Intensive Care Unit Renal Support: In Search of New Directions

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Thursday, 08/29/2012 09:45-10:15

Presenter Disclosure Information

I will discuss off label (US/FDA) use and/or investigational use of citrate solutions for regional anticoagulation during renal replacement therapy in my presentation.

I have financial relationships to disclose:

Employee of: Henry Ford Health System, Detroit, MI
Consultant for: Baxter, Inc
Stockholder in:
Research support from: Cytopherx, Inc
Honoraria from:
Patent: Automated RCA Systems

Objectives

1. Introduce ICU continuous renal replacement therapy (CRRT) equipment and terminology

2. Provide detailed analysis of regional citrate anticoagulation (RCA) during traditional CRRT

3. Possible future directions in ICU extracorporeal organ support

Select CRRT Machines in the USA

Scale-based effluent balancing

1. Gambro Prismaflex

Scale-based effluent balancing

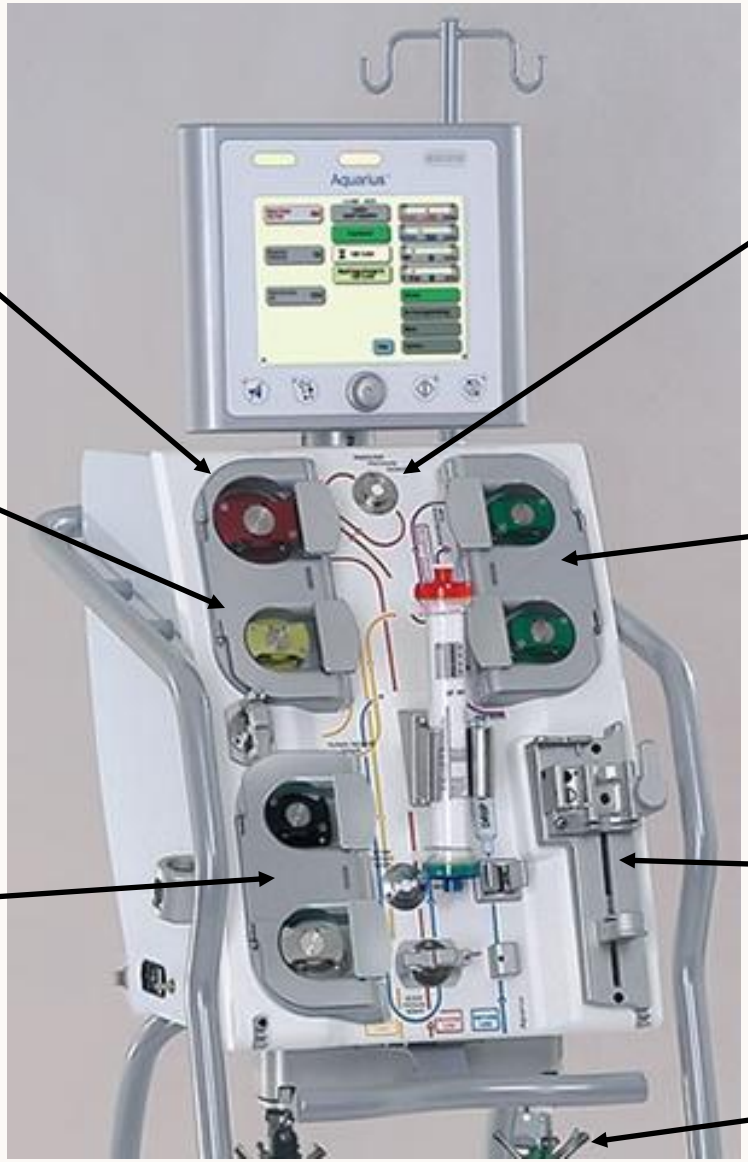
2. Braun Diapact

Sterile effluent balancing chamber

3. NxStage System One

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(Device was withdrawn from the US market)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)

CRRT Device in Europe

Fresenius Multifiltrate™ CRRT System —
Integrated Citrate & Calcium Pumps

Continuous Renal Replacement Therapy (CRRT): Modalities

1. Continuous Arterio-Venous Hemofiltration: CAVH
   The earliest form of CRRT, it used arterial blood pressure to drive blood flow and ultrafiltration in the circuit
2. Continuous Veno-Venous Hemofiltration: CVVH
   It replaced CAVH with a blood pump added to the circuit;
   Pre-dilution CVVH: Replacement fluid infused pre-filter
   Post-dilution CVVH: Replacement fluid infused post-filter
3. Continuous Veno-Venous Hemodialysis: CVVHD
   Uses counter-current dialysis for solute removal; it is being replaced by less expensive sustained low efficiency dialysis (SLED) using online generated dialysis fluid
4. Continuous Veno-Venous Hemodiafiltration: CVVHDF
   The combination of CVVH and CVVHD on a single filter

