Novel Extracorporeal Support Technology for SIRS

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The XXth Budapest Nephrology School

Presenter Disclosure Information

- **I will discuss off label (as defined by the FDA) use and/or investigational use of citrate solutions for regional citrate anticoagulation (RCA) during continuous renal replacement therapy (CRRT) in my presentation**

- **I have financial relationships to disclose:**

- **Employee of: Henry Ford Health System, Detroit, MI**

- **Research support: Site PI, SCD-AKI003, CytoPherx, Inc; Site nephrology PI, Euphrates, Spectral, Inc**
- **US and Japanese Patents: Automated RCA Systems**

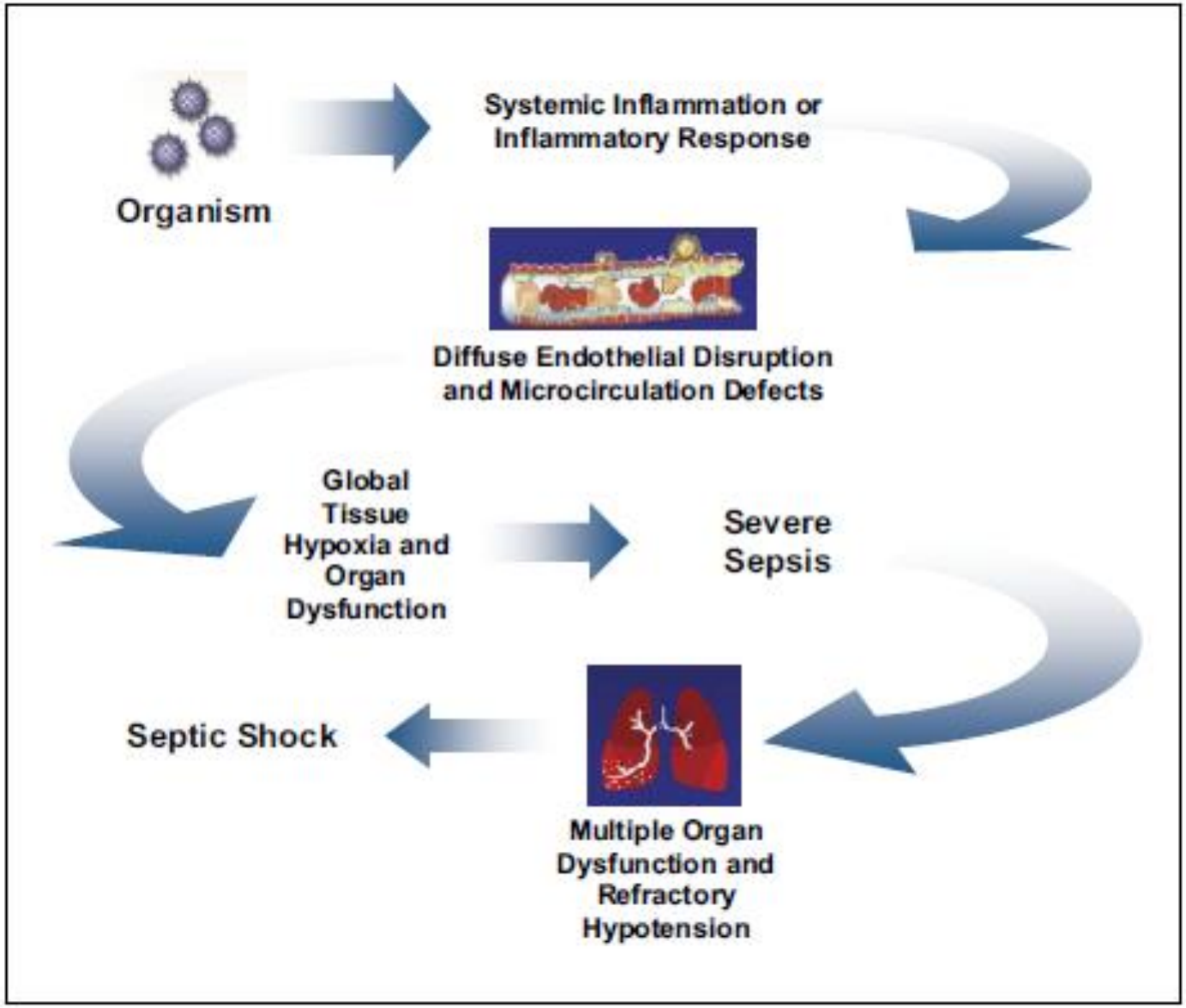
Learning Objectives

1. Understand the rationale for using complex extracorporeal support in SIRS

2. Briefly discuss high volume hemofiltration (HVHF), polymyxine B hemoperfusion, and the selective cytopheretic device

3. Explain why emerging extracorporeal therapies for SIRS may be best deployed in combination with near automated RCA

Infection to Septic Shock



Adapted from: Nguyen et al: Sepsis and Septic Shock…; Ann Emerg Med. 2006;48:28-54.]

Clinical Progression of Sepsis

0% Mortality → 100%

INFECTION
Microorganism invading sterile tissue

SIRS
Host response, with ≥2 of the following:
- T >38.3ºC or <36ºC
- HR >90 /min
- RR >20/min
- Hyperglycemia
- Altered MS
- CRP ↑
- Procalcitonin ↑
- WBC >12,000/mm^3 or <4,000/mm^3 or >10% bands

SEPSIS
- ❑SIRS with
- ❑Presumed confirmed infectious process

SEVERE SEPSIS with MULTI-ORGAN DYSFUNCTION
- ❑**Hemodynamic instability**
- ❑**Acute Kidney Injury**
- ❑**Hemostasis**
- ❑**Acute Lung Injury**
- ❑**Lactic acidosis; abnormal microcirculation**

DEATH
- ❑**Refractory hypotension**
- ❑**Ventillatory Failure**

Dellinger, MD et al: Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012;Crit Care Med 2013; 41:580–637

Sepsis Treatment: Bundles

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4mmol/L

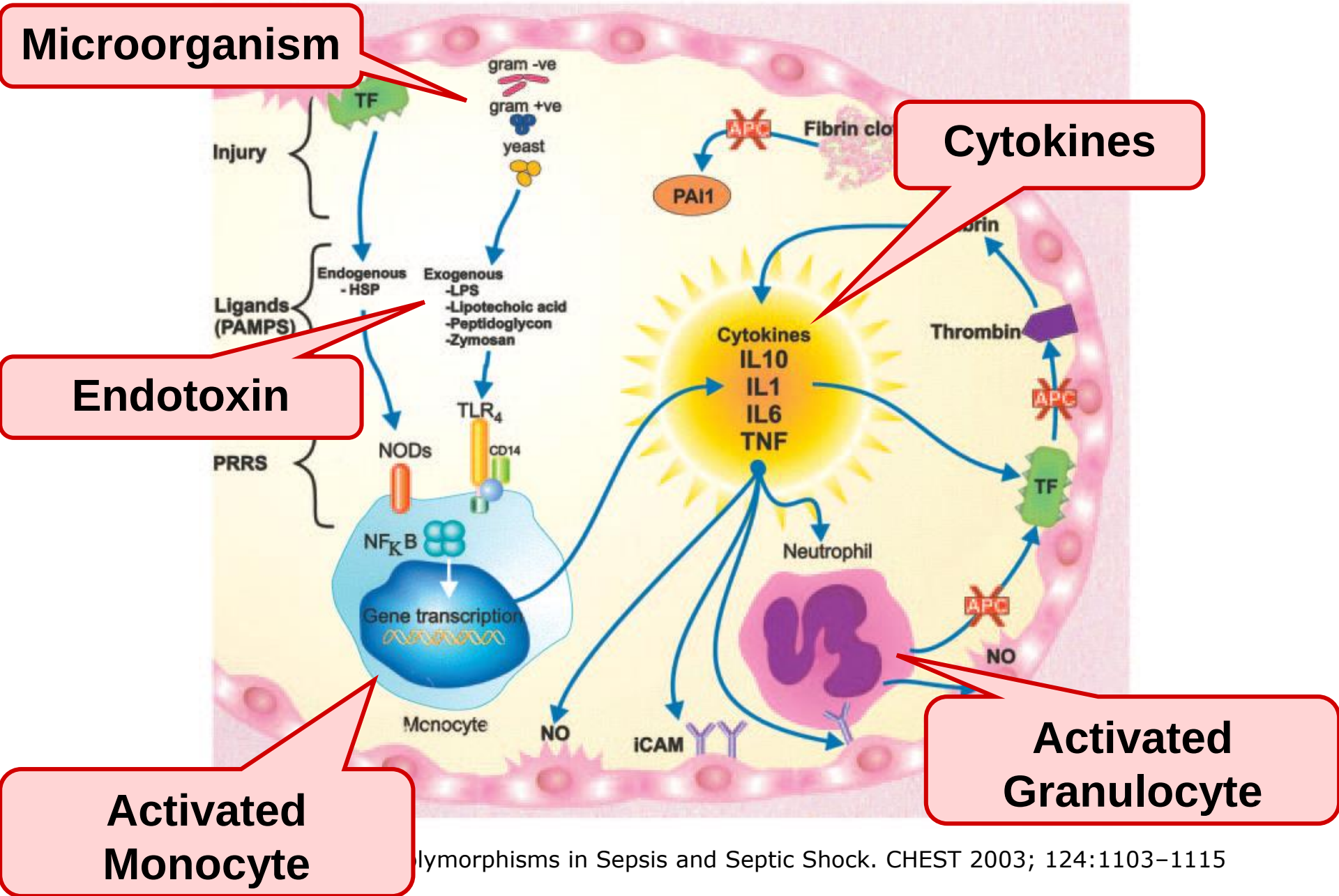
TO BE COMPLETED WITHIN 6 HOURS:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

Dellinger, MD et al: Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012;Crit Care Med 2013; 41:580–637

Extracorporeal Therapy Targets in SIRS



lymorphisms in Sepsis and Septic Shock. CHEST 2003; 124:1103–1115

Extracorporeal Support

- **Veno-venous CO2 removal (VV-ECCO2R)**
  - Allows lung-protective ventilation (LPV; VT <6 ml/kg)
- **Coupled plasma filtration-adsorption (CPFA)**
  - Cytokine and/or plasma element (toxin, protein) removal
- **Cytokine adsorbing hemofilter (CAH)-CHDF**
  - Removes cytokines and endotoxin; provides renal support
- **High Volume Hemofiltration (HVHF)**
  - Cytokine removal; provides renal support
- **Polymyxin B column hemoperfusion**
  - Endotoxin removal, monocyte/granulocyte binding
- **Selective cytopheretic device**
  - Monocyte/granulocyte inactivation; provides renal support

Extracorporeal CO2 Removal

Lung-Protective Ventilation in ALI

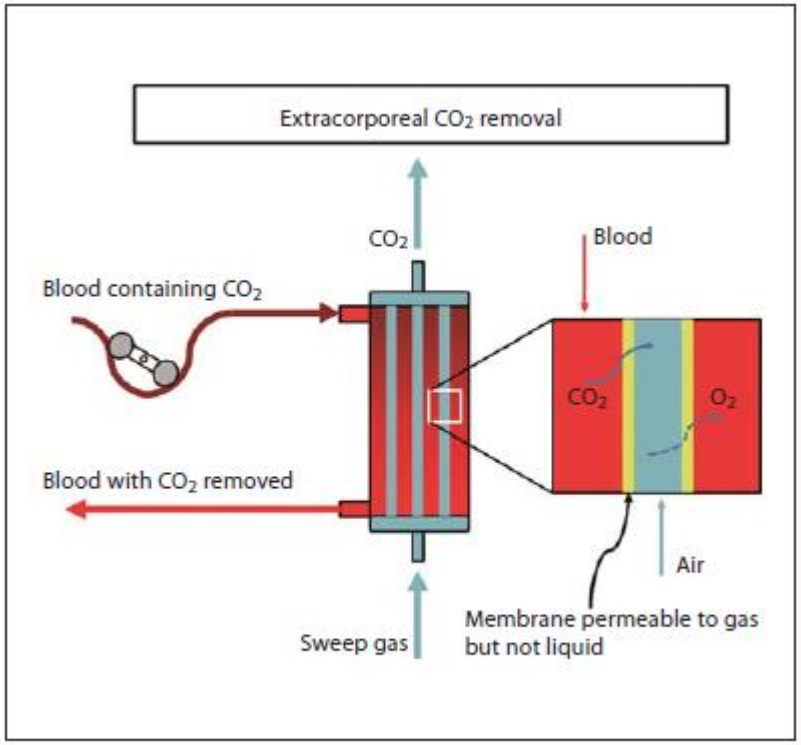


Fig. 1. General scheme of extracorporeal CO_2 removal.

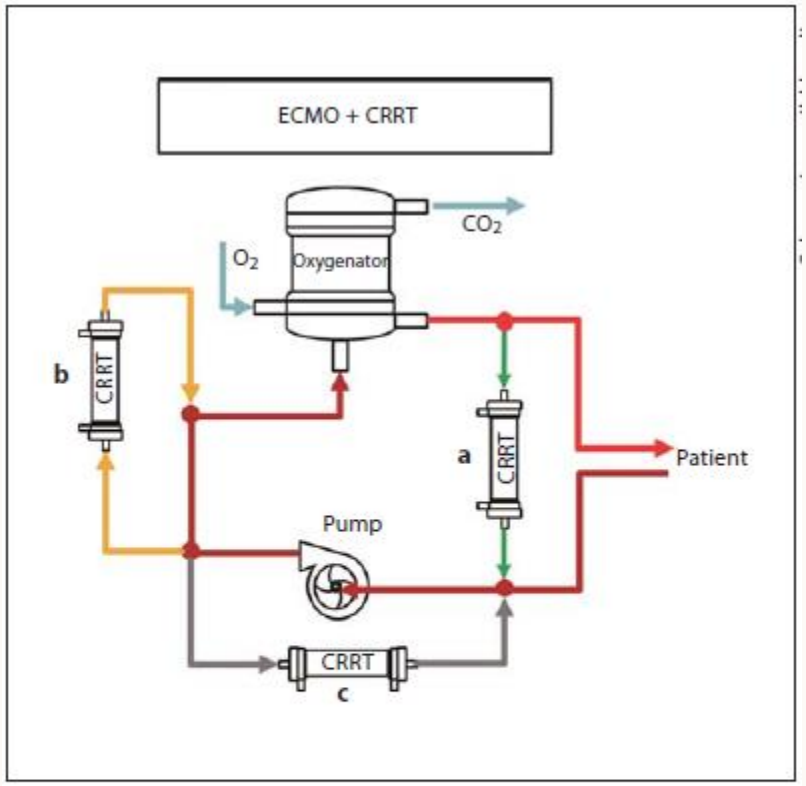


Fig. 5. Possible circuit connections of continuous RRT (CRRT) with ECMO. **a** Continuous RRT 'arterial' pre-pump and continuous RRT 'venous' post-oxygenator [79]. **b** Continuous RRT 'arterial' post-pump pre-filter and continuous RRT 'venous' post-pump and pre-filter [78]. **c** Continuous RRT 'arterial' post-pump pre-oxygenator and continuous RRT 'venous' pre-pump [77].

1. Kaushik et al: Extracorporeal Carbon Dioxide Removal: The Future of Lung Support Lies in the History. Blood Purif 2012;34:94–106

Coupled Plasma Filtration-Adsorption

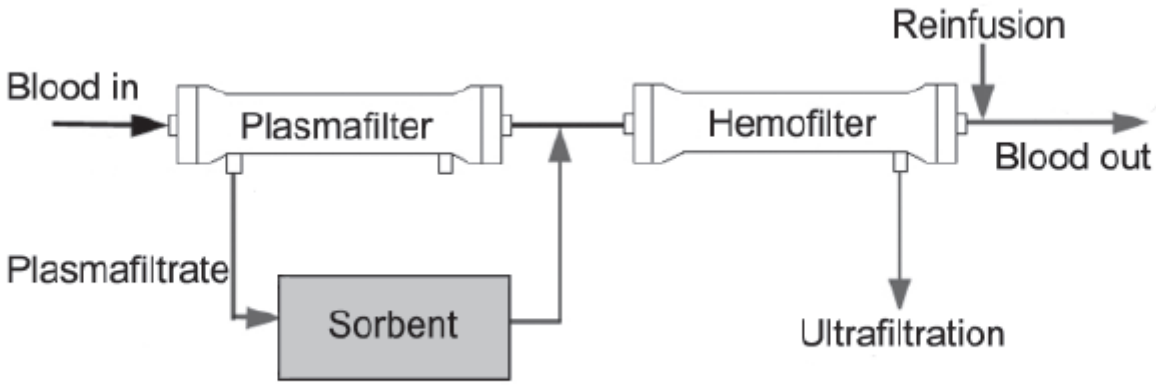


Figure 3. Coupled plasma filtration adsorption circuit.

1. Application

- Cytokine-, endotoxin- and protein-bound toxin removal

2. Limitations

- Complex, large-volume blood circuit at risk of clotting

Rimmelé and Kellum: Clinical Review: Blood purification for sepsis. Critical Care 2011, 15:205
Ronco et al: A pilot study of CPFA in septic shock. Crit Care Med 2002, 30:1250-1255.

Hemofiltration Membranes

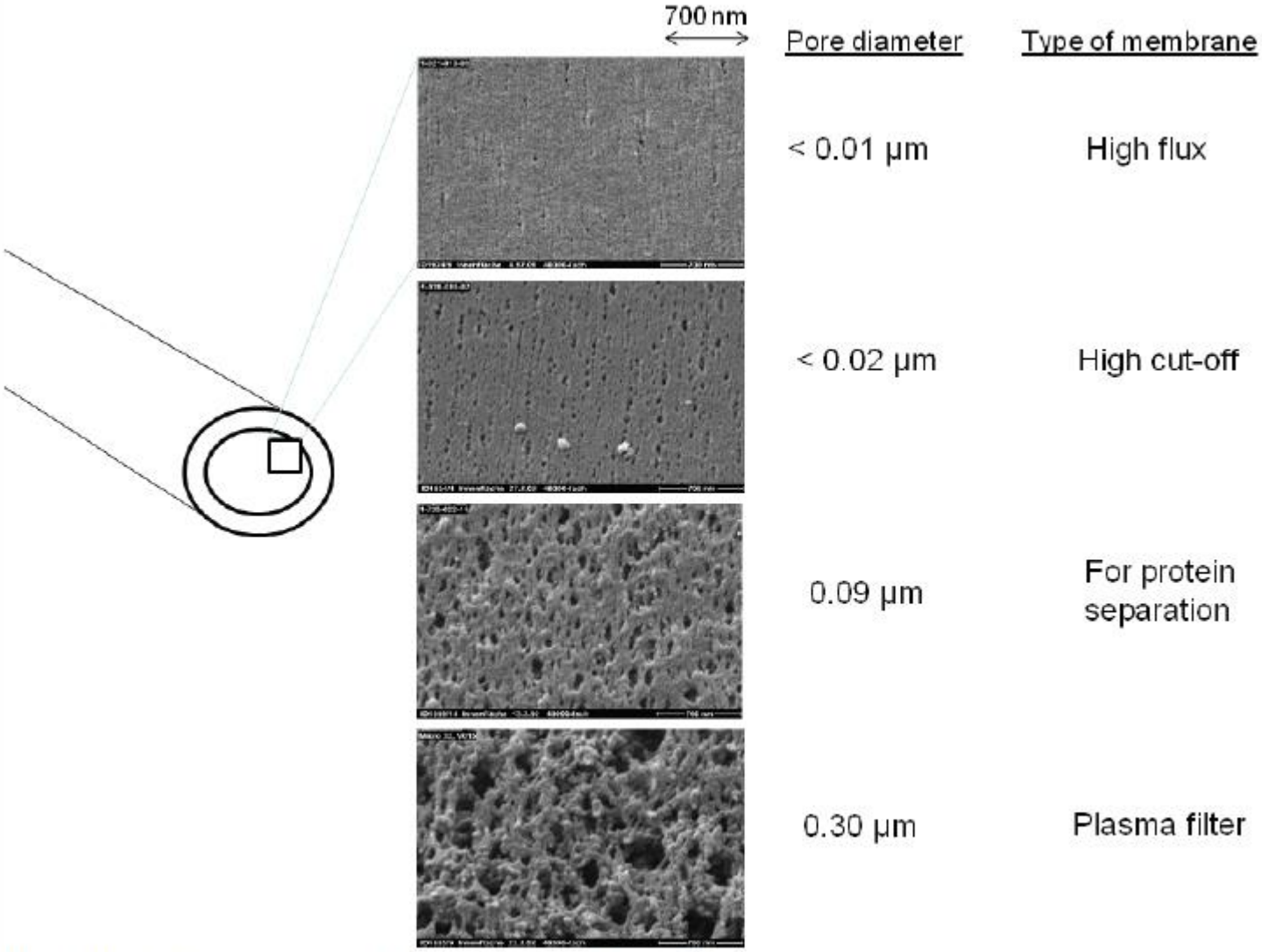


Figure 4. Electronic microscopy images of the internal surface of different filters.

Rimmelé and Kellum: Clinical Review: Blood purification for sepsis. Critical Care 2011, 15:205

High Volume Hemofiltration (HVHF)

Intensive Care Med (2013) 39:1535–1546
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High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial

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On behalf of the IVOIRE Study Group.

