td>
<td>33%</td>
</tr>
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</table>
### Pre/post : Measured Clearance variation

<table>
<thead>
<tr>
<th>Pre/Post</th>
<th>0</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PTM</strong> (mmHg)</td>
<td>90 ± 17</td>
<td>82 ± 15</td>
<td>75 ± 19</td>
<td>70 ± 18</td>
<td>62 ± 15</td>
</tr>
<tr>
<td><strong>ΔP</strong> (mmHg)</td>
<td>64 ± 6</td>
<td>58 ± 7</td>
<td>54 ± 7</td>
<td>52 ± 5</td>
<td>50 ± 5</td>
</tr>
<tr>
<td><strong>CI_{créat}</strong> (ml/min)</td>
<td>17,5 ± 1,2</td>
<td>15,4 ± 1,3</td>
<td>12,5 ± 1,4</td>
<td>10 ± 1,4</td>
<td>9 ± 1,5</td>
</tr>
<tr>
<td><strong>CI_{urée}</strong> (ml/min)</td>
<td>16,4 ± 1</td>
<td>14,3 ± 1,1</td>
<td>11,8 ± 1,1</td>
<td>9,4 ± 1,2</td>
<td>8 ± 1,1</td>
</tr>
</tbody>
</table>
Clearance

FF = Fraction of Plasma water volume reported per molecule filtrated

Sie = Sieving coefficient is capacity of molecule to be filtrated through filter

Clearance = Volume of specific molecule removed by treatment

= [Blood concentration] x Sie x FF
FF and FR with RCA

PRE = PRE + Citrate

POST = POST + Calcium

FF = \[
\frac{POST + PRE + Cit + Cal + FL}{(Qs + PRE + Cit)}
\]

FR = \[
\frac{POST + Cal + FL}{Qs}
\]
CVVH dose in ARF

- Prospective randomized trial: N= 425 in ICU ARF
- CVVH with post-dilution; Qb 145~207 ml/min
- Gr I: Uf=20ml/H/Kg
- **Gr II: Uf=35ml/H/Kg**
- Gr III: Uf=45ml/H/Kg
- **Survival at 15 days after CVVH: (adjusting)**
  - Gr I: 41% < Gr II: 57% (p=0.0007) ∞ Gr III: 58% (p=0.0013)
- Renal recovery of survivors at D15:
  - Gr I: 95%; Gr II: 92%; Gr III: 90%
- Early start in all group survivors
Prospective randomized trial: N= 200 in ICU ARF
CVVHDF with pre-filter replacement fluid; Qb 100~150 ml/min
Survival at ICU discharge or 30 days
Gr I: 56%; Gr II: 49% (p=0.32)
Renal recovery in survivors:
Gr I: 80%; Gr II: 69% (p=0.29)
Gr I: Effluent rate=20ml/H/Kg
Gr II: Effluent rate=35ml/H/Kg
A difference in survival or renal recover: not detected
Dialysis dosing in critically ill patients with AKI

- Multicenter randomized trial: enrollment of 1164 to achieve a 10% difference in mortality rate with statistical power of 90% with P value of 0.05

- Hemodynamically stable: IHD

- Unstable: CVVHDF (total effluent rate: 35 or 20 ml/Kg/Hr) or SLED (6 or 3 times per week)

- Primary end point: 60-day all cause mortality

- Mortality: 53.6% in intensive; 51.5% in less-intensive

- Renal/Non renal organ recovery rate: similar (Palevsky PM et al NEJM 359: 7-20, 2008 (VA/NIH Acute renal failure Trial Network))
Pulse high-volume haemofiltration for treatment of severe sepsis: effects on hemodynamics and survival
Ranistha Ratanarat, Alessandra Brendolan, Pasquale Piccinni, Maurizio Dan, Gabriella Salvatori, Zaccaria Ricci and Claudio Ronco

HVHF 85 ml/kg per hour for 6-8 hours followed by continuous venovenous haemofiltration 35 ml/kg per hour for 16-18 hours). PHVHF was performed with 250 ml/min blood flow rate. The bicarbonate-based replacement fluid was used at a 1:1 ratio in simultaneous pre-dilution and post-dilution. Blood flow rates of 250-300 ml/min, as permitted by the access, were used to achieve a filtration fraction of 20-25% (Not FR) and to prevent premature clotting of extracorporeal circuit.

Conclusion
In summary, PHVHF appears to be feasible and is a promising technique for the treatment of severe sepsis. We demonstrated a clinically and statistically significant beneficial effect of this therapy on vasopressor requirements during treatment and after therapy. It may be a beneficial adjuvant treatment for severe sepsis/septic shock in terms of patient survival, and it represents a compromise between CRRT and HVHF. Further confirmation is required in large, properly designed clinical trials to establish the benefit of PHVHF.

Key messages
- PHVHF represents a feasible compromise between CRRT and HVHF, in which HVHF is applied for short periods of up to 6-8 hours/day and followed by standard dose CVVH.
- PHVHF, when applied in patients with septic shock/severe sepsis, can achieve beneficial effects on vasopressor requirements.
- PHVHF applied on the daily basis and tailored according to clinical response may represent a beneficial adjuvant treatment for severe sepsis/septic shock in terms of patient survival.
Higher dose CRRT improve AKI and Septic AKI survival

- High-volume hemofiltration for septic acute kidney injury: a systematic review and meta-analysis

Edward Clark, Amber O Molnar, Olivier Joannes-Boyau, Patrick M Honoré, Lindsey Sikora and Sean M Bagshaw

Clark et al. Critical Care 2014, 18:R7 http://ccforum.com/content/18/1/R7

Conclusions: Insufficient evidence exists of a therapeutic benefit for routine use of HVHF for septic AKI, other than on an experimental basis. Given the logistic challenges related to patient recruitment along with an incomplete understanding of the biologic mechanisms by which HVHF may modify outcomes, further trials should focus on alternative extracorporeal therapies as an adjuvant therapy for septic AKI rather than HVHF.

