The Role of Dialyzers in Cardiac Protection

Prof. Dr. Eng. Jörg Vienken
BioSciences, Fresenius Medical Care,
Bad Homburg, Germany
With a Sense for Details!

Peter Vienken, 11 years

Prof. Pim Kolff, 88 years
The Role of Dialyzers in Cardiac Protection

- Facts of today, figures of tomorrow
- Physiological approaches and properties of dialysers
- Clinical consequences, new targets
- Conclusion
Future Therapy Modifications? Example USA

Prevalence per age group

→ Consequences: variations of dialysis technology?

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Chronic Kidney Diseases & Cardiovascular Problems *

*Cardiovascular event: hospitalisation due to chronic kidney disease, cardiopathy, myocardial infarction, etc

Methods of Dialysis Intensification

......some with dialyser impact

**Time**
- night
- day

**Location**
- in centre
- home

**Frequency**
- 3 x per week
- every 2. day
- daily

**Dialysis Time**
- 2 hrs
- 4 hrs
- 8 hrs
Elderly patients with high profit from longer dialysis treatment times

Re: Charra et al., 1992

5 years survival in Europe, USA and Tassin

USA, mean dialysis time 3 x 3-4 hrs
Europe, mean dialysis time 3 x 4-5 hrs
Tassin, mean dialysis time 3 x 8 hrs

Age at onset of Dialysis

Re: Charra et al., 1992
Improvement of therapeutic performance by a more frequent or more efficient dialysis

Medicines are nothing in themselves if not properly used.

Herophilus, 300 B.C.
Efficient Dialysis by Solvent drag $\rightarrow$ convective clearance

Convective clearance = $Q_F \times SC$

Membrane type:
- lowflux
- highflux

$SC = \text{sieving coefficient}; \ Q_F = \text{filtrate flux}; \ \text{TMP} = \text{transmembrane pressure}$
Filtration Profiles
Low-flux vs high-flux Dialysers

Filtrate flux ($Q_F$) & membrane permeability

In vitro, human blood, Hct.32 %, TP 6 %, $Q_B = 300$ ml/min

Potential avantage in $K_{convective}$
Sieving by size exclusion with polysulfone membranes

Molecular weight

Zone of impermeability

Zone of permeability

PSu F6
Low flux

PSu F60S
High Flux
Fx60

PSu FX CorDiax

Dialysis

Sieving Coefficient

PSu F60S
High Flux
Fx60

PSu FX CorDiax

\[ \beta_2-m \quad \text{Albumin} \quad \text{IgG} \quad \text{Fibrinogen} \quad \text{IgM} \]
Optimization of Membrane Capillaries for their Use in Hemodiafiltration

Fx-Class (Helixone)                          CordiaX   HDF

Larger internal diameter needed to avoid clotting due to hemoconcentration in post dilution HDF
FX CorDiax
Elimination of Uremic Toxins

Comparison of sieving coefficient
FX 60 and FX CordiaX 60

Comparison of aqueous in vitro clearance
QB: 300 ml/min; QD: 500 ml/min,
(EXcor Lab GmbH, Obernburg, Germany 2011)
Clinical Sequelae following Efficient Treatment Modes

→ HD vs onLine HDF with FX-dialysers

![Bar chart showing number of treatments without and with hypotension for HD and onLine HDF.](Image)
Concept of modern dialysis machines
Synergies between dialyser and monitor

- Sensors
- Control
- Hydraulics
- Dialyser
- Dialysis machine
- Dialysate Sensors
- Blood Sensors
- Patient Sensors
- OCM®
- BTM, BVM
- BPM
BVM: Automatic Adaptation of Relative Bloodvolume Through controlled Ultrafiltration

The same patient, 2 days later
UFV = 3.6L

Treatment with RBV Control
UFV = 3.8L

RBV: relative Bloodvolume
The dialysis membrane is not a one-way street!
Water Quality in OnLine HDF: Better safe than sorry

Reverse Osmosis → Endotoxin Adsorber (Diasafe I) → Endotoxin adsorber (Diasafe II)

Substitution Fluid → Endotoxin Adsorber (PSu-Filter)

Dialysis Fluid
Polysulfone Capillary Membranes: - adsorptive capacity for endotoxins