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Joannes-Boyau et al: IVOIRE Study Intensive Care Med (2013) 39:1535-1546

IVOIRE Study

1. Significance

- Large (n=140) prospective, randomized study of 28-day mortality of septic shock patients treated with HVHF
- Compared HVHF (70 ml/kg/h) with standard volume hemofiltration (SVHF; 35 ml/kg/h)
- Multi-center study stopped prematurely in 2010 due to slow patient accrual and lack of resources

2. Conclusion

- HVHF as in this trial cannot be recommended for septic shock

3. Limitations

- Possibly started too late in course of sepsis
- Not cytokine-adsorbing membrane (polyethersulfone)
- Heparin used instead of citrate for anticoagulation
- Antibiotic dosing; hypophosphatemia management

High Volume Hemofiltration (HVHF)

Table 1 Baseline patient characteristics according to the randomization group

Characteristics	High-volume HF group ($n = 66$)	Standard-volume HF group ($n = 71$)
Age, years	68 (58–77)	70 (58–75)
Male sex (n, %)	45 (68)	38 (54)
Weight (kg)	79 (65–90)	72 (66–85)
SAPS II score	68 (59–78)	64 (52–74)
SOFA score	12 (11–14)	12 (10–14)
Mean arterial pressure (mmHg)	78 (68–88)	80 (71–89)
Cardiac index (L/min)	3.5 (2.9–4.1)	3.3 (2.6–3.8)
SVRI (dyn s^{-1} cm^{-5})	1,277 (880–1,661)	1,333 (967–1,795)
PaO_2/FiO_2 (mmHg)	139 (87–243)	180 (93–243)
Urea (mmol/L)	19.0 (13.3–29.3)	18.5 (11.0–24.3)
Creatinine (μmol/L)	227 (159–319)	210 (159–276)
RIFLE injury/failure	46/20 (70/30)	57/14 (80/20)
Bilirubin (μmol/L)	18 (9–32)	20 (10–39)
ASAT (U/L)	64 (31–172)	105 (47–253)
pH	7.23 (7.13–7.29)	7.25 (7.17–7.32)
Bicarbonate (mmol/L)	17.15 (14.2–19.0)	18.2 (15.0–21.0)
Sodium, Na^+ (mmol/L)	139 (135–143)	137.5 (135–141)
Potassium, K^+ (mmol/L)	4.5 (4.1–5.2)	4.3 (3.9–4.8)
Lactate, arterial (mmol/L)	3.75 (2.12–6.80)	3.80 (2.47–6.40)
Mechanical ventilation	64 (97)	69 (97)
Noradrenaline (μg/kg/min)	0.87 (0.39–1.20)	0.80 (0.40–1.20)
Inotropic score	86.5 (40–125)	81.9 (41–130)
Vasopressor dependency index ($mmHg^{-1}$)	10.9 (4.8–18.6)	10.9 (5.3–16.0)
RRT prior to enrolment	0	0
Days in ICU prior to enrolment (days[a])	2.44 (0–5.31)	1.87 (1.1–2.64)
Surgical procedure/operative (n, %)	34 (51.5)	35 (49.3)
Corticosteroids (n, %)	36 (54.6)	39 (54.9)
Activated protein C (n, %)	7 (10.6)	6 (8.5)
Fluid therapy (mL/kg)[a]	29.9 (24–35.7)	33.8 (26–41.7)
Crystalloids (mL/kg)[a]	13.6 (10.2–16.9)	17.8 (11.7–23.9)
Synthetic colloids (mL/kg)[a]	9.2 (6.7–11.6)	9.8 (7–12.6)
Albumin (mL/kg)[a]	4.2 (2.2–6.2)	4.3 (3–5.7)
Red cells transfusion (mL/kg)[a]	2.9 (1.6–4.2)	1.9 (0.9–2.9)

Data are reported as median (1st–3rd quartile) for quantitative variables or number (%) for qualitative variables, unless otherwise indicated. Fluid therapy and components were fluids received in the 12 h prior to randomization. See "Methods" section for formulas for inotropic score and vasopressor dependency index

SAPS II Simplified Acute Physiology Score II, PaO_2 partial pressure of oxygen in arterial blood, FiO_2 fraction of inspired oxygen, *SOFA* Sequential Organ Failure Assessment, *SVRI* systemic vascular resistance index, *ASAT* aspartate aminotransferase

[a] Expressed as mean (95 % CI)

Joannes-Boyau et al: IVOIRE Study Intensive Care Med (2013) 39:1535-1546

Timing of Immunotherapy of Sepsis

SHOCK, Vol. 39, No. 2, pp. 127–137, 2013

Review Article

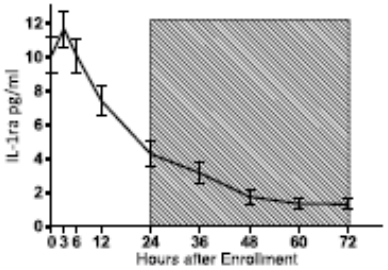
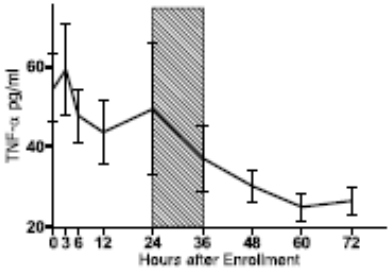
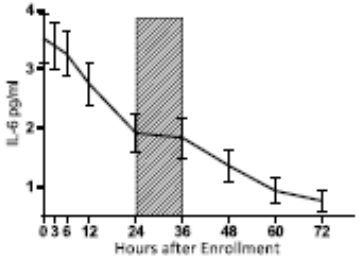
EARLY BIOMARKER ACTIVITY IN SEVERE SEPSIS AND SEPTIC SHOCK AND A CONTEMPORARY REVIEW OF IMMUNOTHERAPY TRIALS: NOT A TIME TO GIVE UP, BUT TO GIVE IT EARLIER

Emanuel P. Rivers,* Anja Kathrin Jaehne,* H. Bryant Nguyen,† Demosthenes G. Papamatheakis,‡ Daniel Singer,§ James J. Yang,‖ Samantha Brown,* and Howard Klausner*

**Department of Emergency Medicine and Surgery, Henry Ford Hospital, Detroit, MI; †Departments of Emergency Medicine and Medicine, Critical Care, Loma Linda University, Loma Linda; and ‡Division of Pulmonary and Critical Care, University of California, San Diego, CA; §Department of Emergency Medicine, Mount Sinai School of Medicine, New York, NY; and ‖Department of Biostatistics and Epidemiology, Henry Ford Hospital, Detroit, Michigan*

Rivers et al: Early biomarker activity in severe sepsis... SHOCK, Vol. 39, No. 2, pp. 127-137, 2013

TABLE 3. **Biomarker activity, temporal description, clinical history, and therapeutic implications**

Early temporal pattern of biomarkers	Literature description of biomarker studies
 IL-1ra levels are highest at 3 h (11.67 ± 11.43 pg/mL) and diminish over 72 h. During the 24- to 36-h interval, circulatory IL-1ra levels have declined by >73% of its peak levels.	IL-1ra plays an anti-inflammatory role (41). Four clinical trials of 1,714 patients have been conducted in humans (42–44). While pooled data show a modestly significant mortality reduction, it is inadequate to gain approval for human use. Enrollment in these studies has been generally within 24–72 h disease onset (44).
 TNF-α levels are the highest at 3 h (59.2 ± 119.1 pg/mL) from presentation followed by a second peak (49.4 ± 170.4) at 24 h. This biomarker is 50% of its peak levels at 48 h.	TNF-α is released during the first 30–90 min in animal and human models after exposure to LPS and decline thereafter (3, 13, 45). In 13 clinical trials comprising >9,413 patients, it is inadequate for general approval for the treatment of sepsis in the United States (46–53). In these studies, the time to drug administration was generally between 24 and 36 h after the onset of diagnosis, which corresponds to 83.4% to 68.3%, respectively, of peak circulatory levels observed (54).
 IL-6 levels are the highest at enrollment (3.53 + 4.26 ng/mL). Levels of IL-6 over time are similar to TNF-α. Levels are maximal at hospital admission and 24–36 h later decline to 50% of the maximum levels.	IL-6 is secreted by T cells and macrophages, stimulates the immune response (55), and is upregulated by TNF-α. The direct antagonism of IL-6 does not improve outcome in animal models (56). In healthy volunteers injected with endotoxin, IL-6 levels peaked at 3 h and reached the baseline concentration at 8 h (57). In ICU-based outcome studies, IL-6 was at its highest concentration at the time of diagnosis (hour 0), with decreasing levels until leveling off at hour 24 (58). Because of the link with TNF, IL-6 levels have been used to determine which patients could benefit from anti–TNF-α therapy (50). We have observed that corresponding levels of IL-6 over time are similar to TNF-α with maximum levels at hospital admission and 24–36 h. These time points are generally before the administration of drug in the aforementioned outcome trials targeting TNF-α.

Barriers to Novel SIRS Therapies

1. **Timing**
   - Intervention usually 36-48 hours after “time zero”
   - Animal studies: intervention sooner than in human trials
   - Understanding of pathophysiology favors earlier intervention
2. **Overestimation of treatment effect**
   - Smaller effect: more subjects for statistical significance
3. **Overestimation of control mortality**
   - Lower control mortality: more subjects needed for statistical significance
   - Clinical mortality risk stratification not accurate enough
   - Biomarker-based subgroup selection (e.g. Gram negative sepsis patients for Euphrates study) rare to date
4. **High complexity CRRT: ? broad use feasible**

CRRT: Risk *vs.* Benefit

RISKS	BENEFITS
Vascular access	Electrolyte control
Electrolyte complications (e.g. hypophosphatemia)	**Citrate anticoagulation**
Acid-base complications	Circuit blood O_2 saturation
Circuit clotting	Circuit blood Hb level
Systemic bleeding	Cytokine adsorption
Hypotension/Hypoxia	Endotoxin removal
Antibiotic removal	Leukocyte inactivation
Worsening SIRS/MODS	**Effluent antibiotic level + chemistry monitoring**

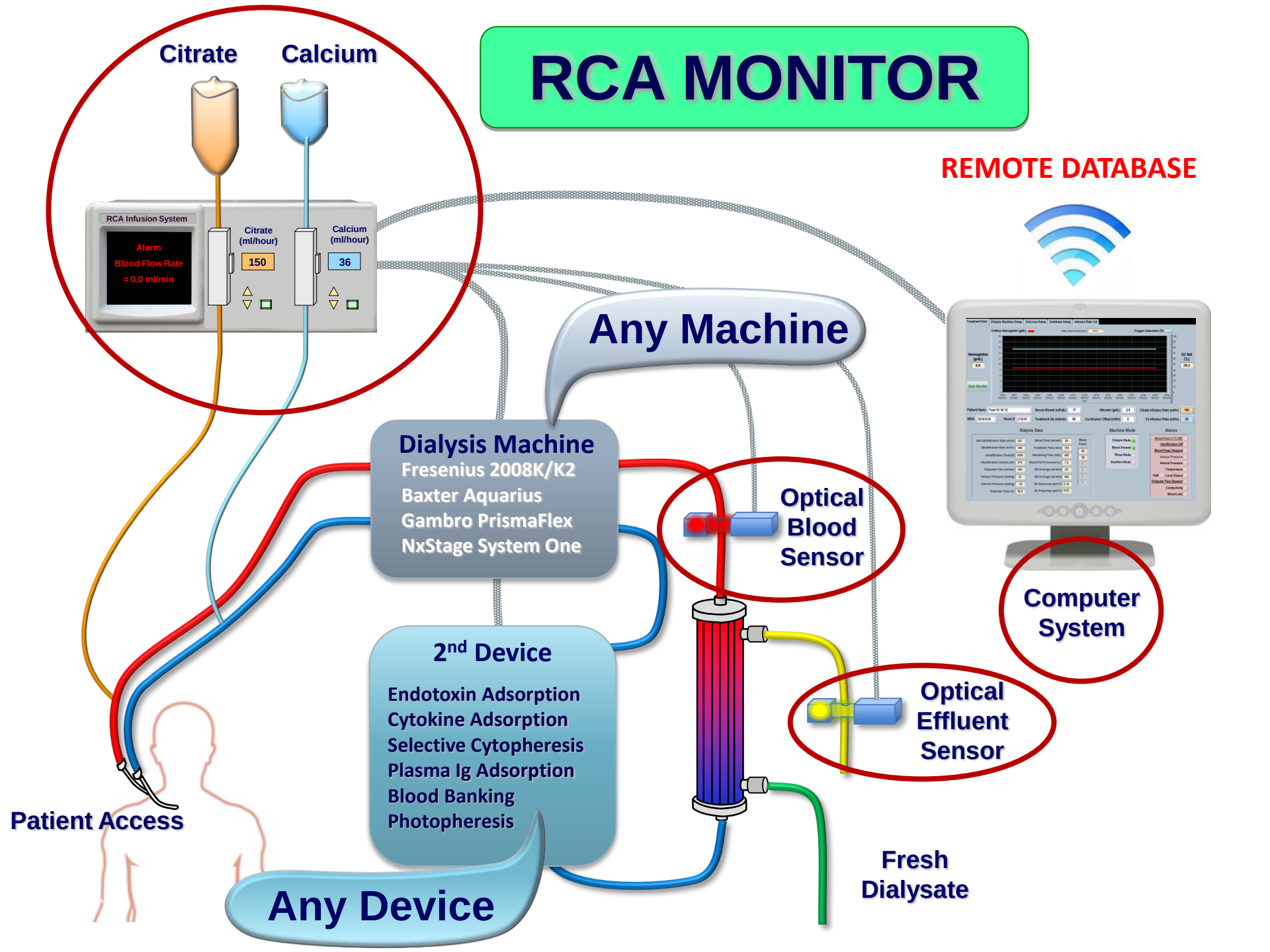
1. Automated RCA

Press for RCA

- Feasible in 1-2 years
- Requires albumin-, citrate- and Ca-sensor development

2. Near-Automated RCA

- Practiced at Henry Ford Hospital
- ICU nurse delivers RCA protocol designed based on the principles of automated RCA
- Uses commercially available equipment in novel combination, incluiding an optical Hct/O_2% sensor


RCA MONITOR
Citrate
Calcium
RCA Infusion System
Alarm
Blood Flow Rate
= 0.0 ml/min
Citrate (ml/hour)
150
Calcium (ml/hour)
36
REMOTE DATABASE
Any Machine
Dialysis Machine
Fresenius 2008K/K2
Baxter Aquarius
Gambro PrismaFlex
NxStage System One
Optical Blood Sensor
Computer System
2nd Device
Endotoxin Adsorption
Cytokine Adsorption
Selective Cytopheresis
Plasma Ig Adsorption
Blood Banking
Photopheresis
Optical Effluent Sensor
Patient Access
Fresh Dialysate
Any Device

Patents & References

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2. Szamosfalvi, B; Frinak, S; Yee, J. “Automated regional citrate anticoagulation: technological barriers and possible solutions.” Blood Purif 2010;29(2): 204-9
3. Yang, Y. J., B. Szamosfalvi, J. Yee, S. Frinak and E. V. Anslyn (2011). "Development of an online citrate/Ca2+ sensing system for dialysis." Analyst 136(2): 317-320
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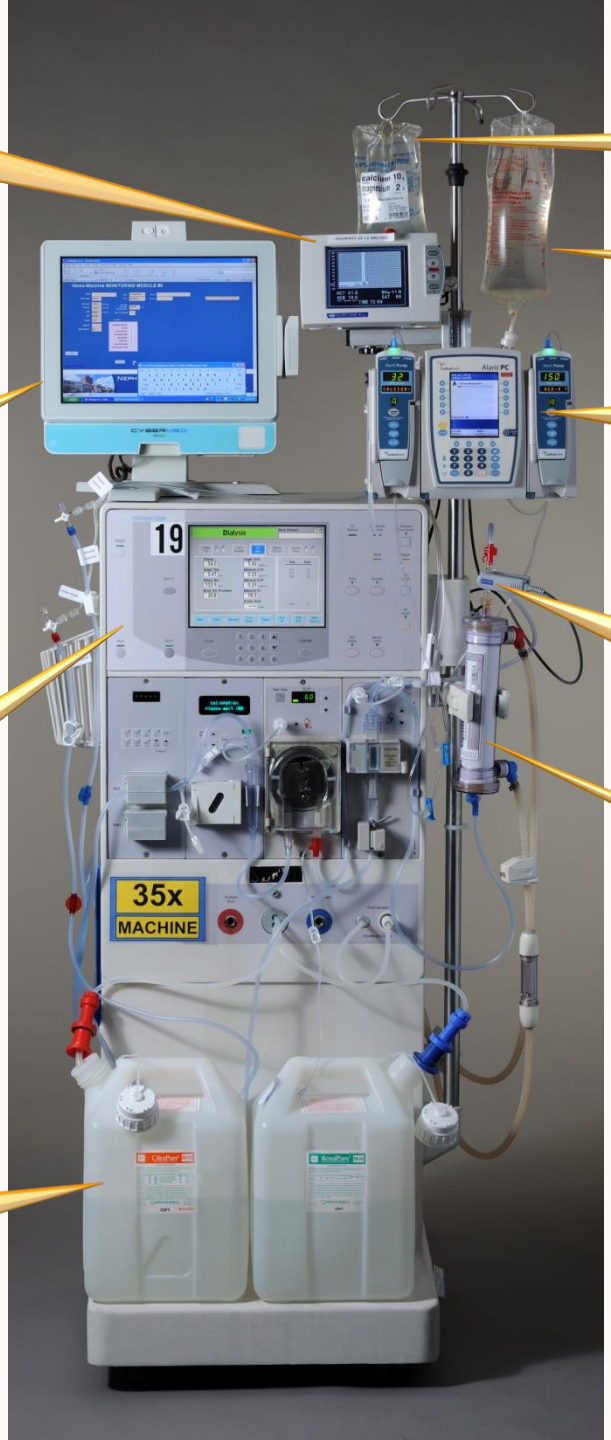
5. ASAIO 58th Conference Renal Abstracts (7) Szamosfalvi, Frinak, Yee, Zasuwa, Yessayan. http://download.lww.com/wolterskluwer_vitalstream_com/PermaLink/ASAIO/A/ASAIO_58_7_2012_05_01_ASAIO_20_SDC20.pdf
6. Budapest Nephrology School, Archived lectures by B. Szamosfalvi 2009-2013. http://bns-hungary.hu/


Hemoglobin Monitor
Calcium
Citrate
Computer System
Infusion Pumps
Hemoglobin Sensor
Dialysis Machine
Dialyzer
Zero Calcium Concentrate
35x
MACHINE

HFH Cost of 72 hours of CRRT ($)

	Traditional CRRT	24-hour SLED-RCA
Filter & Tubing	$300	$45
Fluid/Dialysate	$1000	$50
Citrate/Ca +Lab	$0	$150
Total Cost 72 h	$1,300	$245

SLED-RCA Daily Savings ≈ $350/day/pt

12-month savings at HFHS ≈ $500,000

Henry Ford Hospital ICU Renal Support

	2010 (12 months)	**2012** (10 months)
3-5 hr short HD	2500	2100
SLED Saline (10-hr)	940	70
CVVH 10 or 24-hour	1440	320
SLED-RCA (24-hour)	110	1450
Downtime: SLED-RCA	NA	<5%
RCA Used: % Of All CRRT	4%	80%

Adapted from: Szamosfalvi, B et al: Sensors and Hybrid Therapies. Blood Purif 2012; 34:80–87

24-hour SLED-RCA Program Clinical Performance: 90,000 Patient Treatment Hours to Date

- No citrate accumulation
- No circuit clotting
- No electrolyte abnormalities due to RCA
- Normal systemic iCa even in fulminant liver failure patients

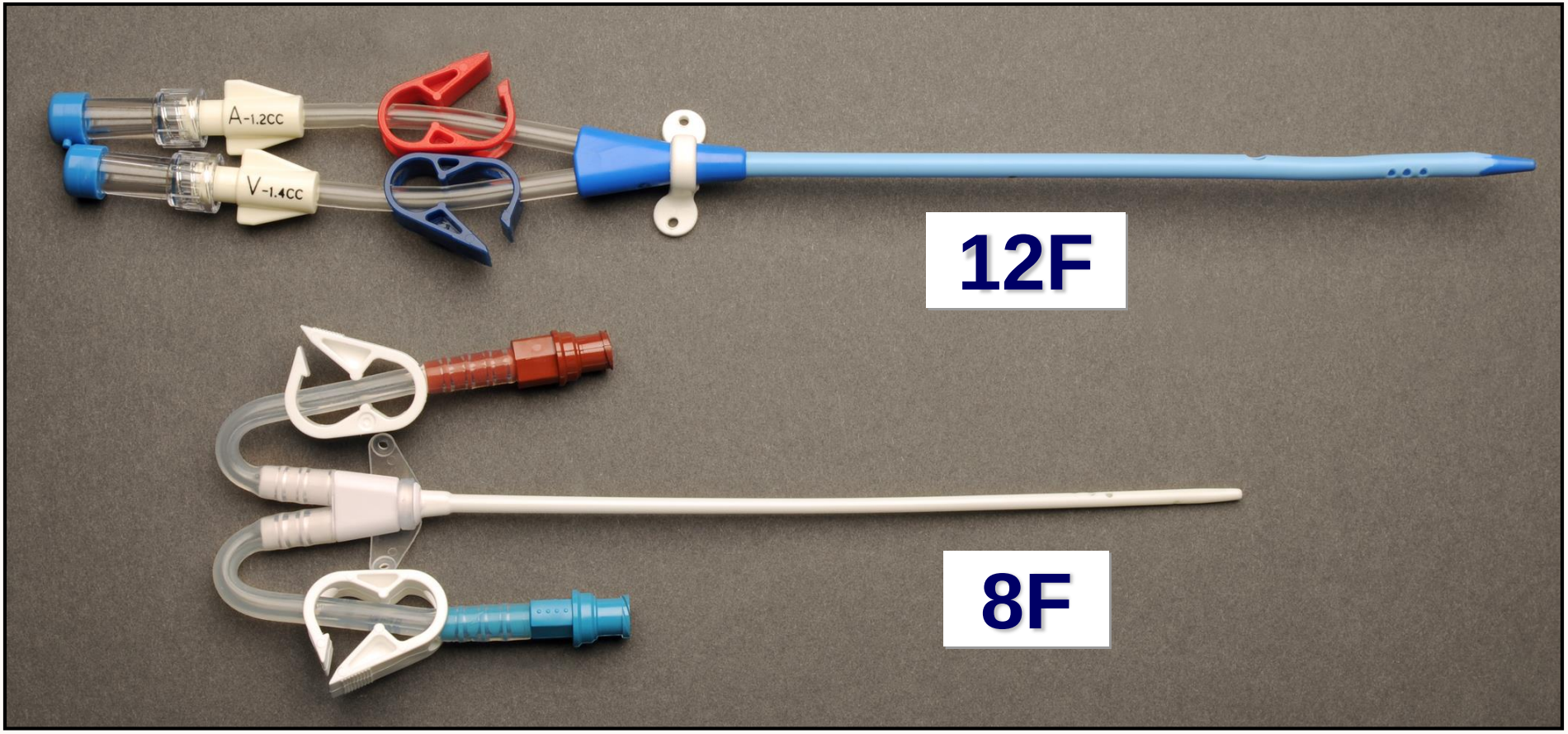
Dialyzer After Saline Rinse Back

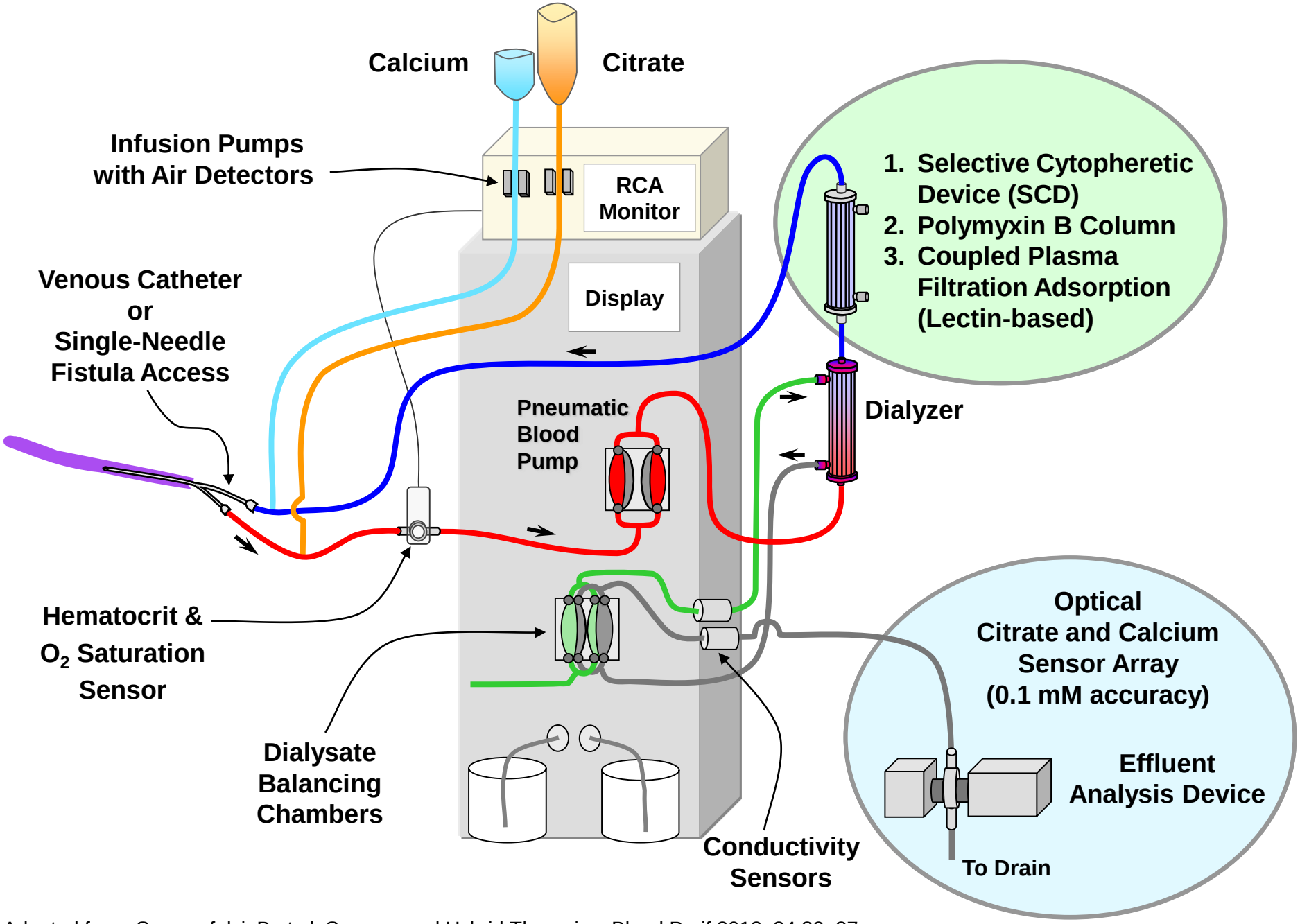
43 hours of dialysis with RCA at blood flow=60 ml/min!