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal</th>
<th>Location</th>
<th>Setting</th>
<th>Jadad scale</th>
<th>Primary end point</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boussekey (2008) [25]</td>
<td>Intensive Care Medicine</td>
<td>France</td>
<td>Single-center ICU</td>
<td>3</td>
<td>75% decrease in vasopressor dose after 24 hours</td>
<td>28 days</td>
</tr>
<tr>
<td>Sanchez (2010) [27]</td>
<td>Intensive Care Medicine (abstract)</td>
<td>Spain</td>
<td>Single-center ICU</td>
<td>1</td>
<td>All-cause mortality at 28 days</td>
<td>-</td>
</tr>
<tr>
<td>Zhang (2012) [28]</td>
<td>Nephrology Dialysis Transplantation</td>
<td>China</td>
<td>Single-center ICU</td>
<td>2</td>
<td>All-cause mortality at 28 days</td>
<td>90 days</td>
</tr>
<tr>
<td>Joannes-Boyau (2013) [26]</td>
<td>Intensive Care Medicine</td>
<td>France, Belgium, the Netherlands</td>
<td>18 ICUs</td>
<td>3</td>
<td>All-cause mortality at 28 days</td>
<td>90 days</td>
</tr>
</tbody>
</table>

*aJadad scale for quality appraisal (total possible score, 5) [19].
*bNo discussion of dropouts or withdrawals for any study.
*cStated primary end point “death from any cause within 28, 60, and 90 days after randomization”.

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Boussekey 2008 Intensive Care Medecine

A pilot randomized study comparing high and low volume hemofiltration on vasopressor used in septic shock


- **Prismaflex®**
- Filter 1.4m² polyethersulfone
- Filter cut-off: 20 kDa
- Blood flow to maintain FF< 20%
- substitution: 1/3 pre- 2/3 post
- 2 Patients group: 65 vs 35 ml/kg/h
- **End protocol after 4 days or if stop NA for more than 4h with MAP > 65 mmHg**
- **If RRT is still required:** 35 ml/kg.h
- **End point:** Decrease for NA with MAP > 65mmHg
  -> responders if decrease for more than 75% of NA after 24h of therapy

**Secondary criteria:**
- Mechanical ventilation Time (NS)
- RRT time (NS)
- Last in ICU (NS)
- ICU Mortality (NS)
- Mortality at D28 (NS)

**Table 4** Evolution of norepinephrine dose [μg/kg min] with regard to the 24 h-responder status

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>LVHF</th>
<th>HVHF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-responders n = 6</td>
<td>Responders n = 4</td>
</tr>
<tr>
<td>0</td>
<td>0.99 (0.54–1.17)</td>
<td>0.38 (0.26–0.44)</td>
</tr>
<tr>
<td>6</td>
<td>0.94 (0.78–1.5)</td>
<td>0.28 (0.17–0.39)</td>
</tr>
<tr>
<td>12</td>
<td>0.81 (0.43–1.69)</td>
<td>0.2 (0.1–0.3)</td>
</tr>
<tr>
<td>18</td>
<td>0.73 (0.35–2.66)</td>
<td>0.04 (0.01–0.1)</td>
</tr>
<tr>
<td>24</td>
<td>0.56 (0.27–2.77)</td>
<td>0 (0–0.05)</td>
</tr>
</tbody>
</table>

Variables are expressed in median and quartiles

LVHF low volume hemofiltration, HVHF high volume hemofiltration

P = 0.004
Effect of the intensity of continuous renal replacement therapy in patients with sepsis and acute kidney injury: single-center randomized clinical trial

Ping Zhang, Yi Yang, Rong Lv, Yuntao Zhang, Wenqing Xie and Jiang hua Chen


Materiel and Method
All patients in both groups were treated with continuous venous hemofiltration (CVVH). Replacement fluid was delivered into the extracorporeal circuit at a pre-dilution/post-dilution ratio of 2/1. The replacement fluid was based on patient body weight at the time of randomization and was 50mL/kg/h (HVHF group) or 85 mL/kg/h (EHVHF group). In the first 3 days, 85 mL/kg/h were applied in all patients from the EHVHF group and 50 mL/kg/h in all patients from the HVHF group. After 3 days, if the renal support needed to be continued, the same dose was adopted.
BELIEVE THOSE WHO ARE SEEKING THE TRUTH.

DOUBT THOSE WHO FIND IT.

Andre Gide
5 Large PRT’s on Dose have been negative, so it is Time to move on to the next Therapy....

Recent High Cut-Off (SepteX) Studies are showing that the Technique is safe concerning Albumin losses...

AN69 ST as Hyper-Adsorptive could be a potential New Therapy especially for HMGB-1 but More data are needed..

AN69 oXiris can Adsorb Endotoxin but Human studies are needed..

AN69 ST can not Run Without Anticoagulation...

AN69 ST seems to show that Adsorption could be superior to Convection in Improving Potentially Survival

PRT’s are Eagerly Awaited but first with AN69-ST and after AN-69 -oXiris