In Vitro Assessment of Dialysis Membrane as an Endotoxin Transfer Barrier: Geometry, Morphology, and Permeability

Artificial Organs, 32(9):701–710 (2008)

*Michael Henrie, *Cheryl Ford, *Marion Andersen, *Eric Stroup, †Jose Diaz-Buxo, ‡Ben Madsen, ‡David Britt, and *Chih-Hu Ho

*Dialyzer R&D Department, Fresenius Medical Care North America, Ogden, UT; †Home Therapies Development, Fresenius Medical Care North America, Charlotte, NC; and ‡Biological Engineering Department, Utah State University, Logan, UT, USA
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Inflammation, the main risk factor of CVD
Microinflammation with Impact on Endothelial Damage in a Co-Culture Model

1. Release of cytokines after stimulation of monocytes with bacterial DNA (1.8 µg/ml) in vitro
2. CD14⁺CD16++ monocytes most efficient
3. ROS activity and apoptosis in overlayer endothelial cells

Results of Study

“Toxins” with Elevated Concentrations in Uremia

**Metabolic substances**
- Homocysteine
- p-cresol sulfate
- Indoxyl sulfate
- Asymmetric-dimethyl-arginine (ADMA)

**Inflammatory mediators**
- Complement factor D
- **C-reactive protein (CRP)**
- Cytokines

**Free radicals & products of oxidative cycle**
- Free radicals
- Reactive oxygen species (ROS)
- Ox-LDL
- Carbonyls
- Advanced glycation end-products (AGEs)
Pathomechanism of CRP at the Endothelium

Re: Verma et al., Circulation 2002
The active Role of CRP in AKI
Agonist not only indicator!

SA-PO905

C-Reactive Protein Exacerbates Renal Ischemia Reperfusion Injury
Melissa A. Pegues, Mark Mccrory, Alexander J. Szalai. Medicine, University of Alabama at Birmingham, Birmingham, AL.

Background: Acute kidney injury (AKI) is a serious complication of hypertensive crisis, cardiovascular surgery, and ischemia reperfusion injury (IRI). Mortality from AKI is as high as 80% due to incomplete knowledge of the mechanisms leading to AKI. It is known that a systemic inflammatory response always accompanies AKI and that increasing levels of the acute phase protein C-reactive protein (CRP) associate with worsening of AKI. These studies were undertaken to determine if CRP is actively involved in AKI-and not just marking its occurrence.

Conclusions: Taken together these data indicate that CRP plays an active role in renal IRI induced AKI, perhaps by depressing expression of the inhibitory FcγRIIb receptor and promoting classically activated macrophage polarization. A better understanding of this damaging sequence in AKI will allow for the development of interventions to shorten the course of AKI, prevent the need for hemodialysis, and improve survival.
Immunhistologic Staining for C-reactive Protein (CRP) in myocardial tissue

60-year old man without renal disease

61-year old uremic man

Re: E Ritz et al., Contrib Nephrol, 149:1-9 (2005)
Background

General Features of CRP

- CRP, an acute phase protein
- Is released from hepatocytes after IL-6 stimulation.
- Activates the classical complement cascade.
- Stimulates mononuclear cells to phagocytosis.
- Promotes endothelial dysfunction through downregulation of eNOS (NO ↓).
- Promotes the proinflammatory milieu through ET1- and IL-6- release from endothelial cells.

→ CRP is not only an indicator for inflammation, but acts as an agonist.
Mechanisms leading to Cell Damage

**Cell membrane**

- FcγRⅡa
- C1q
- CR1
- C4
- C2b
- C3b
- CRP
- sPLA2

**Cytoplasm/Cell interior**

- Phosphatidylcholine
- Phosphatidylserine/ethanolamine
- Sphingomyelin

sPLA2 – secretory phospholipase A2
Erythrocytes and Phosphatidyl-Serine (PS)
Filtered uremic plasma factor(s) induce PS* exposure at red cell surface

*PS: Phosphatidyl-Serine,  n = 8

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Summary and Conclusion

- Cardiovascular problems with high incidence in ESRD
  Increased tendency to be expected due to a higher rate of elderly dialysis patients.

- Highly efficient treatments including sophisticated dialysers with chances to counteract
  → onLine HDF, Sensor-controlled UF, ultrapure water

- In depth understanding of CRP mechanisms with chances for new therapies