Dialyzer New

Dialyzer After 43 Hours

Low blood flow (60ml/min) allows the use of smaller access catheters





Adapted from: Szamosfalvi, B et al: Sensors and Hybrid Therapies. Blood Purif 2012; 34:80–87

Polymyxin B (PMX) Hemoperfusion (HPF)

Safety and Efficacy of Polymyxin B Hemoperfusion (PMX) for Septic Shock (EUPHRATES)

This study is currently recruiting participants.

Verified July 2013 by Spectral Diagnostics (US) Inc.

Sponsor:
Spectral Diagnostics (US) Inc.

Information provided by (Responsible Party):
Spectral Diagnostics (US) Inc.

ClinicalTrials.gov Identifier:
NCT01046669

First received: January 8, 2010
Last updated: July 4, 2013
Last verified: July 2013
History of Changes

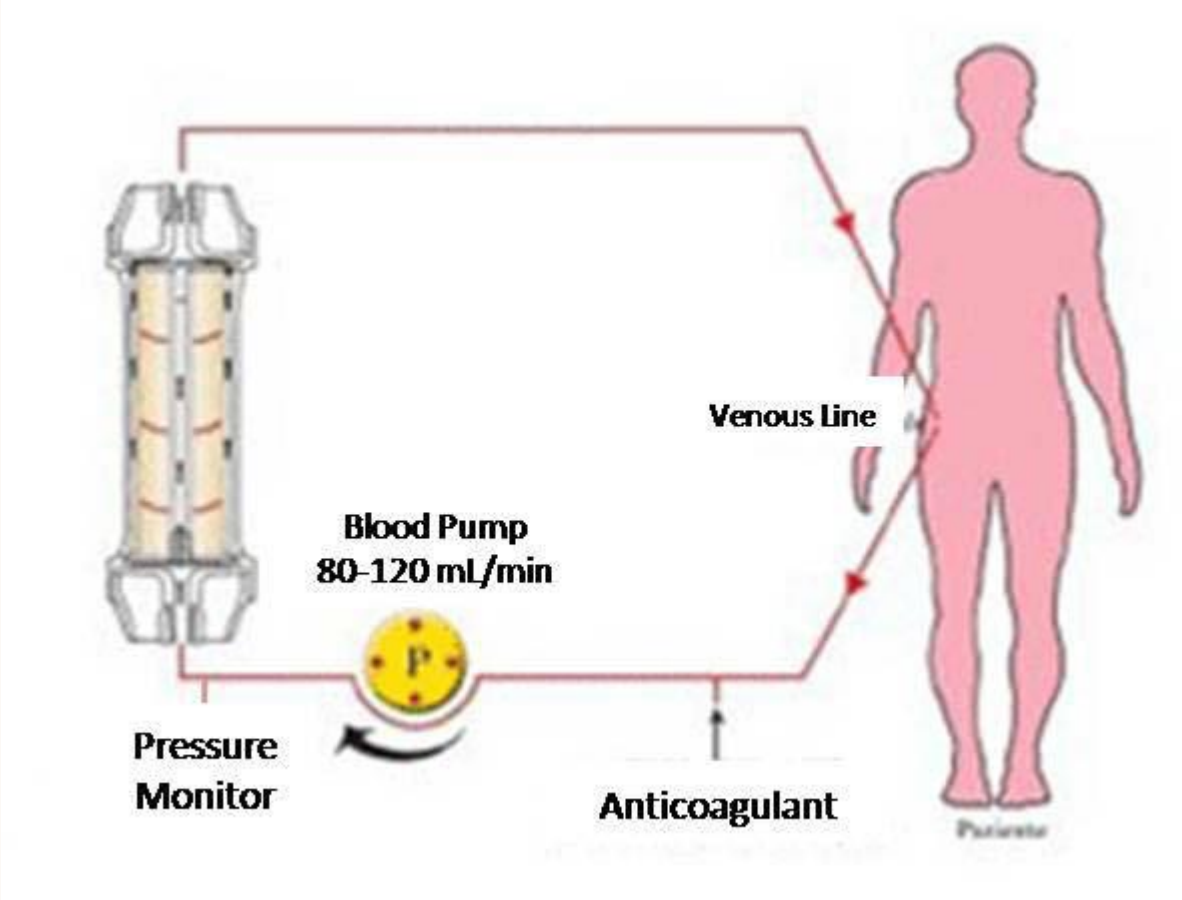
Full Text View | **Tabular View** | **No Study Results Posted** | Disclaimer | How to Read a Study Record

Purpose

To compare the safety and efficacy of the PMX cartridge based on mortality at 28-days in subjects with septic shock who have high levels of endotoxin standard medical care plus use of the PMX cartridge, versus subjects who receive standard medical care alone.

- **Inclusion**: Hypotension requiring vasopressor support; The subject must have received intravenous fluid resuscitation; Documented or suspected infection; Endotoxin Activity Assay ≥ 0.60 EAA units; Evidence of at least 1 new onset organ dysfunction
- Endpoint: 28-day mortality

Polymyxin-B Hemoperfusion (PMX-HPF)
Endotoxin-Removal in Gram- Sepsis



1. Mitaka et al: Polymyxin B immobilized fiber column hemoperfusion SHOCK, Vol. 36, No. 4, pp. 332Y338, 2011

Polymyxin-B Hemoperfusion (PMX-HPF)

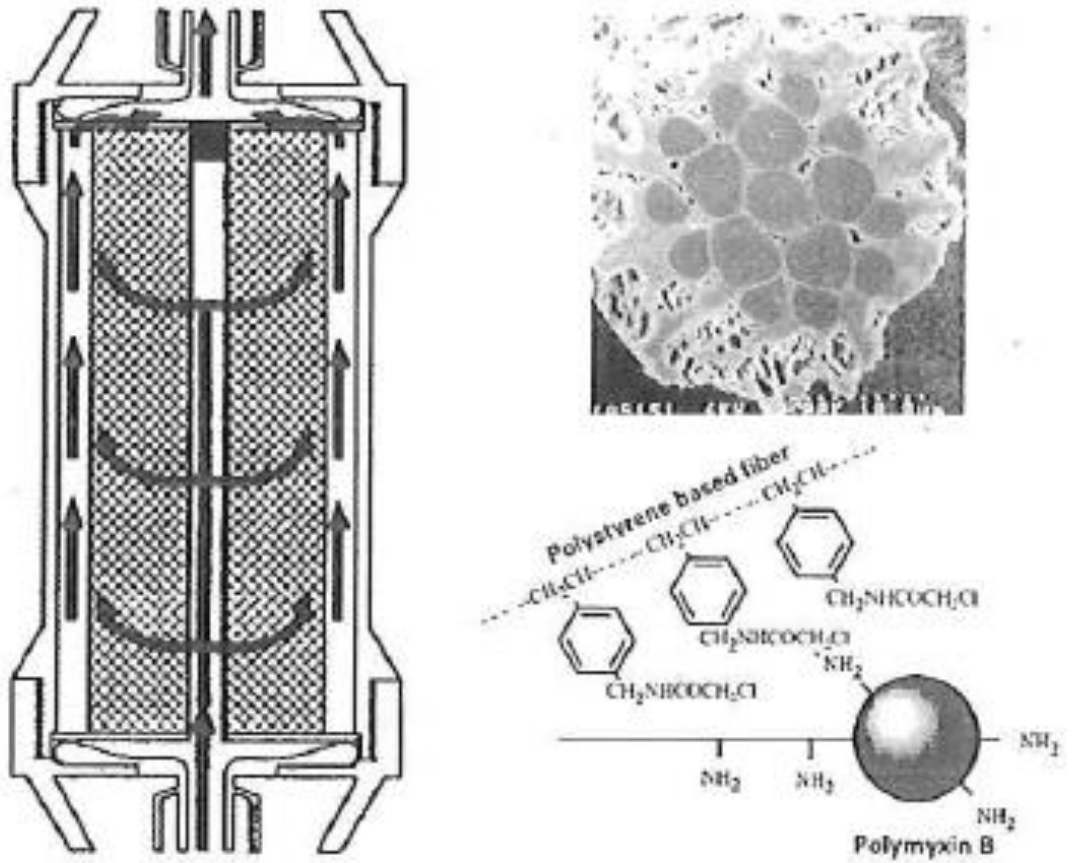


Fig. 1 - *The toraymyxin cartridge contains a fibrous adsorbent made of immobilized polymyxin B covalently bound to α-chloro-acetoamidemethylated polystirene and polypropylene conjugate fiber. In the left panel the typical flow distribution pathways inside the unit are schematically depicted. In the right panel an electron microscopic section of the coated fiber is reported. The chemical binding is described below.*

1. Ronco et al: Blood flow distribution in PMX column IJAO, Vol.24, No. 3, pp. 164-172, 2001

PMX-HPF Features

- **CE approved, meta-analysis favors use[1]**
- **Integration with RCA-CRRT**
  - ? Disruption of ionic endotoxin-PMX binding[2] by citrate
- **Optimal duration of PMX perfusion[3,4]**
  - >2 hours exposure: better outcomes in many diseases
- **Mechanism of action likely more complex[5]:**
  - May include monocyte, leukocyte binding/inactivation
- **Very high cost (9000$/column)**
  - Still appears cost effective[6]

1. Mitaka et al: PMX-HPF in Septic Shock SHOCK, Vol. 36, No. 4, pp. 332-338, 2011
2. Vesentini et al: Molecular interactions of PMX with Endotoxins IJAO Vol. 29, No. 2, pp. 239-250, 2006
3. Kono et al: Evaluation of Different Perfusion Durations in Direct PMX-HPF. Blood Purif 2011;32:75–81
4. Mitaka et al, Duration of PMX-HPF in Septic Shock. SHOCK, Vol. 32, No. 5, pp. 478-483, 2009
5. Kushi et al: PMX-HPF Decreases Macrophage and Monocyte Activity. Ther Apheresis and Dialysis 13(6):515–519
6. Berto et al: Cost-Effectiveness Analysis of PMX-HPF Blood Purif 2011;32:331–340

Selective Cytopheretic Device

Efficacy Study of a Selective Cytopheretic Device (SCD) in Patients With Acute Kidney Injury

This study is currently recruiting participants.

Verified January 2013 by CytoPherx, Inc

Sponsor:
CytoPherx, Inc

Information provided by (Responsible Party):
CytoPherx, Inc

ClinicalTrials.gov Identifier:
NCT01400893

First received: July 21, 2011
Last updated: January 14, 2013
Last verified: January 2013
History of Changes

Full Text View | **Tabular View** | **No Study Results Posted** | Disclaimer | How to Read a Study Record

Purpose

The purpose of this protocol is to evaluate the safety of a selective **cytopheretic device** (SCD) in patients that are on continuous renal replacement th
acute kidney injury (AKI).

- **Inclusion**: Presence of severe sepsis; ATN due to hemodynamic or toxic etiology; Must be able to tolerate regional citrate anticoagulation and CRRT
- Endpoint: 60-day mortality after randomization

REGULATION AND MODULATION OF NEUTROPHIL KINETICS

Adverse Neutrophil Activation

Systemic Inflammatory Response Syndrome (SIRS)

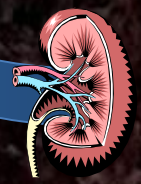
Endothelial Dysfunction

Capillary Leak & Occlusion

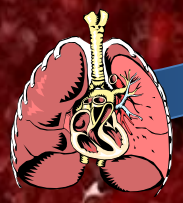
Neutrophil Tissue Infiltration

Poor Tissue Perfusion Ischemia

Toxic Tissue Injury



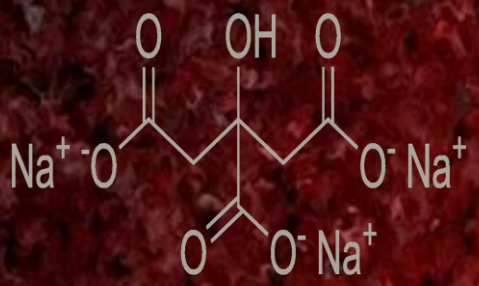
Multi-Organ Failure
ARF/ ARDS



Slide courtesy of Prof. D.H. Humes, Univ. of Michigan

Selective Cytopheretic Device (SCD)

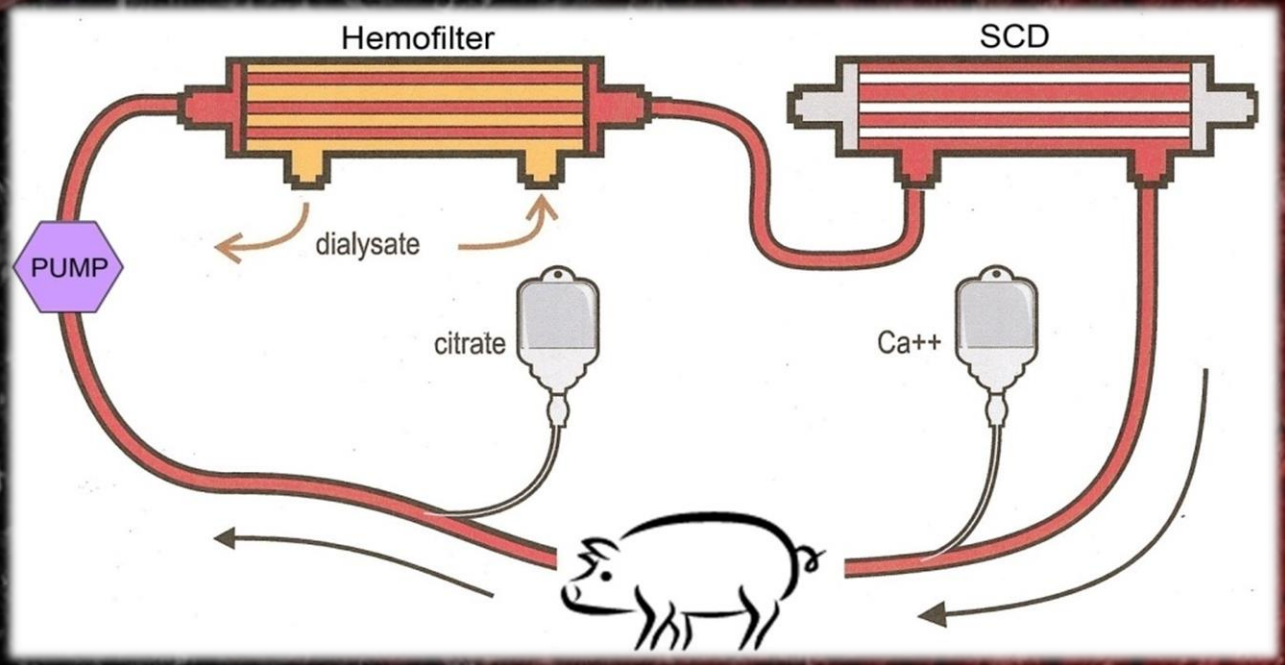
Cell processing therapeutic device which modulates neutrophil kinetics in a low iCa++ environment



0.25 - 0.4 mmol/l iCa++

Slide courtesy of Prof. D.H. Humes, Univ. of Michigan

Porcine Model of Septic Shock

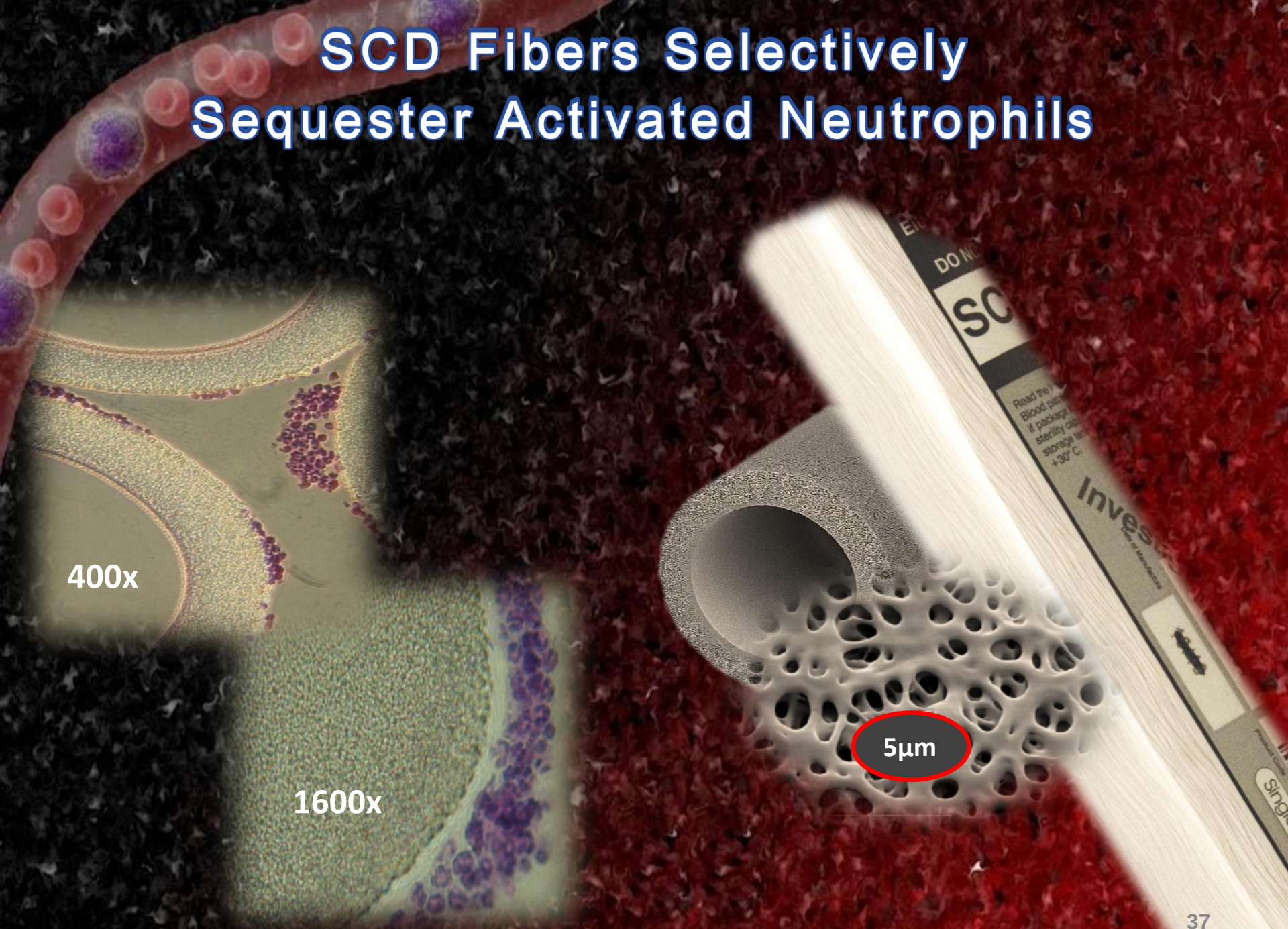


Conventional single-pump extracorporeal circuit using a polysulfone hemofiltration cartridge along with the SCD

- Cardiac output
- Pulmonary vascular resistance
- Hematocrit
- Myeloperoxidase
- CD11b expression
- Immunohisto analysis of lung tissue
- Survival Time

Slide courtesy of Prof. D.H. Humes, Univ. of Michigan

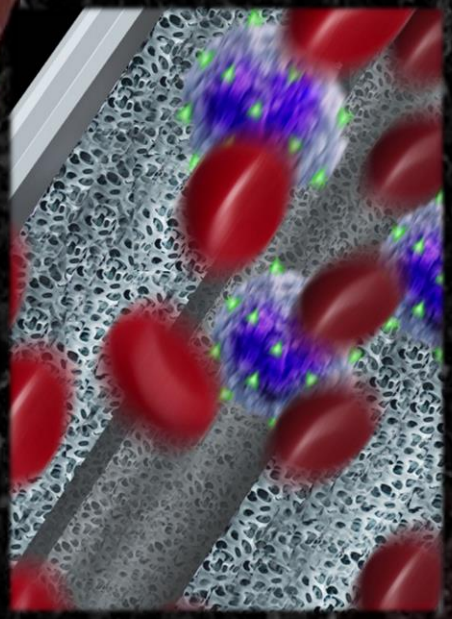
SCD Fibers Selectively Sequester Activated Neutrophils



Slide courtesy of Prof. D.H. Humes, Univ. of Michigan

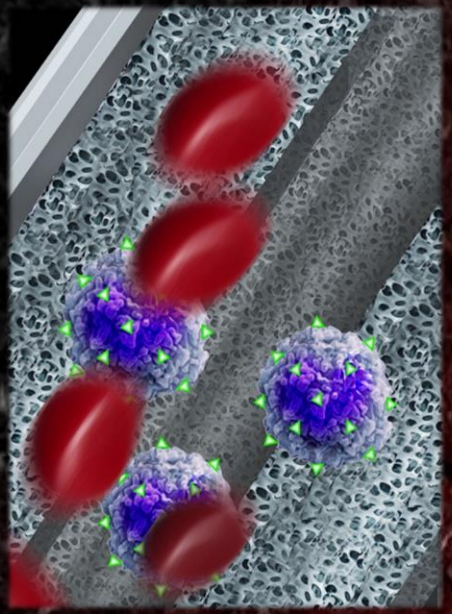
Catch & Modulate, then Release

Blood flows outside and between fibers



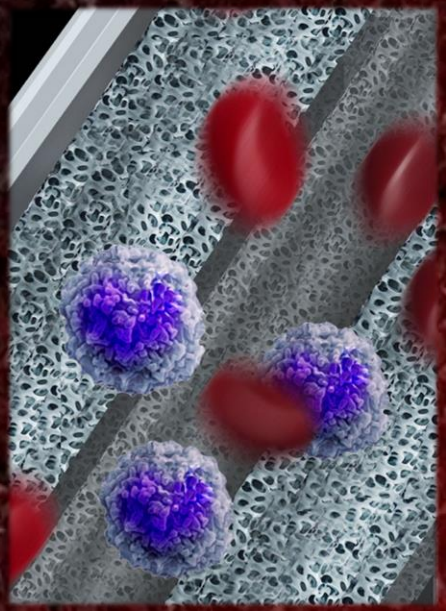
Flow rate and shear forces mimics capillary sheer

Neutrophils become sequestered



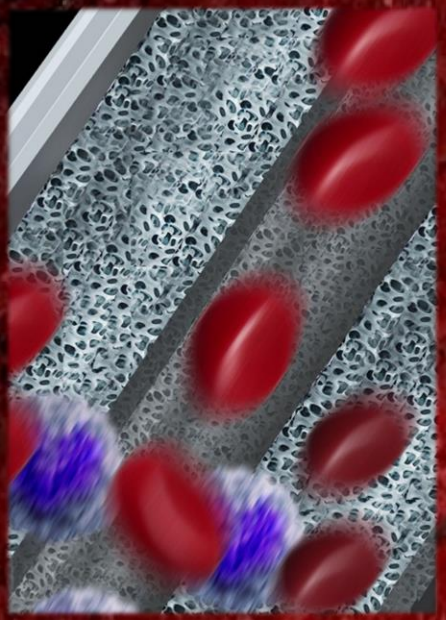
5x binding affinity activated neutrophils vs. non-activated

Low iCa++ alters phenotype of sequestered cells



0.2 -0.4 mmol/l iCa^{++} environment created by citrate anticoagulation

Neutrophils release & return to circulation

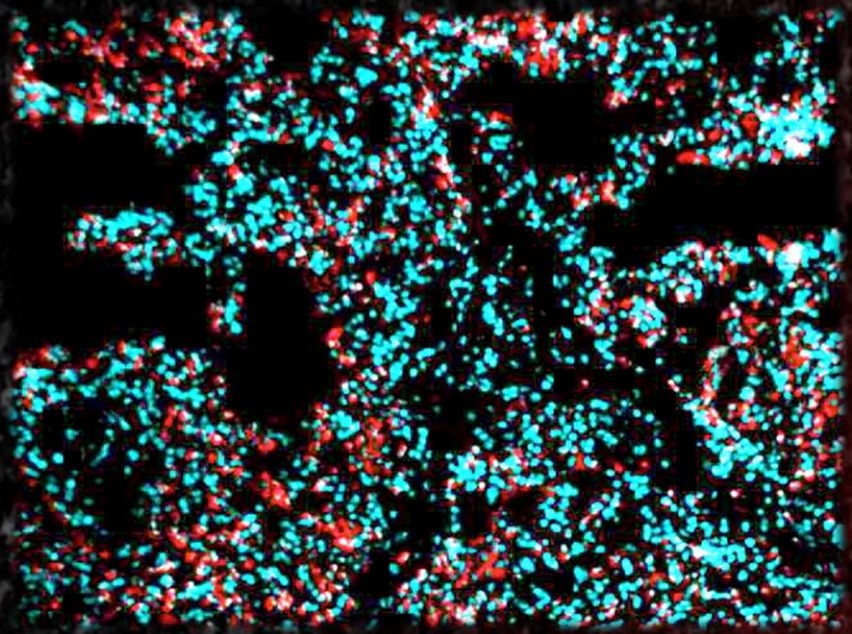


Increased apoptotic rate down regulates activation

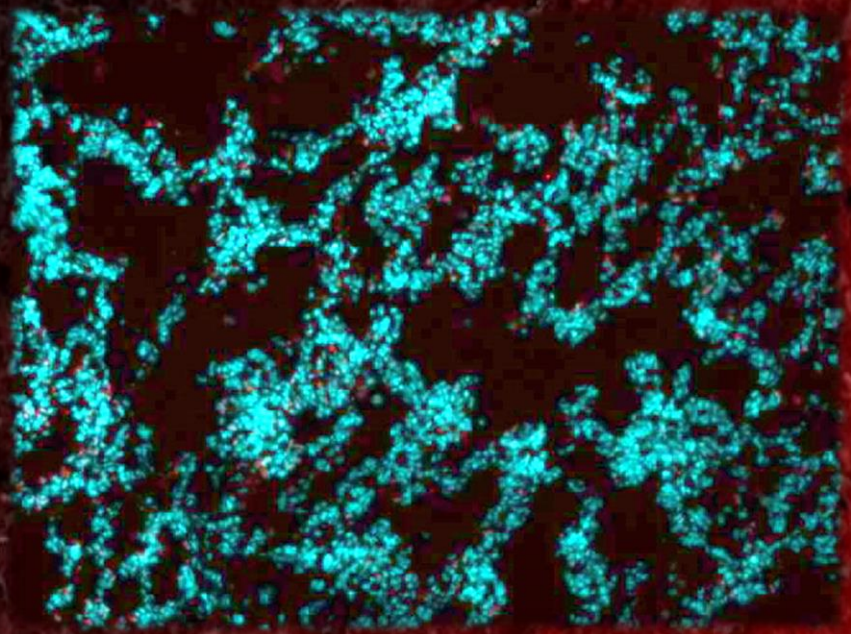
Slide courtesy of Prof. D.H. Humes, Univ. of Michigan

Porcine Model of Septic Shock: Leukocyte Infiltration Into Lung

Control



Treated



Slide courtesy of Prof. D.H. Humes, Univ. of Michigan

SCD - Multi Organ Failure/Sepsis Requiring Dialysis

CLINICAL RESULTS

Clinical Trial I — **Completed**

Retrospective
data analysis
n = 24 Pts
33.3% Mortality

A Selective Cytopheretic Inhibitory Device (SCD) to Treat the Immunological Dysregulation of Acute and Chronic Renal Failure, H. David Humes, et al
Blood Purification

Large Animal
Porcine Sepsis
Studies
n = 29

Completed

Clinical Trial II — **Completed**

China
Safety &
Dose Response
n = 9 Pts
33.3% Mortality

The Effects of a Novel Therapeutic Device on Acute Kidney Injury Outcomes in the Intensive Care Unit: A Pilot Study, Ding F., Yevzlin AS, et al. I
ASAIO J. Sep-Oct:57(5):426-32

Clinical Trial III — **Completed 3/7/2011**

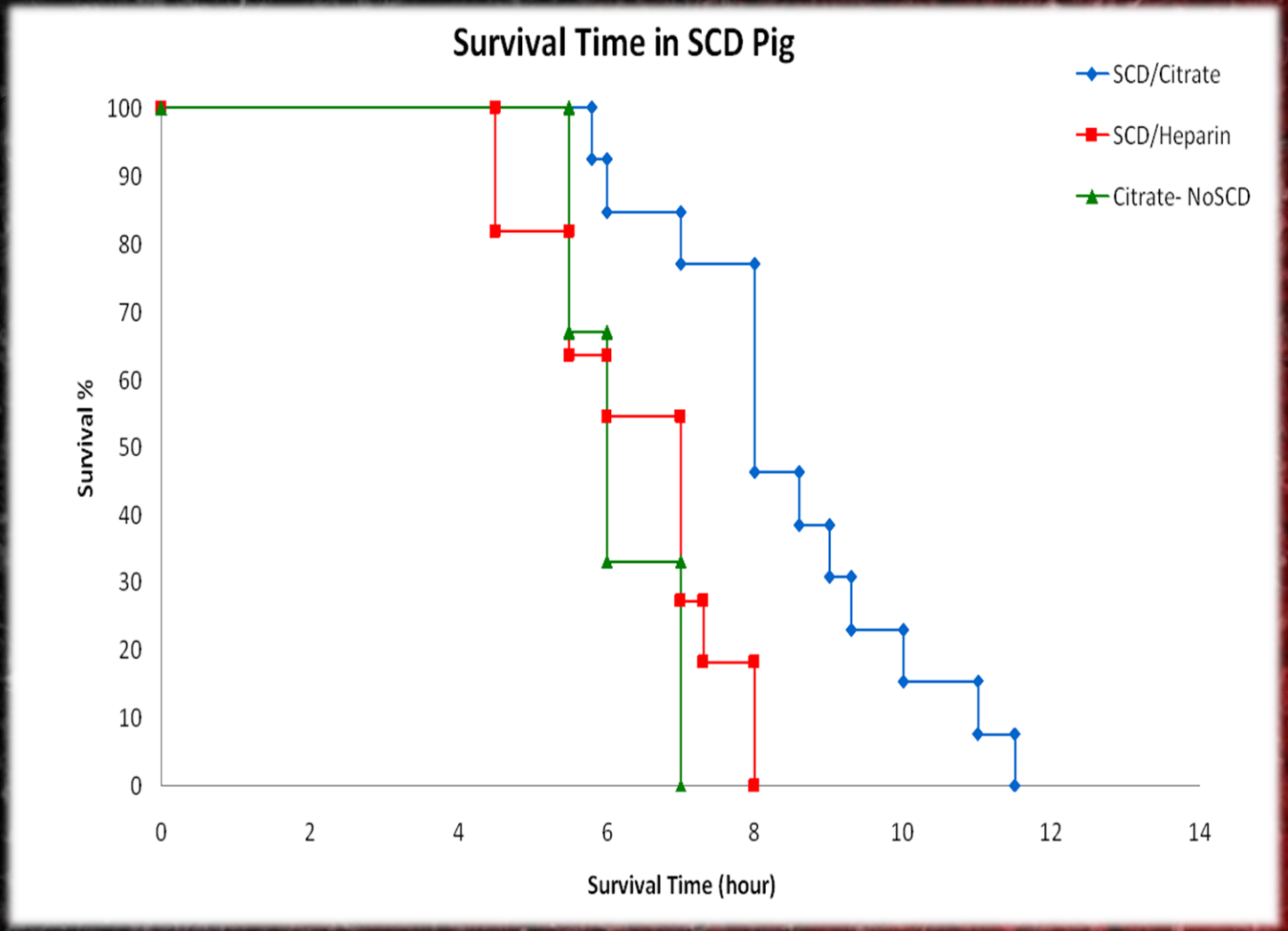
Pilot
Safety Study
n = 35 Pts
31.4 % Mortality

Safety Study of a Selective Cytopheretic Device (SCD) in Patients with Acute Renal Failure
FDA NCT01072682

Approved 6/24/11
Enrollment Q3 11 – Q2 13

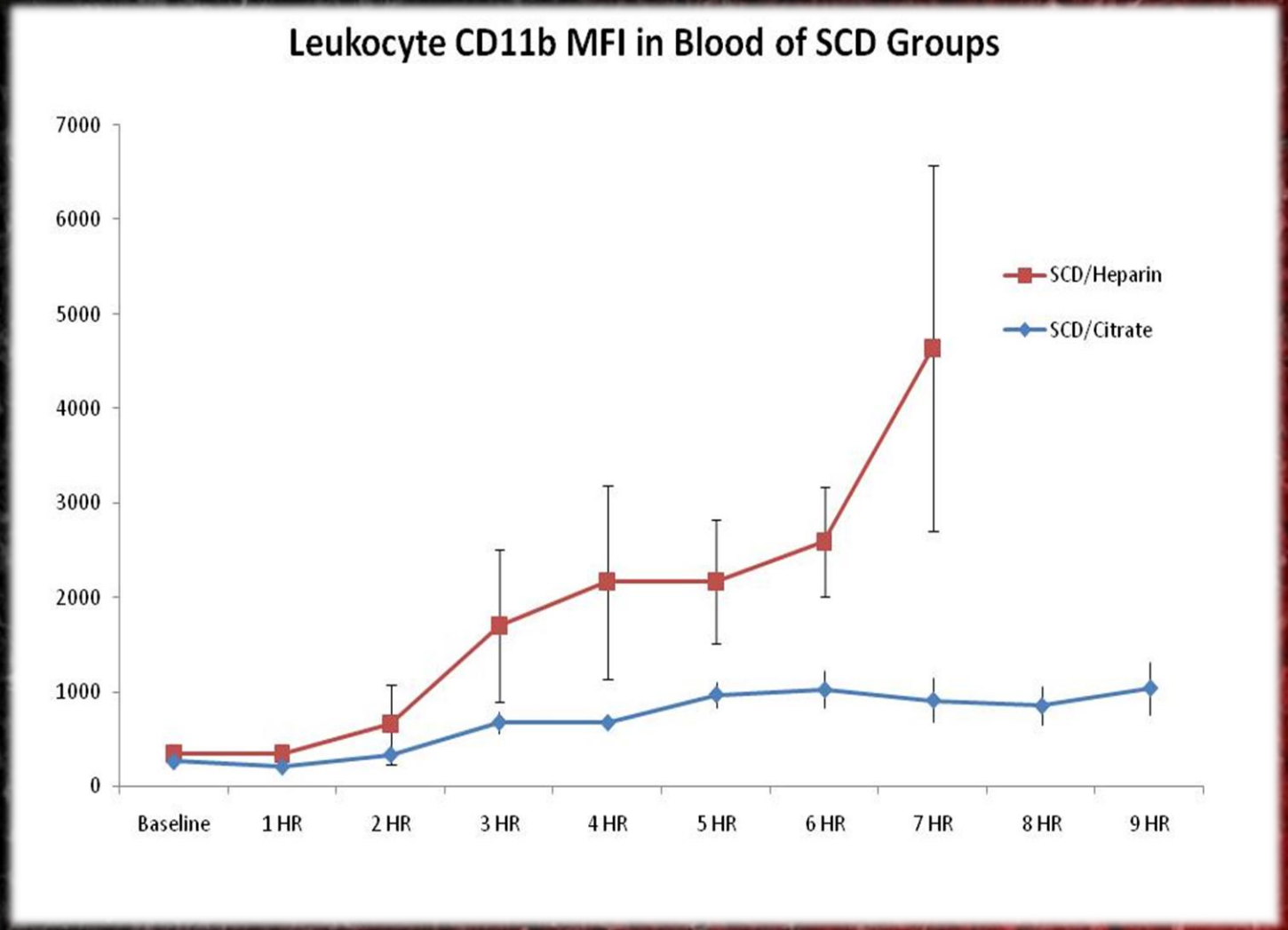
Pivotal
Safety and
Efficacy
n = 344 Pts
Projected
mortality < 35%

Porcine Model of Septic Shock



Slide courtesy of Prof. D.H. Humes, Univ. of Michigan

Porcine Model of Septic Shock



Slide courtesy of Prof. D.H. Humes, Univ. of Michigan

Select CRRT Machines in the USA

Scale-based effluent balancing

1. Gambro Prismaflex

Scale-based effluent balancing

2. Braun Diapact

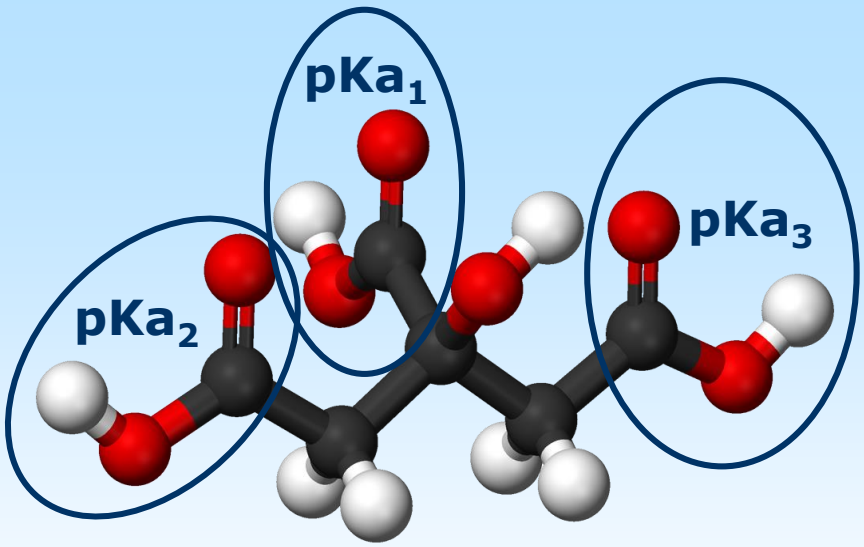
Sterile effluent balancing chamber

3. NxStage System One

Near-Automated RCA for 24-hour CRRT (CVVHD) during SCD Intervention

Citric Acid / Citrate

Fundamental Properties



$pKa_1 = 3.09$

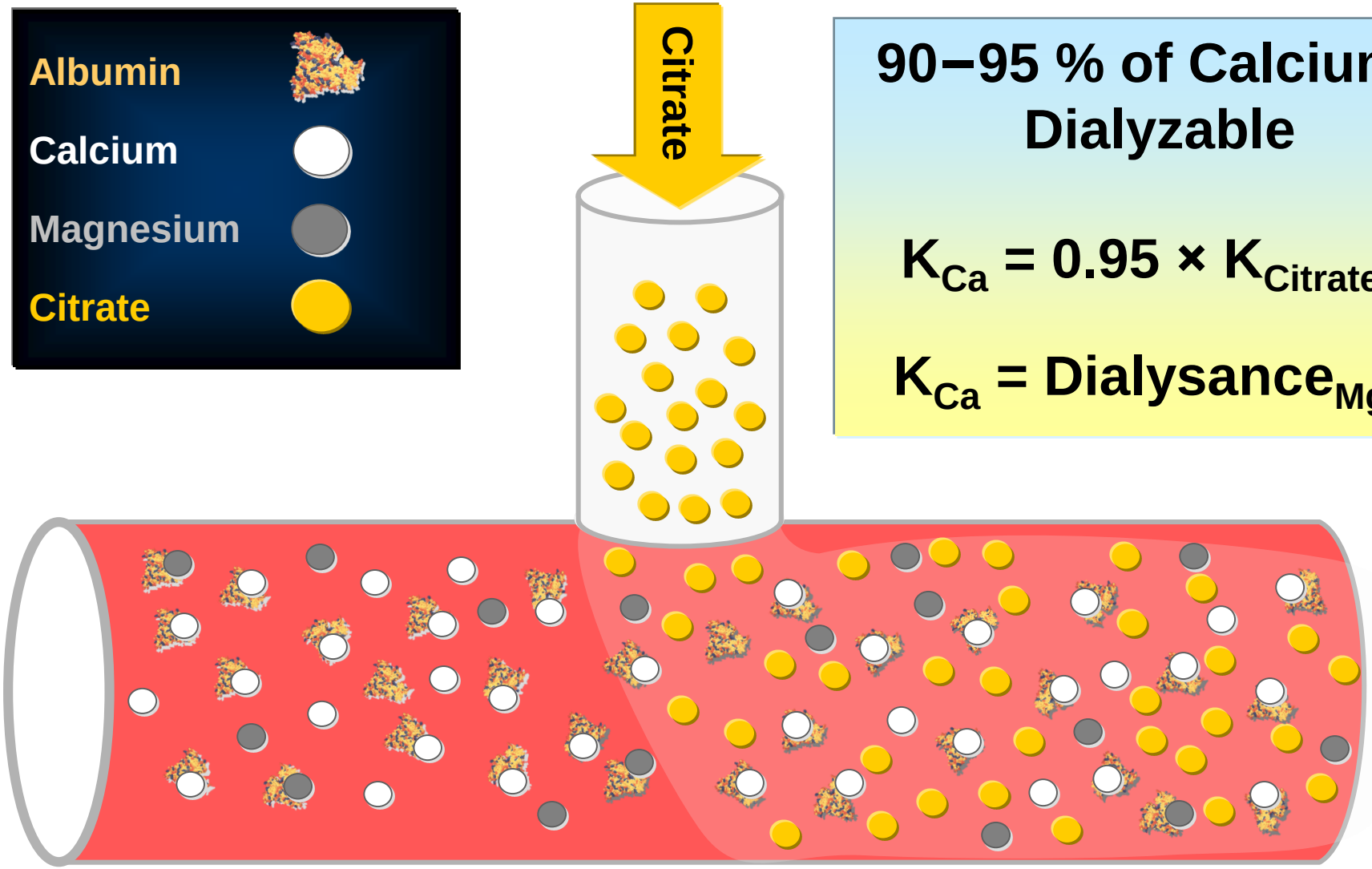
$pKa_2 = 4.75$

$pKa_3 = 5.41$

- **Only citrate^{3-} in plasma**
- **Molecular weight:**
  - Citrate^{3-} 189 Da
  - Ca-Citrate^{-} 229 Da
- **No RBC entry**
- **Metabolized to HCO_3^-**
- **Anti-inflammatory:** Blocks WBC, PLT and Complement Activation

1. Walser M, J Clin Invest. 1961 April; 40(4): 723–730
2. Whitfield LR et al, Thrombosis Research 1981; 21: 681-684
3. Crismon et al, J Appl Physiol 1961; 16(6):1103-1108
4. Janssen et al, Blood Purif 1994; 12:308-316
5. Dawson, R. M. C., et al., Data for Biochemical Research, Oxford, Clarendon Press, 1959.

Citrate Effects on Plasma



90–95 % of Calcium Dialyzable

$$K_{Ca} = 0.95 \times K_{Citrate}$$

$$K_{Ca} = \text{Dialysance}_{Mg}$$

Commercial Citrate Solutions

ACD-A Solution	
Na^+	225 mM
$Citrate^{3-}$	75 mM
Citric acid	38 mM
Dextrose	124 mM

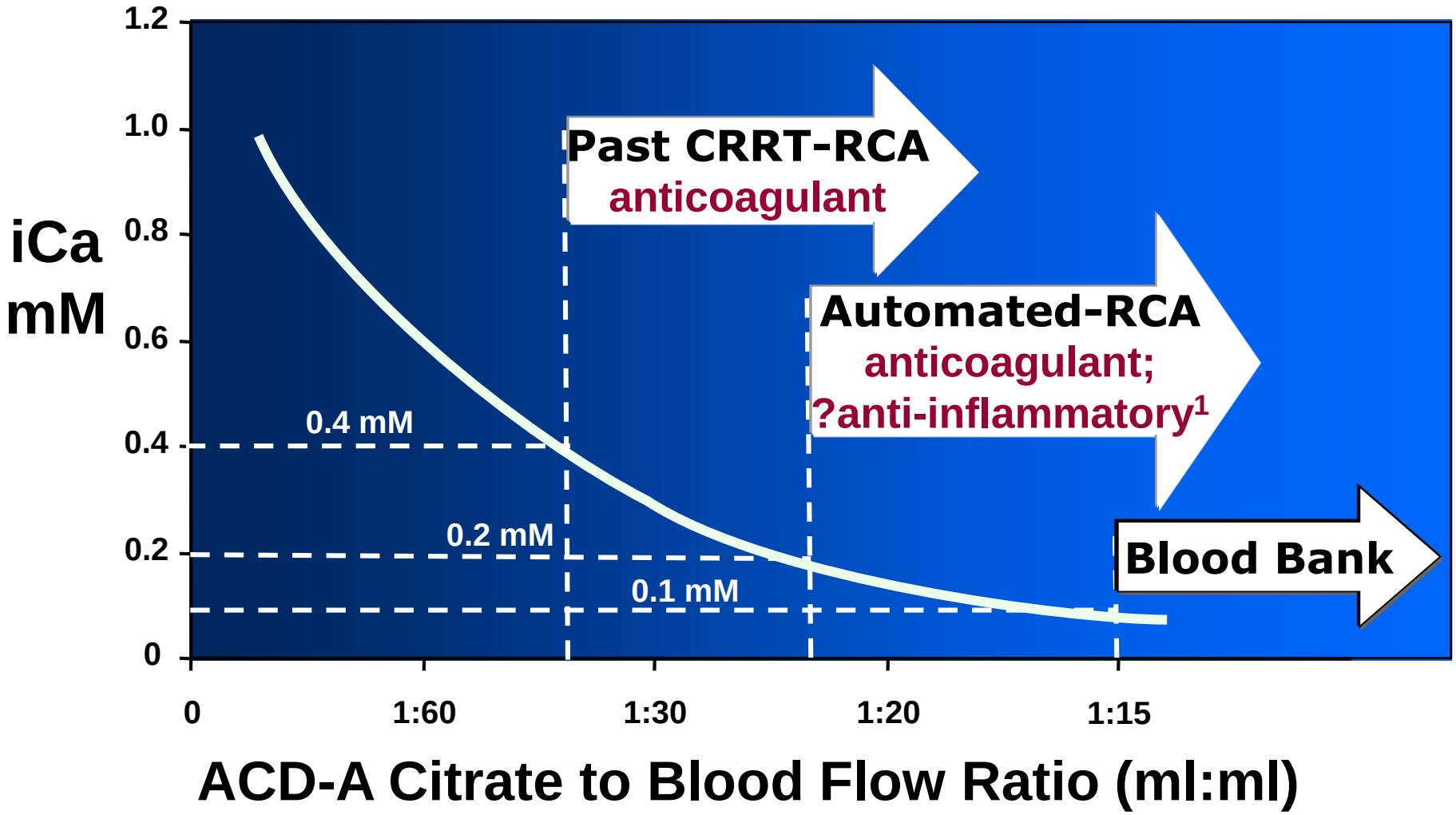
4%-TSC Solution	
Na^+	408 mM
$Citrate^{3-}$	136 mM
Citric acid	0 mM
Dextrose	0 mM

FIXED Q_{Cit} (ml/h) = 2 x QB (ml/min) for 4%-TSC

FIXED Q_{Cit} (ml/h) = 2.5 x QB (ml/min) for ACD-A

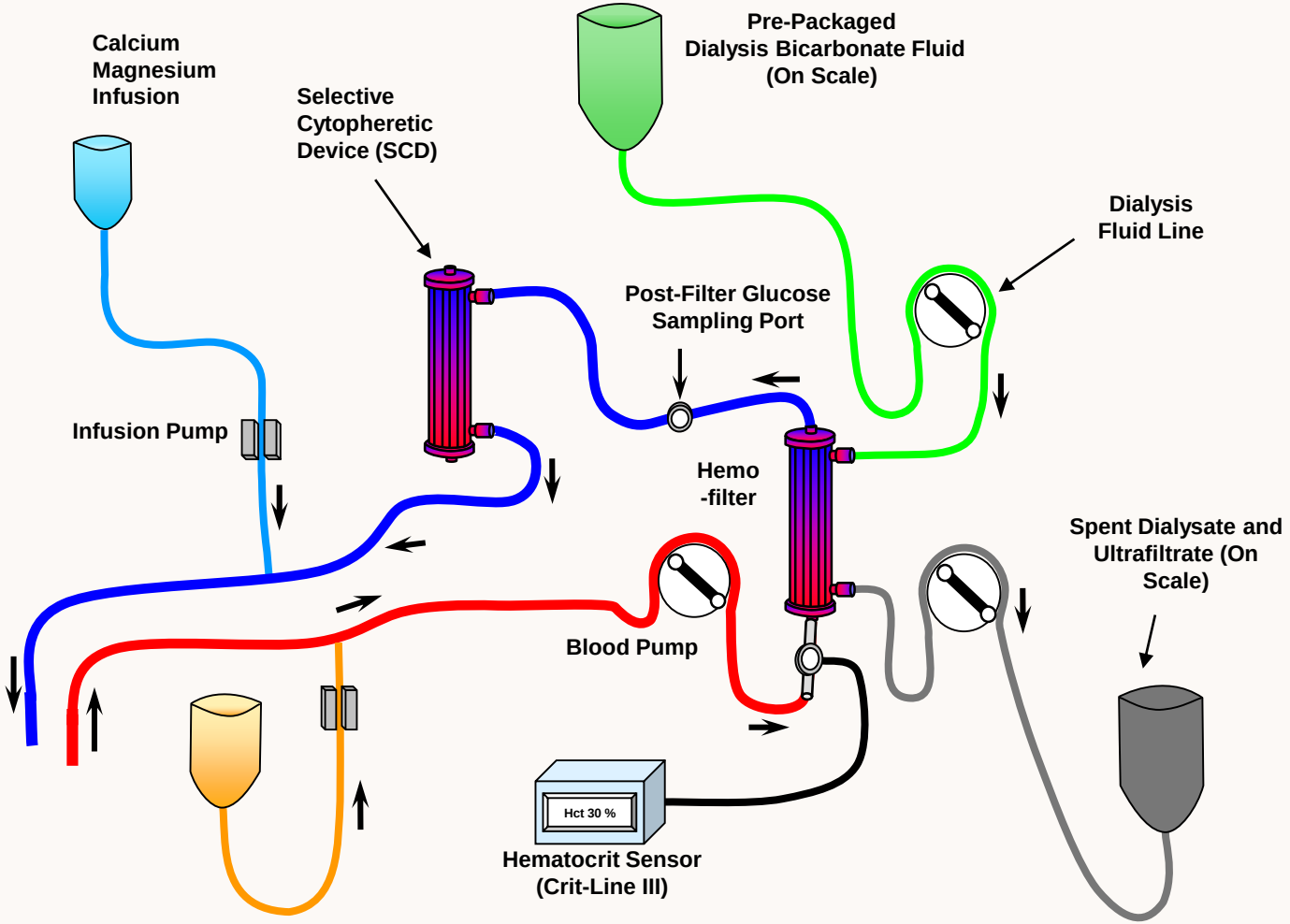
(Ex: QB 60 ml/min $\longrightarrow$ Q_{Cit} 150 ml/h for ACD-A)

Citrate to Blood Flow Ratio: Defines Effects and Efficacy of RCA

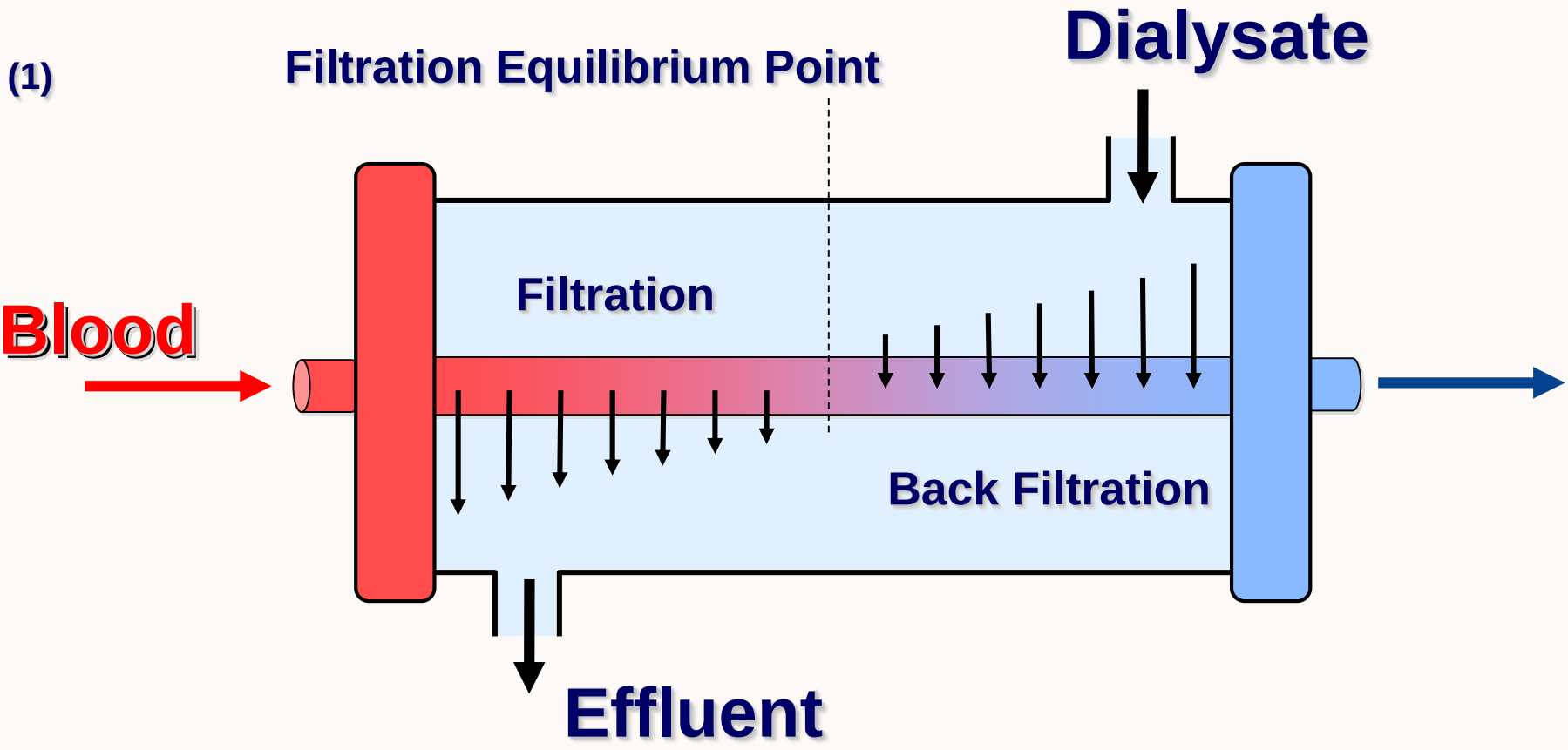


1. J. Hartmann et al: Anticoagulation In Combined Membrane/Adsorption Systems *Contributions, Sec. Biol. Med. Sci. XXIX/2 (2008) 39–49*

The CVVHD-SCD System with Citrate- and Calcium Infusion Pumps



2011: Internal Convection, Adsorption



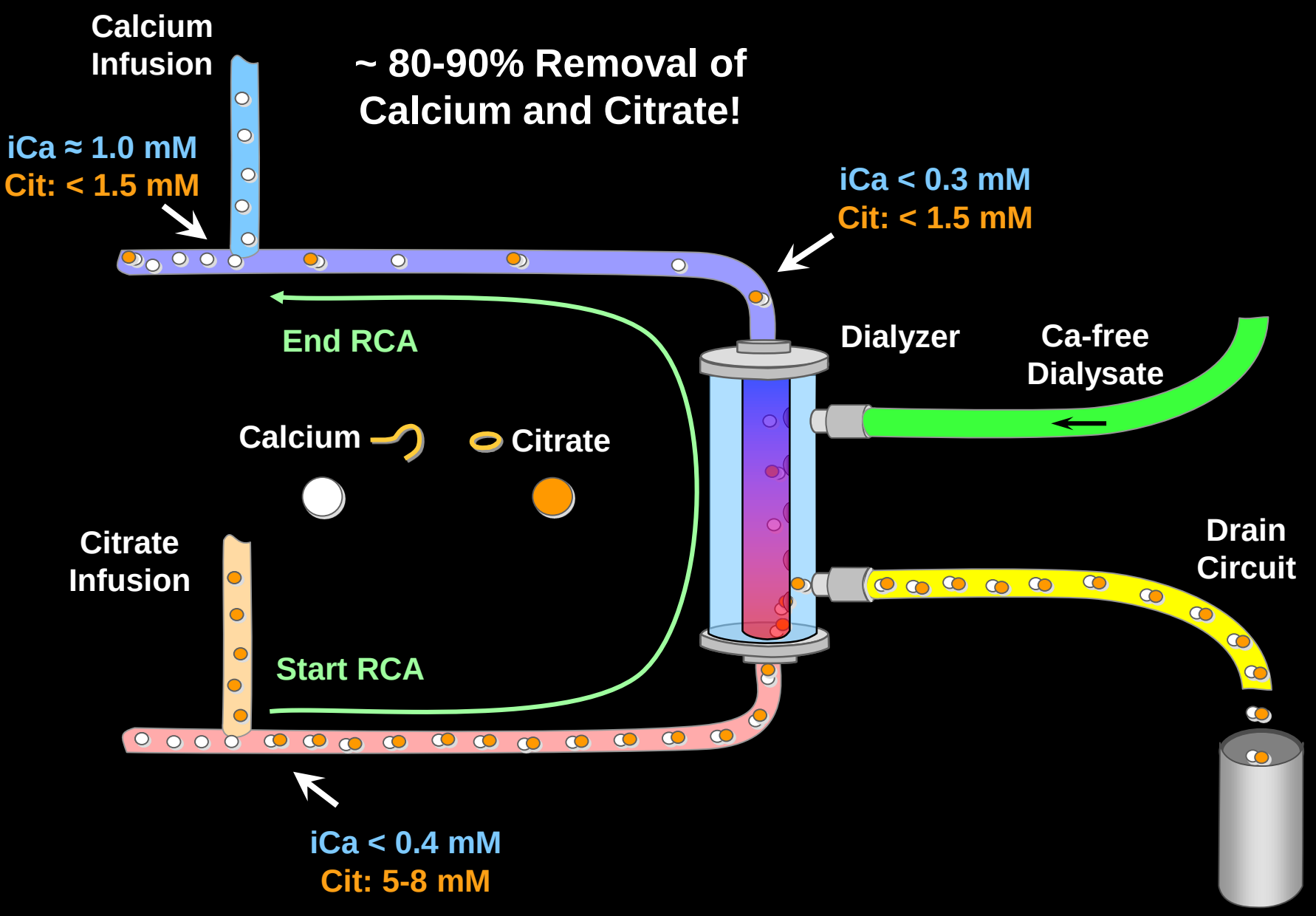
Middle-molecule clearance equal or greater in CVVHD than CVVH[2]

1. Adapted from Depner T and Garred L: Solute transport mechanisms in dialysis; in Replacement of Renal Function by Dialysis, 5th edition; p85
2. Messer, J et al. Middle-Molecule Clearance in CRRT: In Vitro Convection, Diffusion and Dialyzer Area. ASAIO Journal 2009; 55:224-226

Uniform 24-hour CVVHD-RCA Prescription

1. **CVVHD Prescription with high-flux filter**
   - **QB = 70 ml/min**
   - QD = 3.2 L/hour (Ca-free)
   - QCit = 150 ml/h (ACD-A) (fixed)
   - QCa = 25-50 ml/h (from table)
   - QNetUF = 0-500 ml/h
   - 24-hour (continuous)
2. **Other Features**
   - Continuous online display of the hematocrit and central venous O_2 saturation

"Truly Regional" Citrate Anticoagulation



CVVHD Replacement Fluid

Na^+	**140**	**mM**
K^+	4	mM
HCO_3^-	**35**	**mM**
Mg^{2+}	0.75	mM
Cl^-	110.5	mM
Ca^{2+}	0	mM
Dextrose	5.5	mM

Na^+	**140**	**mM**
K^+	2	mM
HCO_3^-	**35**	**mM**
Mg^{2+}	0.75	mM
Cl^-	108.5	mM
Ca^{2+}	0	mM
Dextrose	5.5	mM

Citrate Extraction Ratio = 80-90%

Parameters Used to Model the Systemic Citrate Concentration, C(t)

QP: **Plasma flow** (L/h)

C_{Inf}: **Citrate infused** into 1 L of plasma in the arterial limb of the blood circuit (mmol/L)

E_{Cit}: **Extraction ratio of citrate** in a single-pass on the artificial kidney

Kinetic Analysis of RCA for 24-hour CVVHD

Prescribed Flows	
(Hct	30 %)
QB	70 ml/min
QP	2.9 L/h
QCit	150 ml/min
QD	3.2 L/h
QCa	40 ml/h

Kinetic Parameters	
Cinf =	5.8 mM
Ecit =	**0.85**
Cmax ≤	1 mM
C Load, G =	2.6 mmol/h
K_{urea} =	3 L/h
G/K_{urea} =	**0.9 mmol/L**

Kinetic Analysis of RCA for 24-hour CVVHD

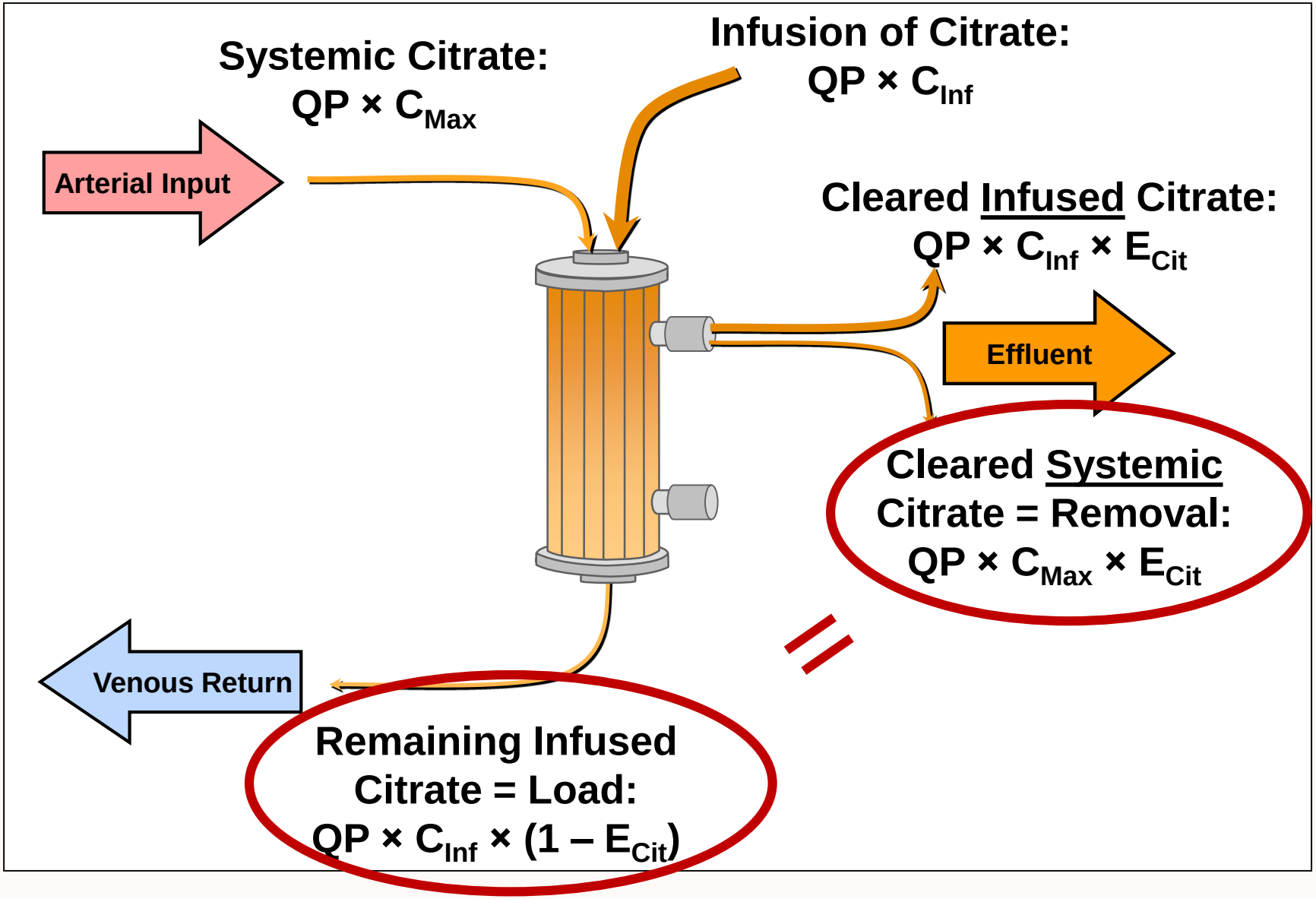
- **Na^+** mass balance neutral at serum **$Na^+ \approx 140\text{-}142$**
- **HCO_3^-** mass balance neutral at **$HCO_3^- \approx 25–30$**
- **Ca** infusion dosed to maintain systemic **iCa ≥ 1.15**
- The high Ecit (>80%) prevents dangerous (> 1.5 mM) citrate accumulation even in shock liver patients
- Filter glucose dialysance may be checked at the bedside to indirectly monitor citrate clearance

Kinetic Modeling:

The Key to

Safe Regional Citrate Anticoagulation

Citrate Concentrations in the Dialyzer Without Body Metabolism



Maximum Systemic Citrate Level (C_{Max})

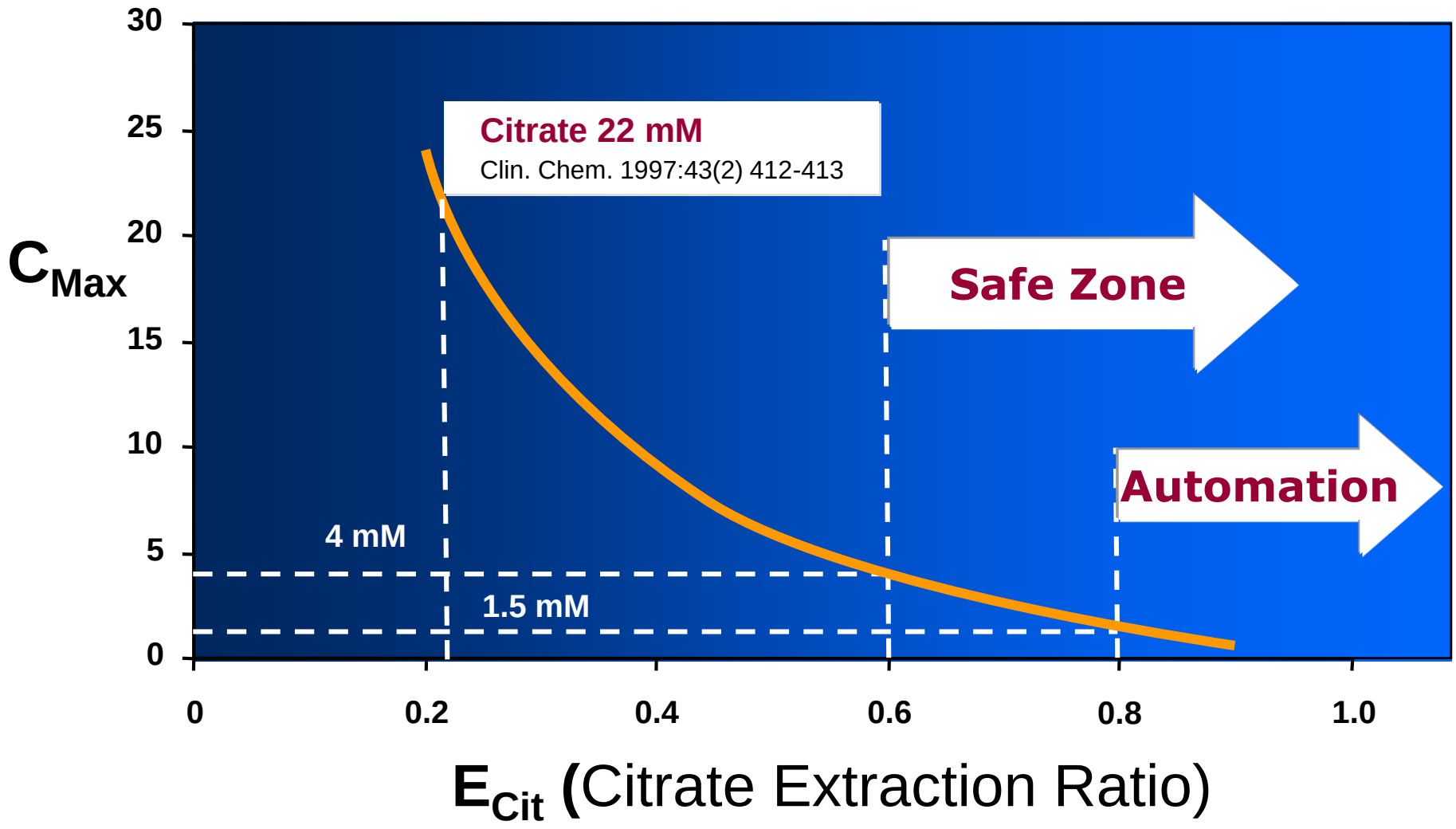
Steady State

Citrate Load = Citrate Removal

$$C_{Max} = C_{Inf} \times \frac{1 - E_{Cit}}{E_{Cit}}$$

Szamosfalvi B et al: United States Patent Application 20080015487

Relationship of C_{Max} to E_{Cit}

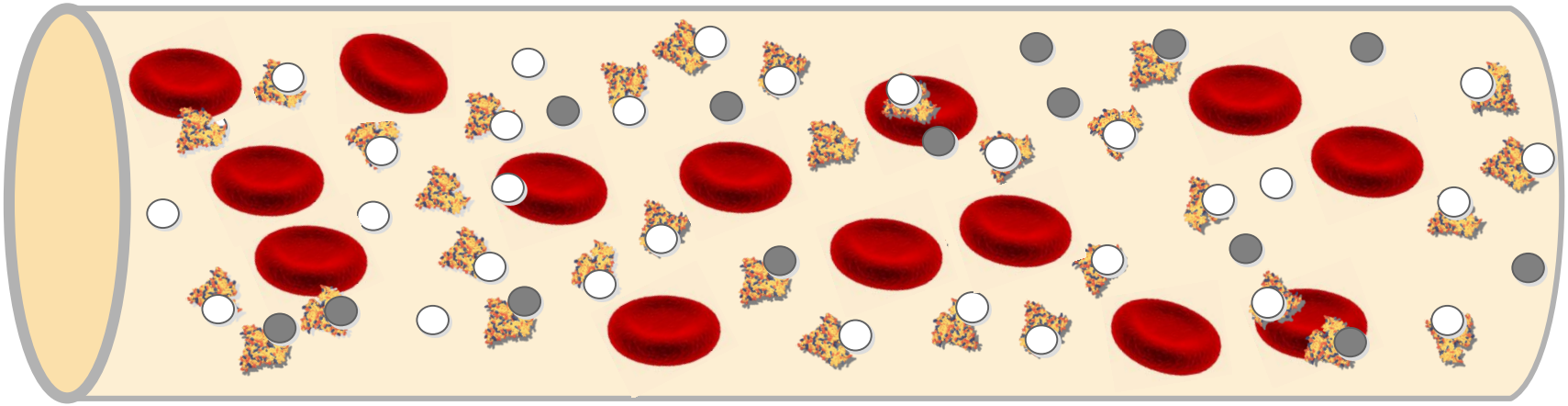


136 mM Calcium Solution

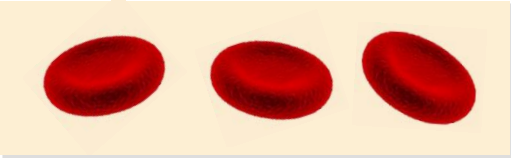
For ACD-A or 4%-TSC		
Ca^{2+}	136	mM
Mg^{2+}	20	mM
Na^{+}	140	mM
Cl^{-}	452	mM

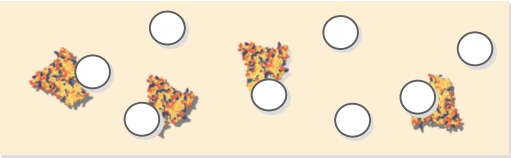
- Ca^{2+} infusion restores Ca^{2+} mass balance
- Na^{+} mass balance is restored by the dialysis fluid
- Dextrose mass balance set by dialysis fluid dextrose
- At QB of 60 ml/min, QCa = 30−50 (40) ml/hour

Hematocrit Defines Circuit Plasma Flow



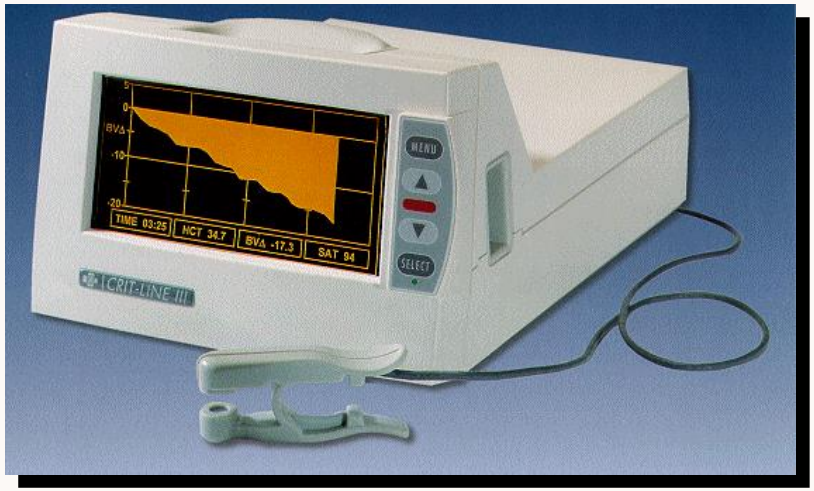
More Red Cells → **Less plasma flow** →





Less Ca-Free Plasma to Restore to Target Total Ca → **Decrease Ca Infusion Rate**

Optical Hemoglobin Monitor



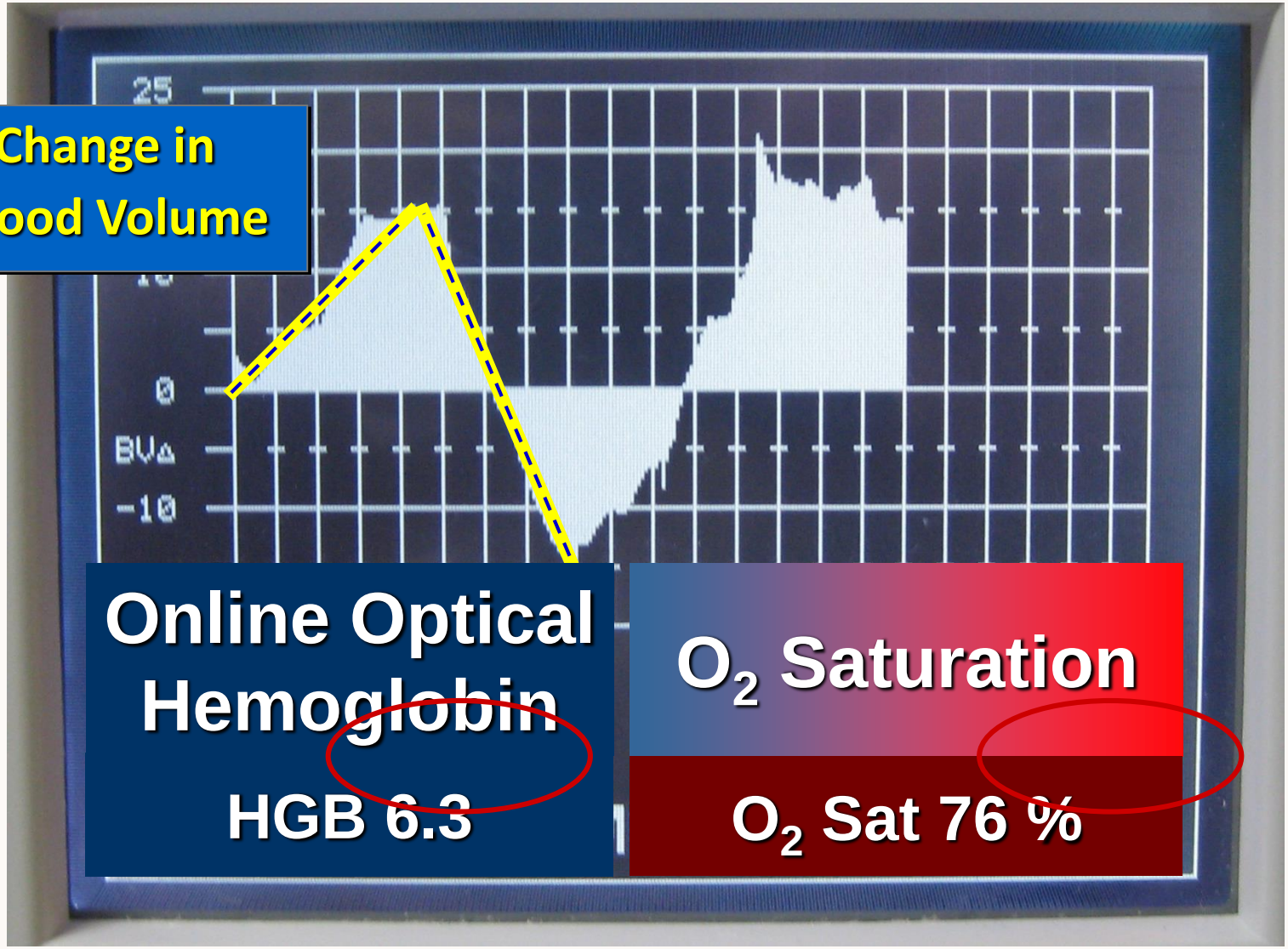
- Probe clips on blood circuit
- No-contact technology
  - Light absorption based
- Measures hematocrit
- Measures O_2 saturation

©Fresenius

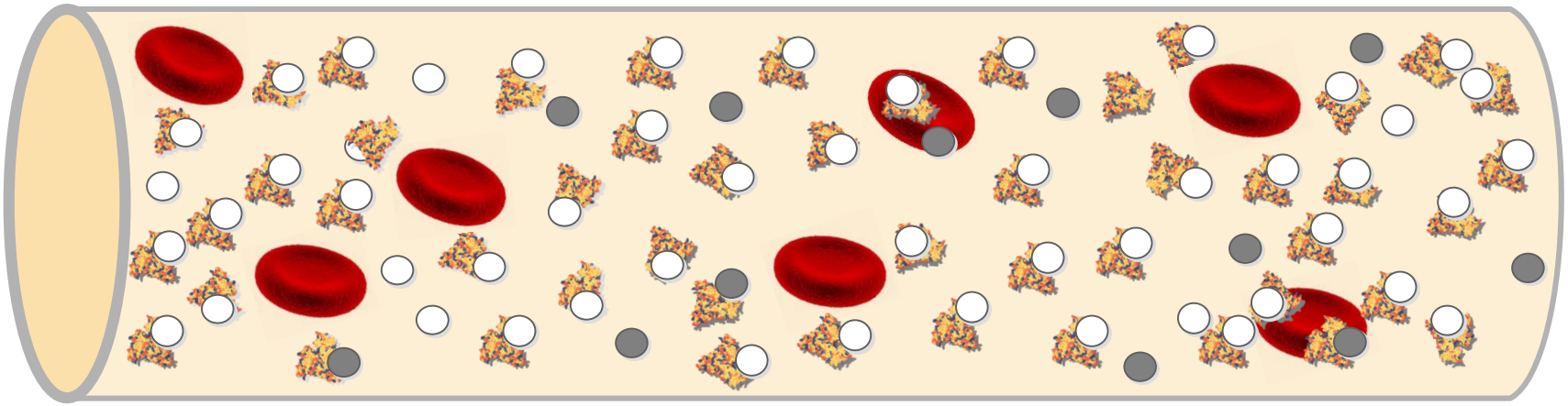
©Fresenius

Hemametrics Crit-Line III TQA™—
Online Hematocrit and O_2 saturation Sensor

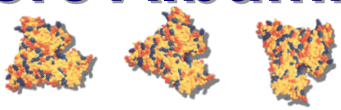
Hemoglobin & O_2 Saturation Monitor



Albumin Defines Plasma Total Calcium Goal



More Albumin → **More Albumin Bound Ca** →



Higher Total Ca Needed for Normal Ionized Ca → **Increase Ca Infusion Rate**

Ca-Infusion Rate for 24-h CVVHD (ml/hr)

Ca/Mg solution (10 gm CaCl2 + 2 gm MgCl2 in 0.5 L 0.9% saline)

Hb g/dL ALB g/dL	6-6.9	7-7.9	8-8.9	9-9.9	10-10.9	11-11.9	12-12.9	13-13.9	14-14.9	15-15.9
0.3-0.7	33	32	32	31	30	29	29	28	27	26
0.8-1.2	35	34	33	33	32	31	30	29	28	27
1.3-1.7	36	36	35	34	34	33	32	31	30	29
1.8-2.2	38	[illegible]	[illegible]	[illegible]	[illegible]	34	34	32	31	30
2.3-2.7	40	[illegible]	[illegible]	[illegible]	[illegible]	36	35	34	33	31
2.8-3.2	42	[illegible]	[illegible]	[illegible]	[illegible]	38	37	36	34	33
3.3-3.7	44	[illegible]	[illegible]	[illegible]	[illegible]	39	38	37	36	34
3.8-4.2	46	45	44	43	42	41	40	39	37	36
4.3-4.7	47	47	46	45	44	43	42	40	39	37
4.8-5.2	49	49	48	47	46	45	43	42	40	39
5.3-5.7	51	50	49	48	47	46	45	43	42	40

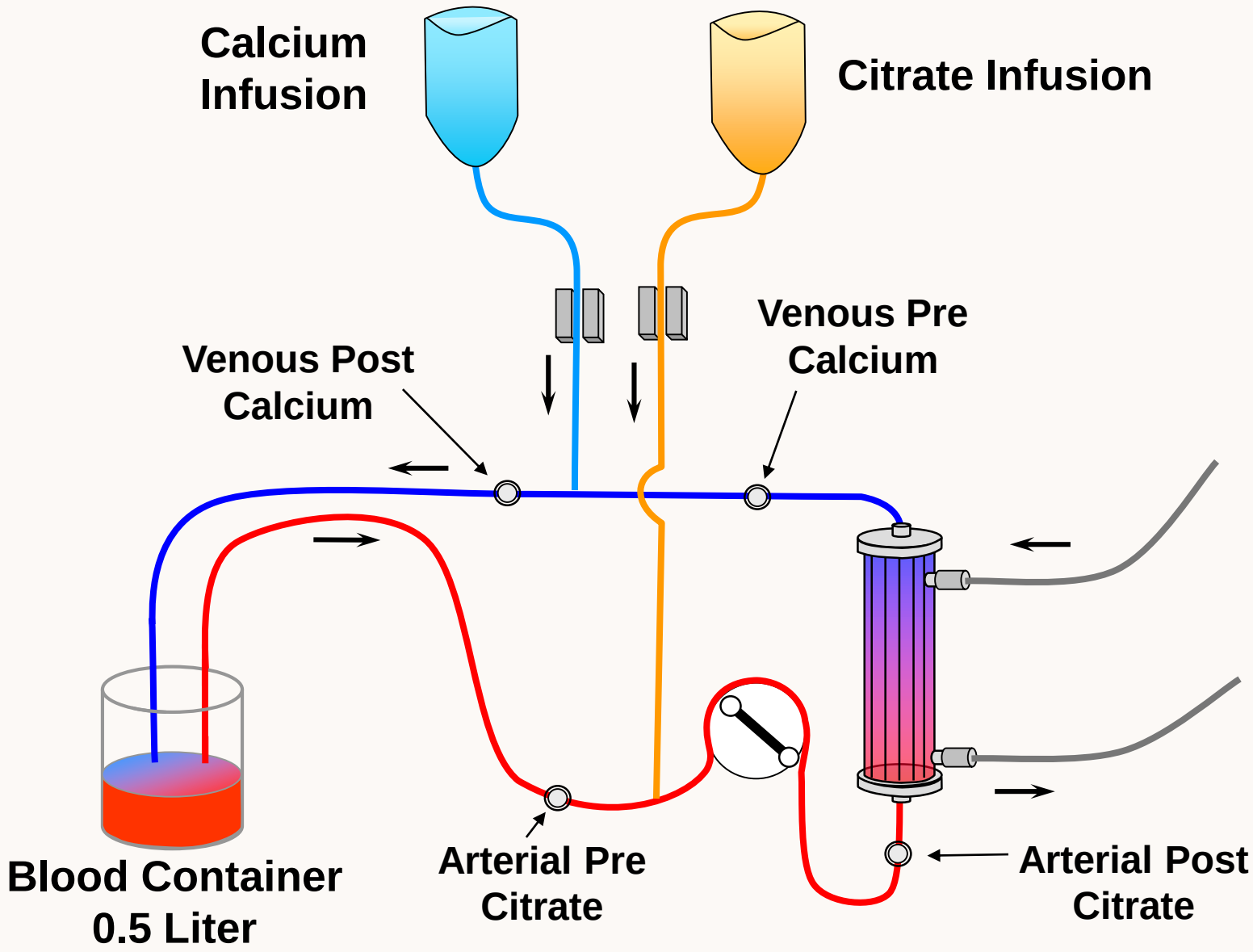
39 Starting Value

36 New Value

Simple, Predictive Ca-Infusion Dosing

- The blood flow rate is fixed
- The hematocrit sensor allows calculation of the plasma flow rate
- The systemic albumin level is known
- The Ca-infusion rate is easily predicted

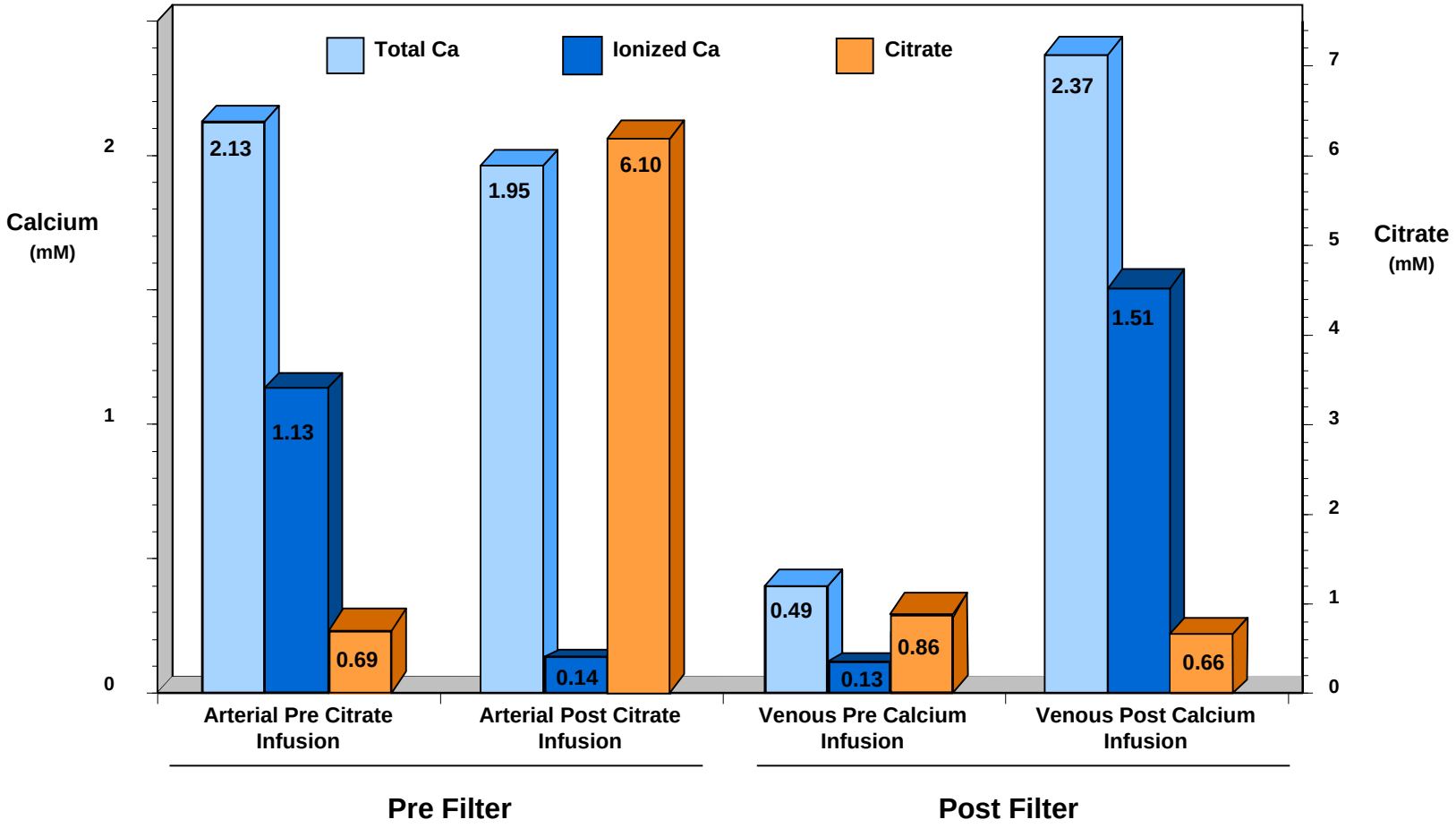
CVVHD-RCA *in vitro* Dialysis



Adapted from Szamosfalvi B et al: Automated Regional Citrate Anticoagulation…; Blood Purif 2010;29:204-209

CVVHDF Circuit Citrate/Ca Data

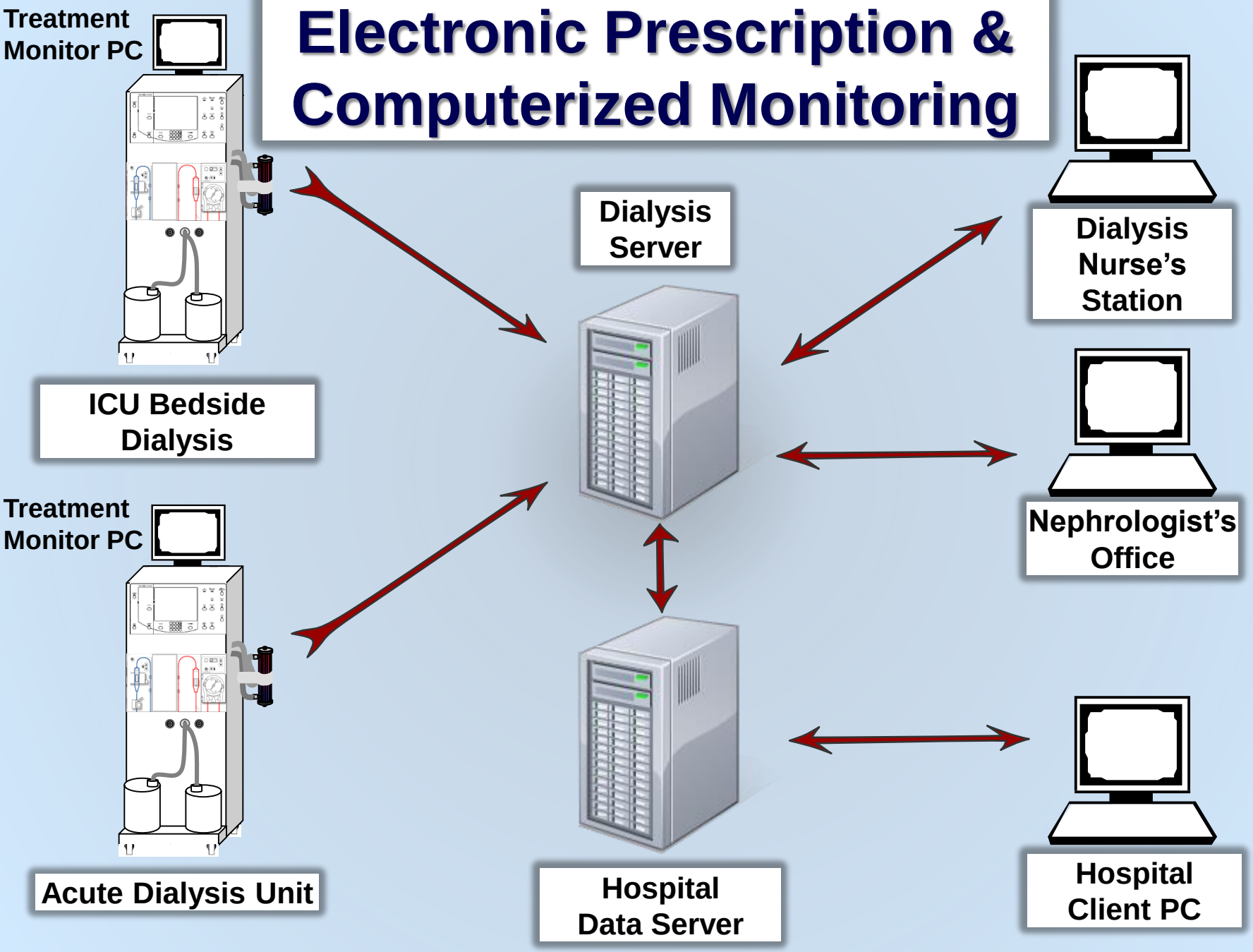
Sham Hemodiafiltration at Hct 30% (repeated at Hct = 21-45%)



CVVHDF using a Rexeed 15S dialyzer with blood flow = 80 ml/min, ACDA citrate infusion rate = 200 ml/h, postdilution replacement fluid flow rate = 0.8 L/h, dialysis fluid flow rate = 2.4 L/h, 136 mM calcium infusion rate = 44 ml/h. The ultrafiltration setting was = 240 ml/h (Qcit + QCa).

Dealing with Complexity: "In The Cloud" Electronic Prescription Generation and Telemetry Monitoring

Electronic Prescription & Computerized Monitoring



24•hr SLED WITH CITRATE ANTICOAGULATION ORDER/NOTE

ADD IPD DIALYSIS ORDER

Entry Date: 10/27/2010 02:26:24 PM User Log: bszamos1: Add 10/27/10

Name : (L, F) Patient Test MRN: 15184704 Room Number: 1000c

Treatment Type:24 HOUR SLED WITH CITRATE

☑ Set machine in Hemodialysis Mode for 9 hours 59 minutes
(Re-setup every 10 hours for continuous treatment)

Contact Isolation: ◉ NO ○ YES Cause:

(required values to calculate infusion rates)

ALB: 2.6 g/dL HGB: 9.1 g/dL HCO_3: 18 mEq/L

☑ Citrate Dextrose (ACD-A) at 150 ml/hr

☑ 37 mL/Hr

136 mM Ca in 0.9% saline (10 gm $CaCl_2$ + 2 gm $MgCl_2$/500 mL)

Calculate Infusion

(Select initial Calcium infusion rate from the 24-hour SLED-RCA Table.
Adjust the Ca/Mg infusion rate per 24-hour SLED-RCA protocol.)

Ultrafiltration CALCULATOR

Desired NET UltraFiltration Goal 200 ml/hr as tolerated

Effective NET UltraFiltration Goal 200 ml/hr

TOTAL goal in 10 hours 3870 (ml) (Net goal + remove Citrate 1200 or 1500 + Ca/Mg ~400 ml infused in 10 hours)

Dialysate temperature 36.5 C Sodium Program: No

TESTS & MEDICATIONS

1.

Fluid Flow Rates & Dialyzer

☑ Rexeed 15-SX FILTER

☑ 60 Blood FLow (ml/min)

☑ 400 Dialysate Flow (ml/min)

Dialysate Bath

Potassium	Calcium	Phosphorus
○ 2 mEq/L	☑ 0 mEq/L	○ 0 mg/dL
○ 3 mEq/L		◉ 3.2 mg/dL
◉ 4 mEq/L		

Sodium: 142 mEq/L

Bicarbonate: 32 mEq/L

Special Orders

Age: 69 Sex: ◉ Male ○ Female Height: 180 (cm)

Weight: 90 kg

Calculate Volume Vol.: 45 (L)

1. ☑ Document DELIVERED Kt/V
2. ☑ Document Average QB/Kecn (Ionic dialysance)
3. ☑ Measure Access Recirculation

Labs Date: 10/26/2010

Calcium: 8.6 mg/dL Ionized Calcium: 1.12 mmo/L

Magnesium: 2.1 mg/dL Phosphorus: 3.6 mg/dL

Na: 137 mEq/L PROTEIN: 6.2 mg/dL

K: 4.3 mEq/L BUN: 57 mg/dL

Cl: 105 mEq/L Cret: 3 mg/dL

Henry Ford Health System (24-hr)

SUSTAINED LOW EFFICIENCY DIALYSIS (SLED) WITH REGIONAL CITRATE ANTICOAGULATION (RCA) ORDER/NOTE

Room Number: **1000c**

DATE: **10/27/2010 14:26:24**

NAME: **Patient Test**

MRN: **15184704**

Treatment Type: 24 HOUR SLED WITH CITRATE

☑ Set machine in Hemodialysis Mode for 9 hours 59 minutes (Re-setup every 10 hours for continuous treatment)

Isolation: ☑ NO ☐ YES Cause:

Citrate and Calcium infusion rates during RCA

☑ **Citrate Dextrose (ACD-A) at 150 ml/hr**

☑ **Calcium/Magnesium (Ca/Mg) in 0.9% saline (10 gm $CaCl_2$ + 2 gm $MgCl_2$ /500 mL)**

Ca/Mg Infusion RATE: 37 **mL/Hour**

(Select initial Ca/Mg infusion rate from 24-hour SLED-RCA Table 1. Adjust the Ca/Mg infusion rate per 24-hour RCA protocol.)

Ultrafiltration CALCULATION: UF RATE 387 ml/hr

Patient NET Goal PER HOUR 200 ml/hr (as tolerated)

TOTAL goal in 10 hours 3870 (ml) (Net goal + remove Citrate 1200 or 1500 ml + Ca/Mg ~400 ml infused in 10 hours)

Dialysate temperature 36.5 C Sodium Program: No

TESTS & MEDICATIONS

1.
2.
3.

Fluid Flow Rates & Dialyzer

FILTER: **REXEED15-SX**
BLOOD FLOW: **60** ml/min
DIALYSATE FLOW: **400** ml/min

Dialysate Bath

Potassium	Calcium	Phosphorus
☐ 2 mEq/L	☑ 0 mEq/L	☐ 0 mg/dL
☐ 3 mEq/L		☑ 3.2 mg/dL
☑ 4 mEq/L	Sodium: 142 mEq/L	Bicarb: 32 mEq/L

Special Orders
Volume: 45 Liters

☑ 1. Document DELIVERED Kt/V

☑ 2. Document Average Kecn (Ionic dialysance)

Lab Date: 10/26/2010

Albumin: **2.6** g/dL	Protein: **6.2** g/dL
Calcium: 8.6 mg/dL	Ionized Calcium: 1.12 mmol/L
Magnesium: 2.1 mg/dL	Hemoglobin: **9.1** g/dL
Phosphorus: 3.6 mg/dL	
Na: 137 mEq/L	HCO3: **18** mEq/L
K: 4.3 mEq/L	BUN: 57 mg/dL
Cl: 105 mEq/L	Creatinine: 3 mg/dL
Hepatitis BsAg : 10/25/2010	**NEGATIVE**
C.difficile toxin : 10/22/2010	**NEGATIVE**

Patient Evaluation: History:

60 y.o male status post CABG 10/12/2010; course complicated by HAP, VDRF and anuric AKI. CRRT was started 10/20/2010.

Exam: T : **36.5** BP: **100** / **50** HR: **110** RR: **18** W: **90** kg

Attending Physician Attestation:

1. Patient Seen on Dialysis Init: ____ hr: ____ min: ____

RCA Logger 171.vi
File Edit Operate Window Help
Treatment Data
Dialysis Machine Data
Dialysis Machine Setup
Crit-Line Setup
Database Setup
Infusion Rate Cal
Settings for Testing
Critline Time from Start (sec)
76224
Monitor ON
Hemoglobin (g/dL)
10.8
Start Monitor
Oxygen Saturation (%)
71.3
Time
Select Treatment Type
24 Hour SLED with Citrate
Treatment Qb (ml/min)
60
MRN
Room #
Patient Name
Alarms
Blood Flow ≠ Tx QB
Blood Pump Stopped
Ultrafiltration Off
Dialysate Flow Stopped
Machine Mode
Dialysis Mode
Rinse Mode
Blood Sensed
Disinfect Mode
11:56 AM
2/8/2013
RCA Log
MCHDIA7

24-hour SLED-RCA Telemetry

ker Pro - [LabViewLoggerV4 (Gerards-Mac-mini.local)]

Edit View Insert Format Records Scripts Window Help

MONITOR

SLED TELEMETRY V4

MACHINE 7

Date:

NAME: MRN: ROOM:

OFFLINE

BloodFlowRate		DialysisMode	
Ven Pressure	mm Hg	BloodSensed	
Art Pressure	mm Hg	UGUFgoal	
GRAPH KE		ConductivityAlarm	
Dial Temp		ArterialAlarm	
Dial Flow		VenousAlarm	
UFrate		HGB	
Blood Volume		O_2sat	
RemainingTime		SVV	
UFvolume		CI	
EKdeliveredKtV		ScvO2	
QB average		Rx Qb = Mach Qb	
QD average			
Treatment Time			
spKtV			

MACHINE 8

Date: 05/09/2013 09:29:23

NAME: MRN: ROOM:

ONLINE SLED 24 hr

BloodFlowRate	59	DialysisMode	DIT
Ven Pressure	9 mm Hg	BloodSensed	BST
Art Pressure	-6 mm Hg	UGUFgoal	1890
GRAPH KE	57	ConductivityAlarm	ACF
Dial Temp	36.4	ArterialAlarm	ARF
Dial Flow	400	VenousAlarm	AVF
UFrate	190	HGB	9.1
Blood Volume	0	O_2sat	74.4
RemainingTime	596	SVV	8.0
UFvolume	12	CI	3.8
EKdeliveredKtV	0.0	ScvO2	80.0
QB average	60	Rx Qb = Mach Qb	T
QD average	400		
Treatment Time	3		
spKtV	0.00		

MACHINE 9

Date: 05/09/2013 08:40:45

NAME: MRN: ROOM:

OFFLINE SLED 24 hr

BloodFlowRate	0	DialysisMode	DIT
Ven Pressure	1 mm Hg	BloodSensed	BSF
Art Pressure	2 mm Hg	UGUFgoal	3000
GRAPH KE	47	ConductivityAlarm	ACF
Dial Temp	42.0	ArterialAlarm	ARF
Dial Flow	300	VenousAlarm	AVF
UFrate	0	HGB	5.4
Blood Volume	0	O_2sat	77.2
RemainingTime	0	SVV	
UFvolume	0	CI	
EKdeliveredKtV	0.0	ScvO2	
QB average	0	Rx Qb = Mach Qb	F
QD average	0		
Treatment Time	0		
spKtV	0.00		

MACHINE 10

Date: 05/09/2013 09:30:13

NAME: MRN: ROOM:

ONLINE SLED 24 hr

BloodFlowRate	0	DialysisMode	DIT
Ven Pressure	1 mm Hg	BloodSensed	BSF
Art Pressure	-2 mm Hg	UGUFgoal	210
KE	0	ConductivityAlarm	ACT
Dial Temp	37.2	ArterialAlarm	ARF
Dial Flow	300	VenousAlarm	AVF
UFrate	0	HGB	4.5
Blood Volume	0	O_2sat	76.7
RemainingTime	0	SVV	
UFvolume	0	CI	
EKdeliveredKtV	0.0	ScvO2	
QB average	0	Rx Qb = Mach Qb	F
QD average	0		
Treatment Time	0		
spKtV	0.00		

MACHINE 11

Date: 05/09/2013 09:30:08

NAME: MRN: ROOM:

ONLINE SLED 24 hr

BloodFlowRate	57	DialysisMode	DIT
Ven Pressure	20 mm Hg	BloodSensed	BST
Art Pressure	-5 mm Hg	UGUFgoal	3870
GRAPH KE	55	ConductivityAlarm	ACF
Dial Temp	36.5	ArterialAlarm	ARF
Dial Flow	400	VenousAlarm	AVF
UFrate	390	HGB	7.9
Blood Volume	19	O_2sat	74.6
RemainingTime	277	SVV	
UFvolume	2059	CI	
EKdeliveredKtV	0.0	ScvO2	
QB average	60	Rx Qb = Mach Qb	T
QD average	400		
Treatment Time	322		
spKtV	0.00		

MACHINE 12

Date:

NAME: MRN: ROOM:

OFFLINE

BloodFlowRate		DialysisMode	
Ven Pressure	mm Hg	BloodSensed	
Art Pressure	mm Hg	UGUFgoal	
KE		ConductivityAlarm	
Dial Temp		ArterialAlarm	
Dial Flow		VenousAlarm	
UFrate		HGB	
Blood Volume		O_2sat	
RemainingTime		SVV	
UFvolume		CI	
EKdeliveredKtV		ScvO2	
QB average		Rx Qb = Mach Qb	
QD average			
Treatment Time			
spKtV			

Summary

- **CRRT systems are logical platforms for extracorporeal support therapies for SIRS**
- **Near-Automated CRRT-RCA is feasible with present technology and allows large-scale, safe use of RCA <u>without contraindications</u>**
- **Very early start (<6 hours) extracorporeal support and careful patient selection (possibly with biomarkers) may afford a greater chance of success in sepsis trials**

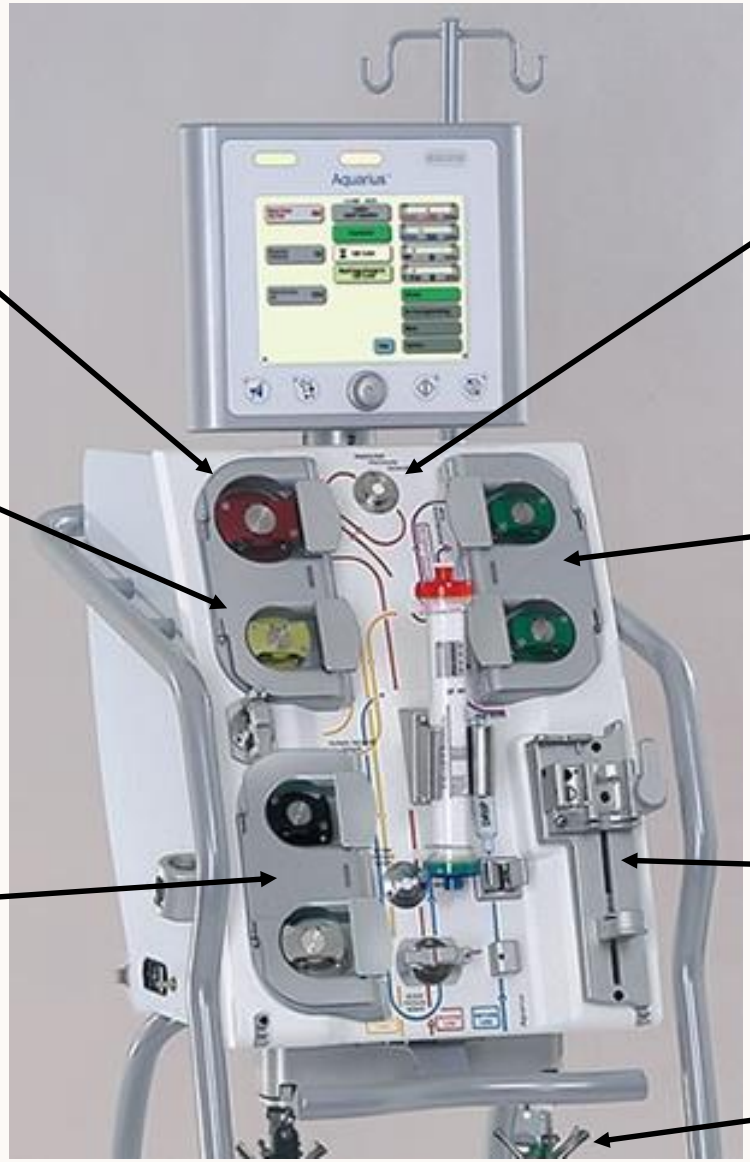
HFH "Citrate Group"

- Balazs Szamosfalvi, MD
- Stanley Frinak, MSEE
- Jerry Yee, MD
- Gary Zasuwa
- Prof. Eric Anslyn
- CRRT Technician Team
- ICU Teams
- Greenfield Health System

Future Directions with HVHF and Online Chemistry Sensing

CRRT Machine With Citrate- and Ca pumps

(Device was withdrawn from the US market)



Blood Pump

Filter Effluent Pump

Calcium- and Citrate Pumps

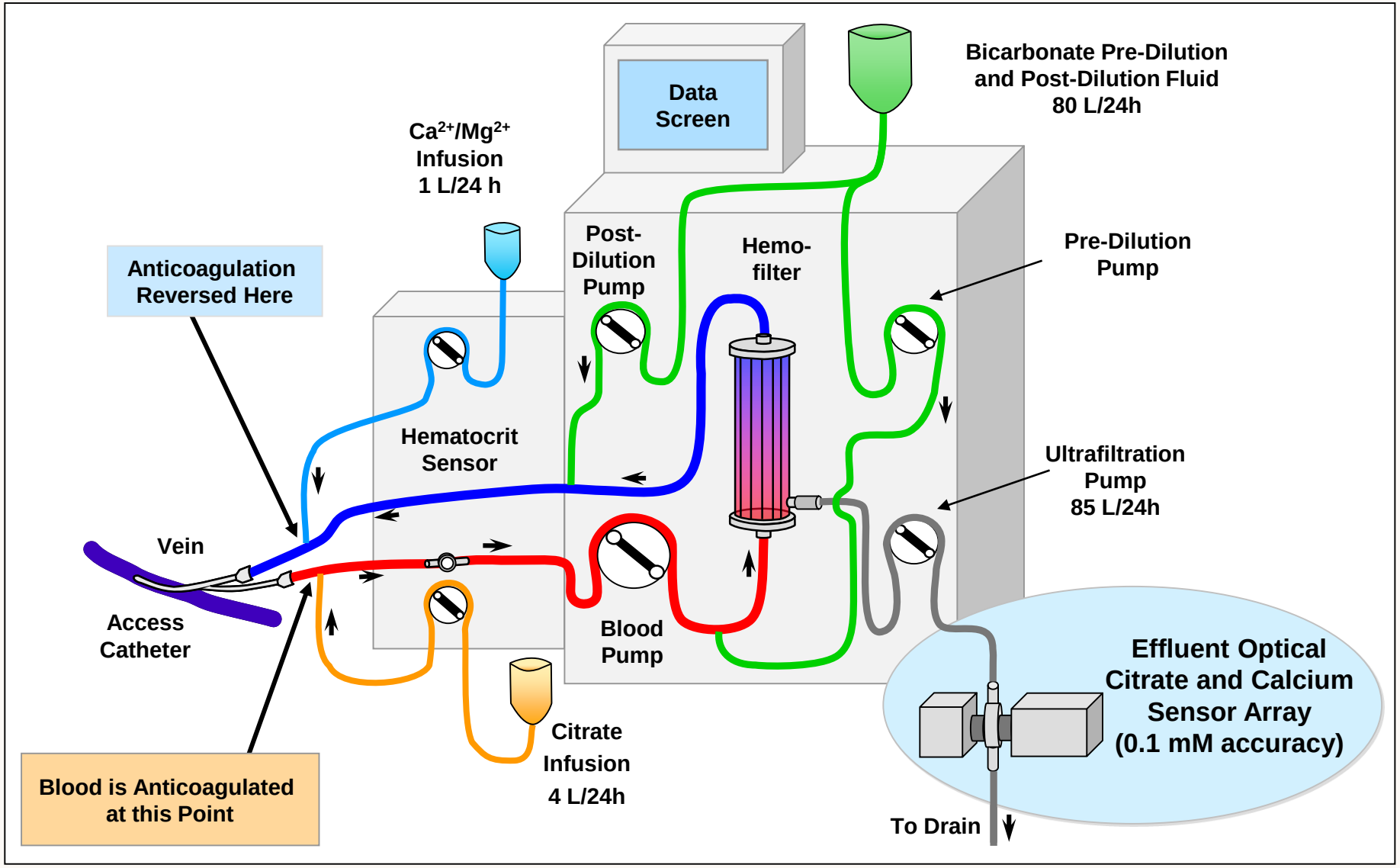
Pressure Pod

Replacement- and/or Dialysis Fluid Pumps

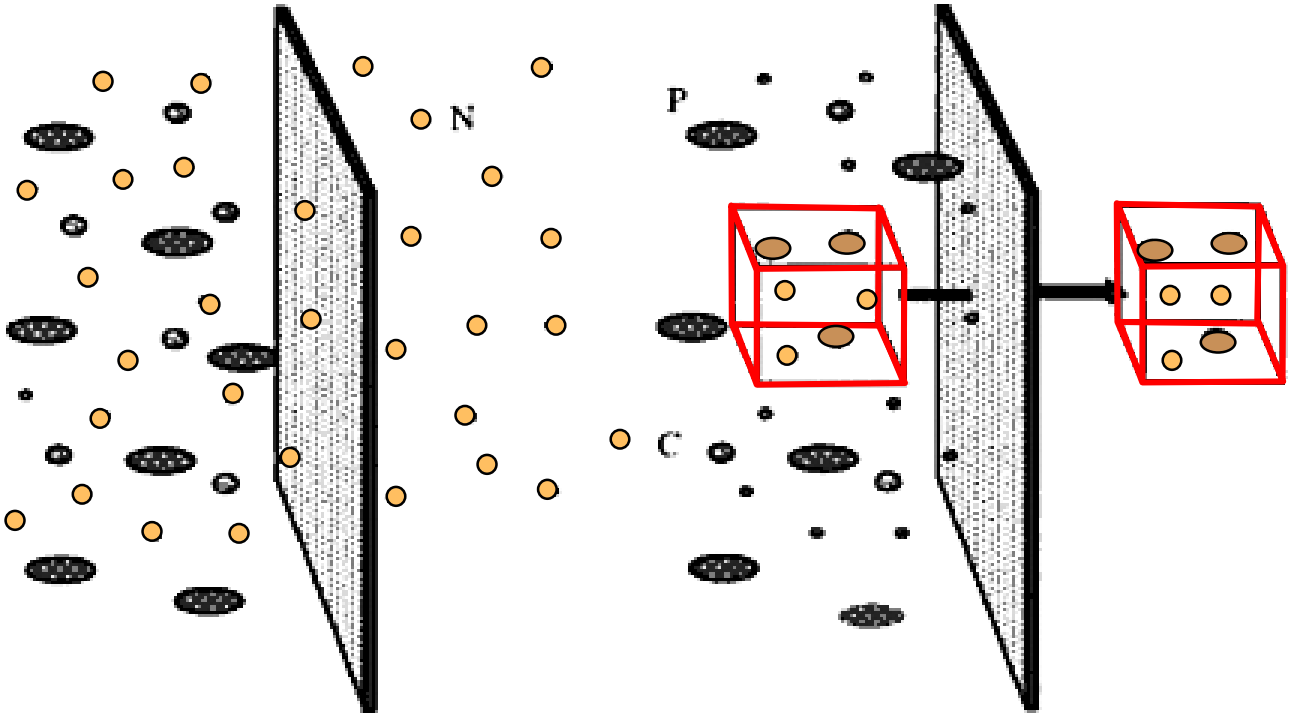
Heparin Syringe Pump

Scales x2 (up to 23 kg)

RCA for Simultaneous Pre-and Post-Dilution High Volume Hemofiltration for SIRS



Mechanisms of Solute Removal in Different Blood Purification Techniques



Diffusion

Convection

Ronco et al: Continuous renal replacement techniques; in Replacement of Renal Function by Dialysis, 5th edition; p700

Patient Systemic Chemistry Monitoring Using Effluent Solute Sensing

- **Measure delivered blood flow**
- **Measure delivered plasma flow**
- **Avoid blood clotting/biofouling completely (RCA)**
- **Sieving coefficient of solute(s) of interest = 1**
- **Measure access recirculation**
- **Know flow rate and composition of all fluids**

THE SYSTEMIC SOLUTE LEVEL IS CALCULATED!

1. Szamosfalvi et al.: System And Method For Delivery Of Regional Citrate Anticoagulation To Extracorporeal Blood Circuits US Patent 8133194
2. Roth et al.: Infrared spectroscopy in hemodialysis: reagent-free monitoring of patient detoxification. Anal Bioanal Chem (2012) 403:391–399

Effluent Solute Targets

- **Citrate Sensor**
  - Liver function monitor
- **Calcium Sensor**
  - Secondary safety monitor
- **Glucose Sensor**
  - Detect systemic hypoglycemia
- **Lactate Sensor**
  - Tissue perfusion indicator
- **Antibiotic Sensor**
  - Raman- or NIR spectroscopy (any antibiotic)

Filter Effluent Optical Sensing

Anal Bioanal Chem (2012) 403:391–399
DOI 10.1007/s00216-012-5880-3

PAPER IN FOREFRONT

Infrared spectroscopy in hemodialysis: reagent-free monitoring of patient detoxification by infrared spectroscopy

Andreas Roth · Fabian Dornuf · Oliver Klein · Daniel Schneditz · Hildegard Hafner-Gießauf · Werner Mäntele

Received: 22 December 2011 / Revised: 31 January 2012 / Accepted: 14 February 2012 / Published online: 6 March 2012
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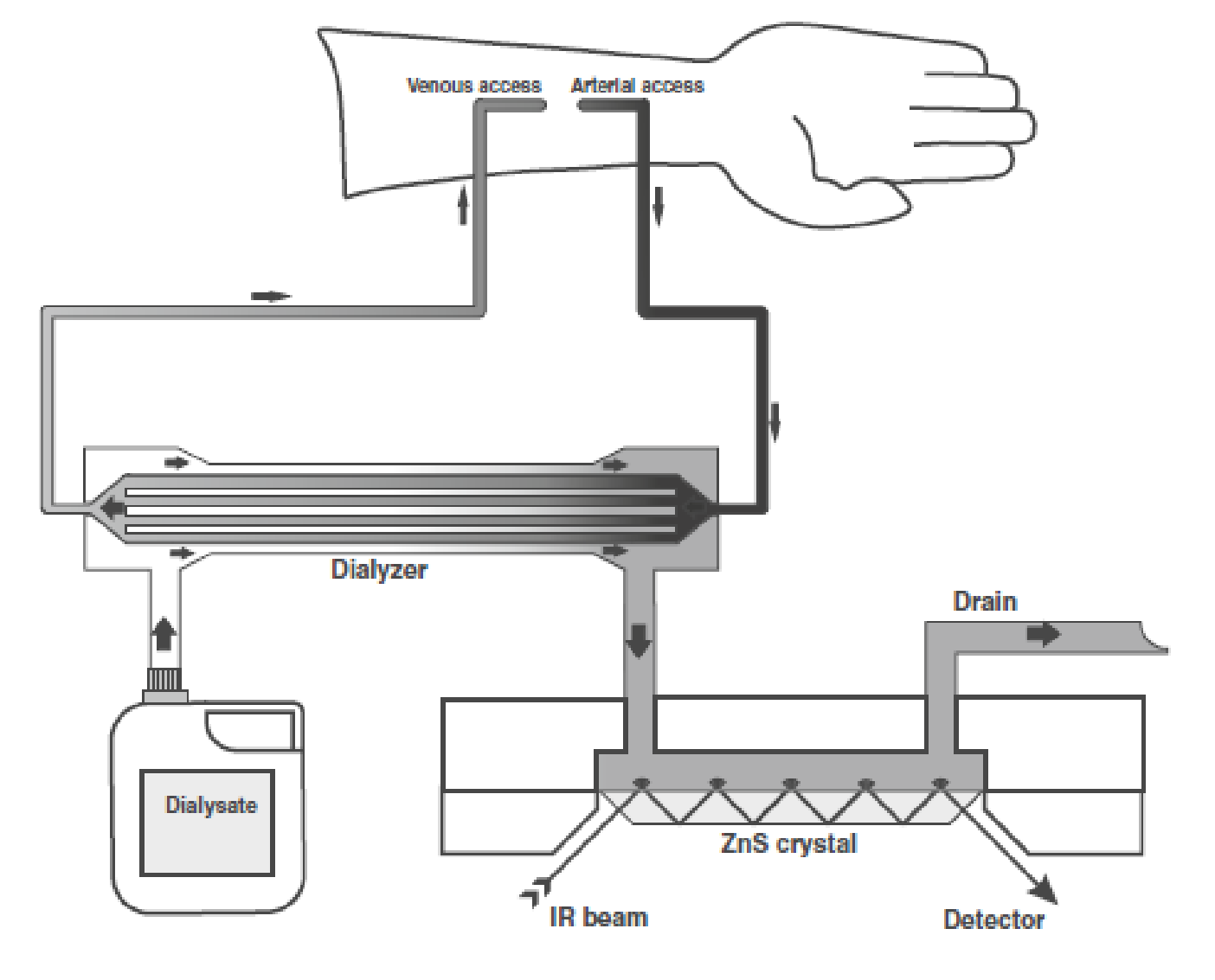
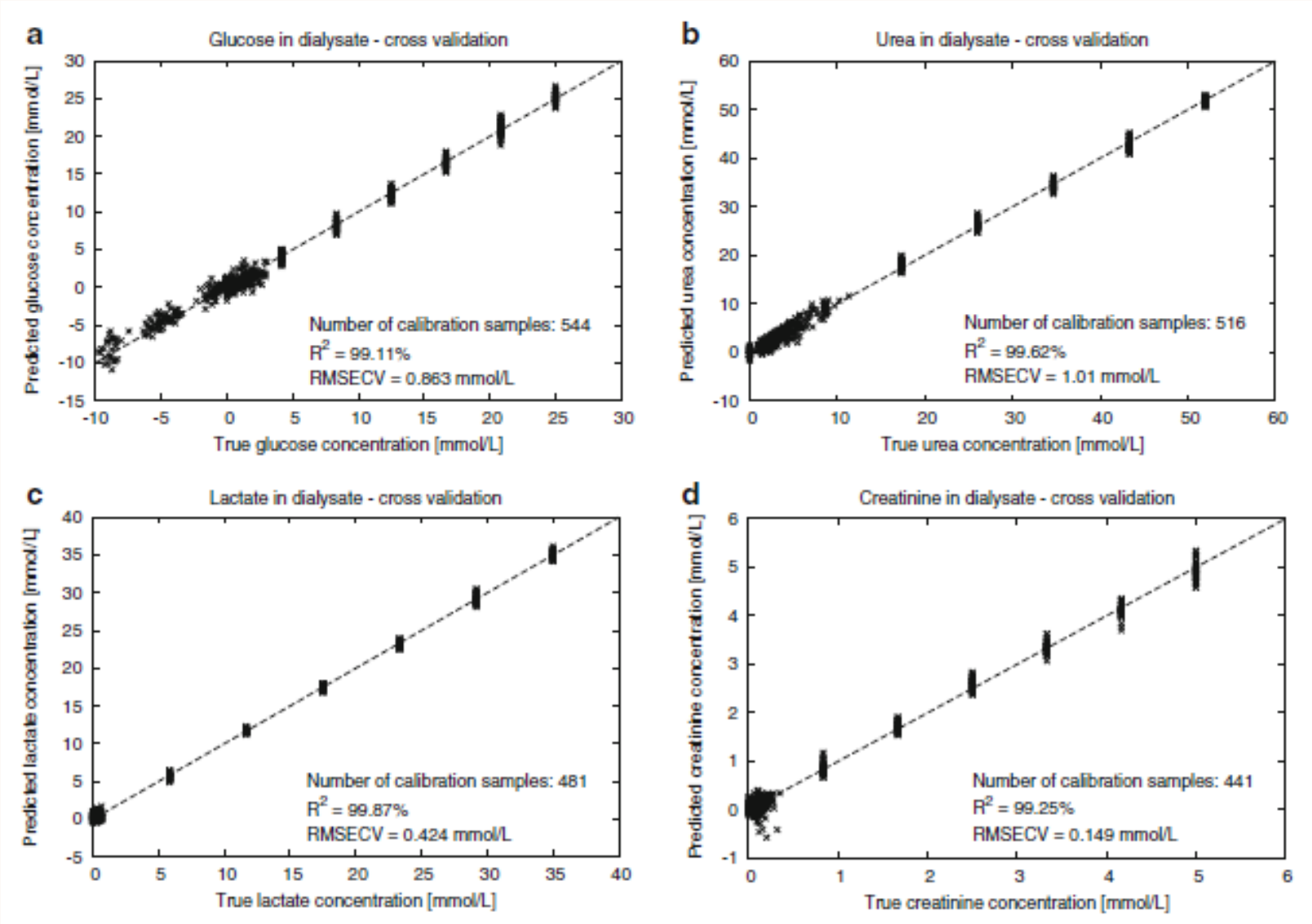
- Continuous, contactless glucose-, lactate-, phosphate-, antibiotic sensing from the filter effluent
- Requires strong anticoagulation (RCA) to keep membrane performance stable and relationship between effluent and plasma solute levels predictable

Filter Effluent Optical Sensing



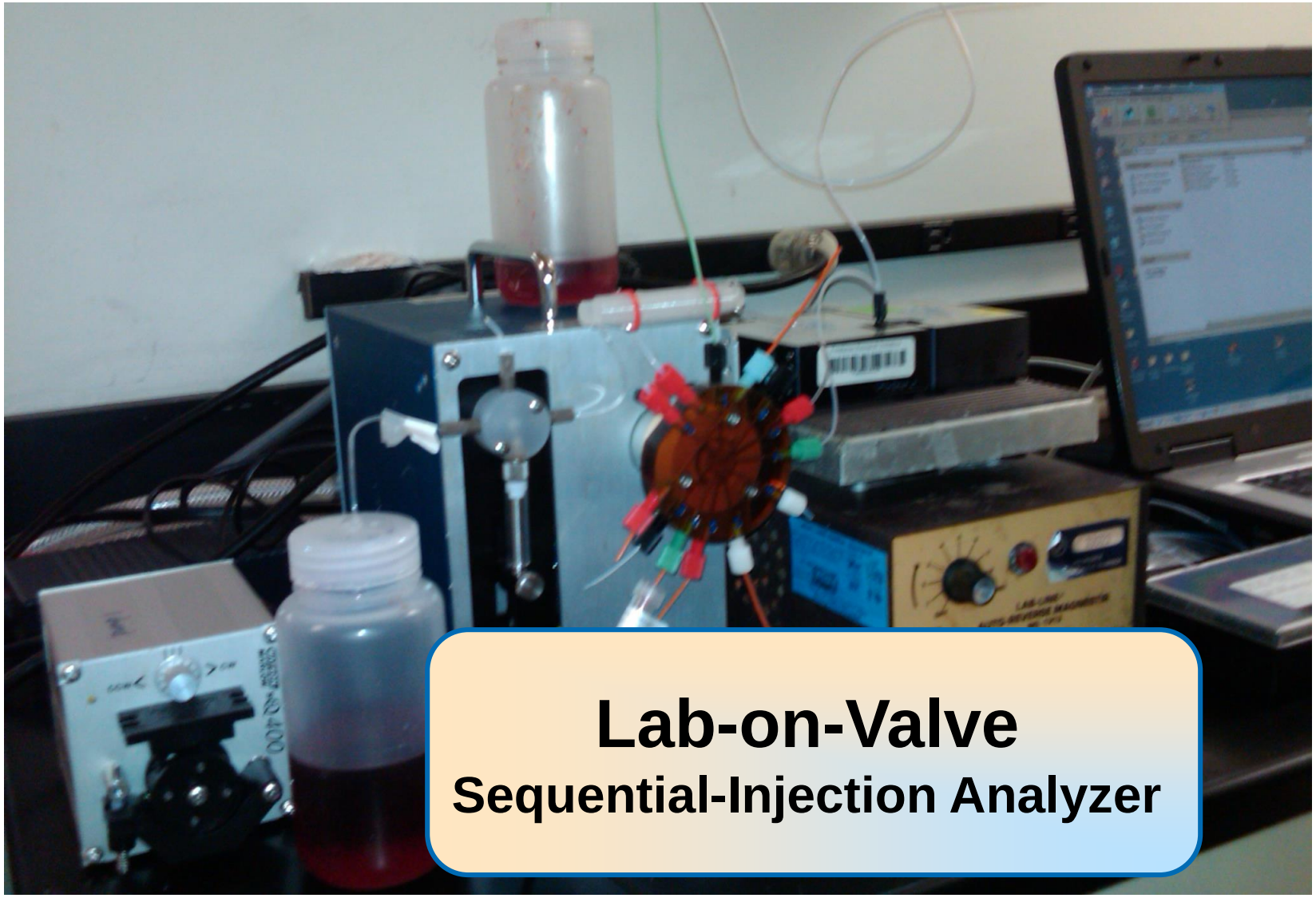
Adapted from Roth and Dornuf et al: Infrared spectroscopy in hemodialysis... Anal Bioanal Chem (2012) 403:391–399

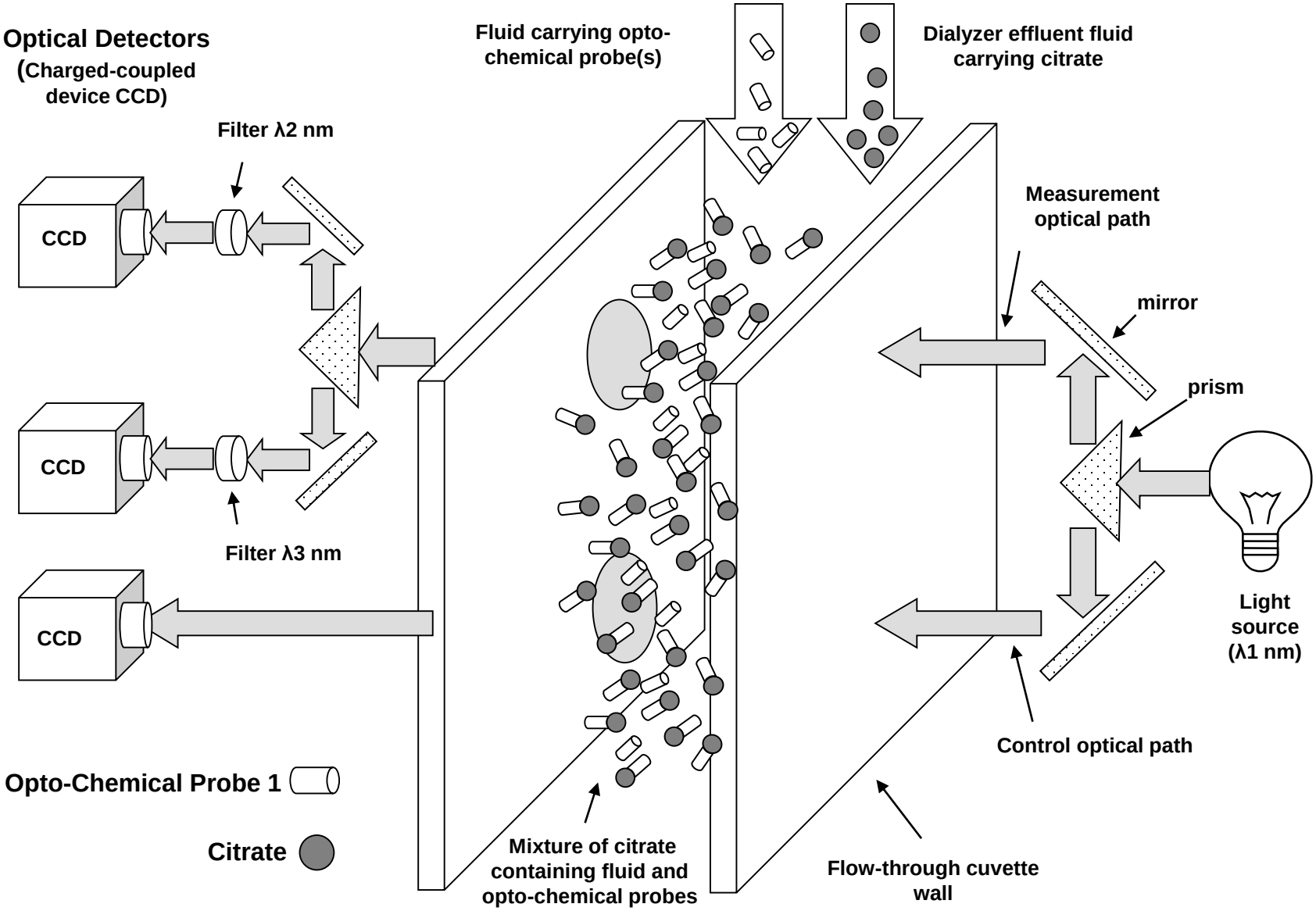
Filter Effluent Optical Sensing



Adapted from Roth and Dornuf et al: Infrared spectroscopy in hemodialysis... Anal Bioanal Chem (2012) 403:391–399

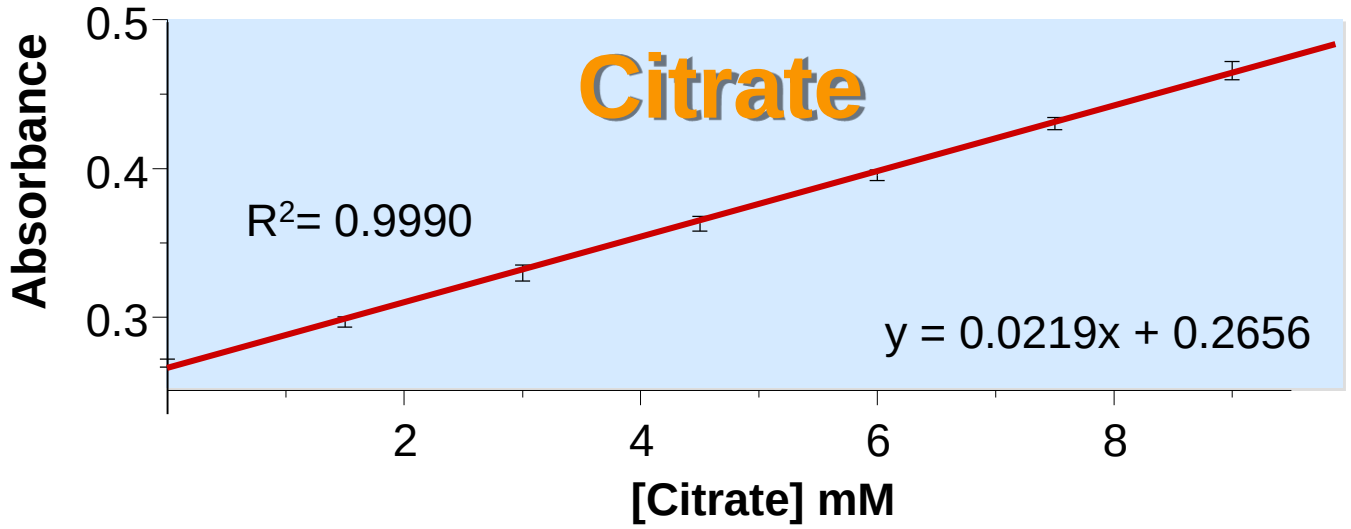
System for Measurement of Effluent Citrate and Calcium

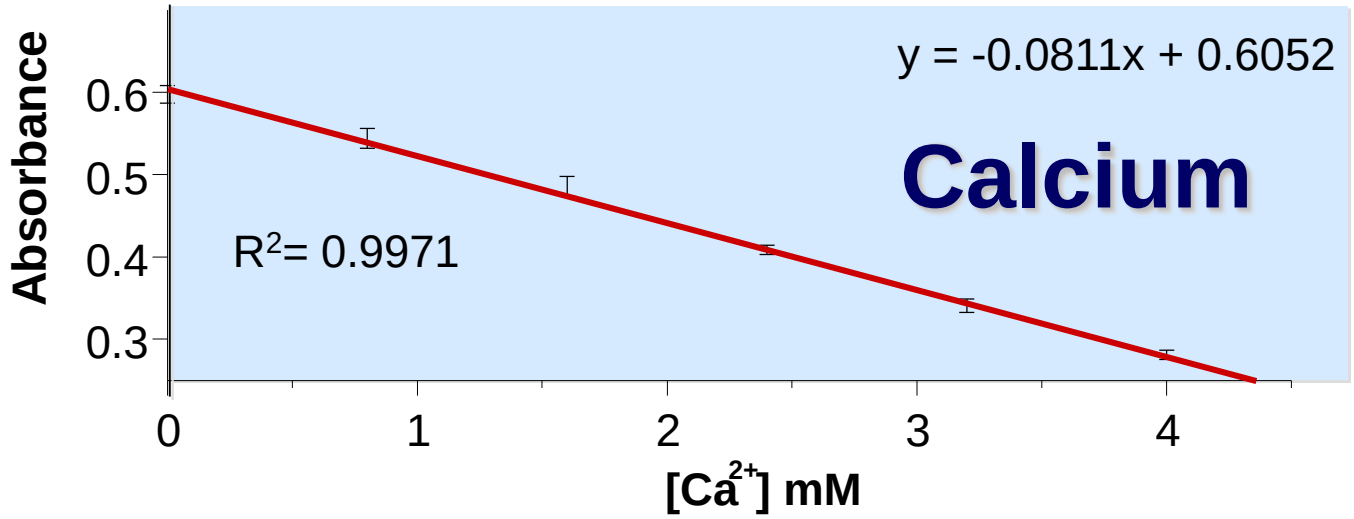




Description of a citrate, calcium and magnesium sensor for use in a continuously flowing fluid circuit. The system mixes the opto-chemical probes and the drain fluid containing citrate, calcium and magnesium before making the optical measurements. Probe binding results in changes in light absorption and or emission at specific wavelenghts. Changes in light intensity are detected and converted into electronic signals. The total citrate, calcium and magnesium concentrations are determined by a processing unit using calculations based on the obtained data.

Online Effluent Citrate- and Calcium Sensor





Adapted from Yang, Y. J., B. Szamosfalvi, J. Yee, S. Frinak and E. V. Anslyn (2011). "Development of an online citrate/Ca2+ sensing system for dialysis." Analyst 136(2): 317-320

RCA Renal Support 2012 → Future

Near-automated RCA at low blood flows without complications

Hematocrit and central venous O_2 saturation monitoring

Computerized CVVHD-RCA prescribing & telemetry monitoring

Focus: EASE OF USE,
<u>LOW COST</u> for Early Start CRRT

Antibiotic Dosing: easier with less downtime and clotting

<u>Improved Biocompatibility</u>

↓ WBC, PLT & complement activation

Ultrapure dialysate, Acetate-free

<u>Developing Therapies</u>

Columns for removal of endotoxin, cytokines, inflammatory cells, protein-bound toxins

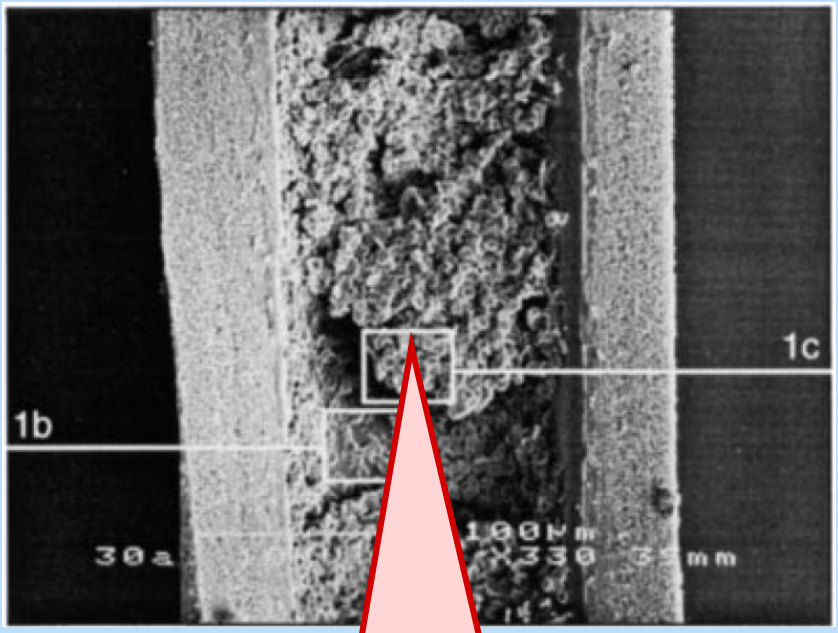
OUTCOME:

<u>(?) Improved Survival & Renal Recovery</u>

Heparin versus Citrate

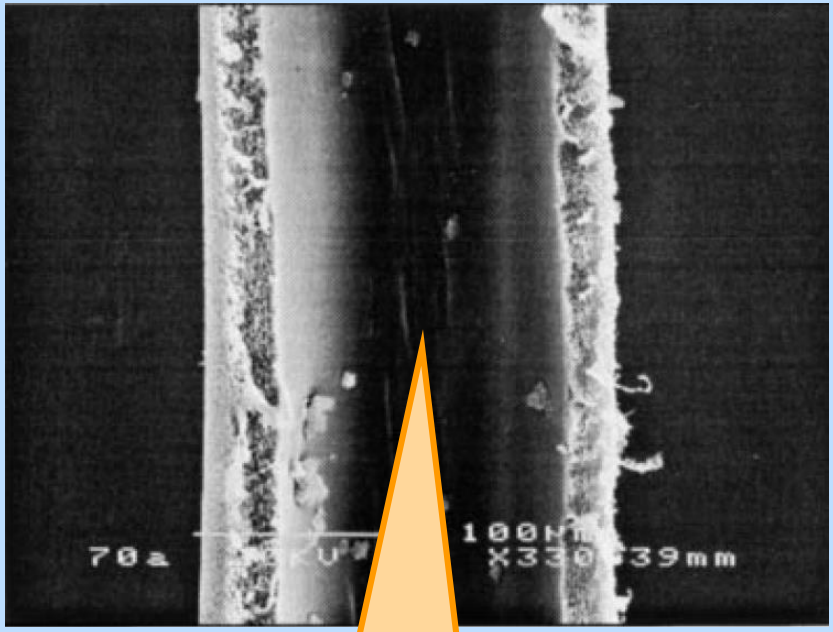
Scanning Electron Micrograph
Polysulfone Dialyzer Hollow Fiber

Heparin



Clotted Fiber

Citrate



Clean Fiber

Hofbauer et al: Effect of anticoagulation on blood membrane interactions during dialysis; Kidney Int, Vol 56 (1999): pp 1578-1583