The ATN Study (2008)

1. Significance
   - Large, randomized clinical outcomes study for intensity of CRTT and intermittent HD in acute renal failure
   - Compared CRRT with 20 ml/kg/h versus 35 ml/kg/h filter effluent flow rate
   - Compared intermittent HD 1.2-1.4 single-pool urea Kt/V per session 3x/week versus 6x/week
2. Conclusions[1]
   - "Intensive renal support in critically ill patients with acute kidney injury did not decrease mortality, improve recovery of kidney function, or reduce the rate of non-renal organ failure as compared with less-intensive therapy involving a defined dose of intermittent hemodialysis three times per week and continuous renal-replacement therapy at 20 ml per kilogram per hour."

1. Palevsky P et al: Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury; N Engl J Med 2008;359:7-20.

The RENAL Study (2009)

1. Significance

- Large, multicenter, randomized clinical study of the intensity of CRRT in acute kidney injury for 90-day mortality endpoint
- Compared CRRT with 25 ml/kg/hour versus 40 ml/kg/hour filter effluent flow rate

2. Conclusions[1]

- “In critically ill patients with acute kidney injury, treatment with higher-intensity continuous renal-replacement therapy did not reduce mortality at 90 days.”

1. Bellomo R et al: Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients; N Engl J Med 2009;361:1627-38.

ICU Renal Support 2011

- Prescribe 25-30 ml/kg/h filter effluent rate
- 24-hour continuous therapy with early start
- Regional citrate anticoagulation[1,2]
- (?) Plasma adsorption: protein-bound toxin, cytokine and endotoxin removal; liver support[3,4]
- (?) Selective cytopheretic device: ameliorate severe inflammatory response syndrome[5]
- (?)Online measured small solute clearance: for dosing of dialysis and medications

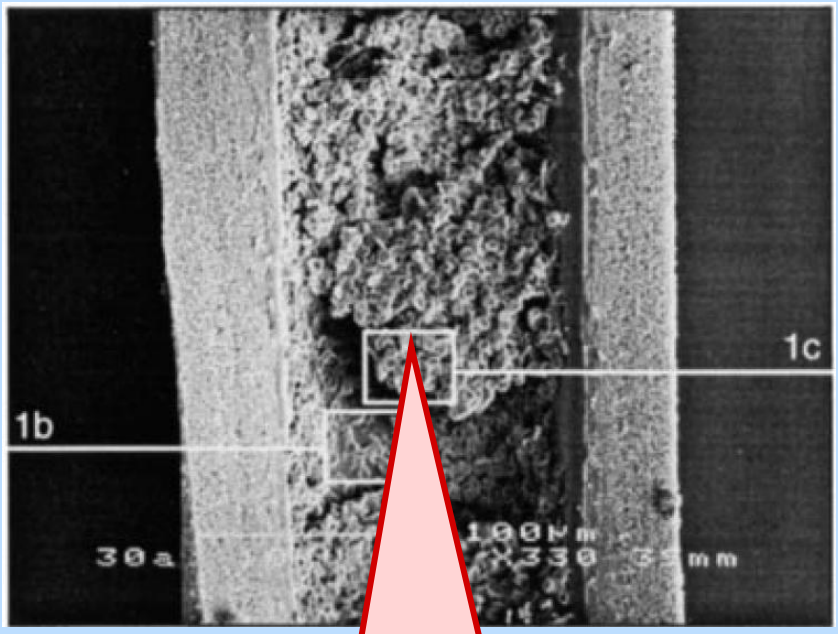
1. Davenport A et al, Citrate anticoagulation…; NDT Plus (2009) 2: 439–447
2. Oudemans-van Straaten HM, Citrate Anticoagulation…; Blood Purif 2010;29:191-196
3. Cruz DN et al, Early Use of Polymyxin B Hemoperfusion…; JAMA. 2009;301(23):2445-2452
4. Intermittent Modular Plasma Adsorption of Cytokines and Toxins (IMPACT); Minntech Corp.
5. Humes HD et al, A Selective Cytopheretic Inhibitory Device… Blood Purif 2010;29:183-190

Chemistry and Kinetic Model of RCA

Heparin versus Citrate

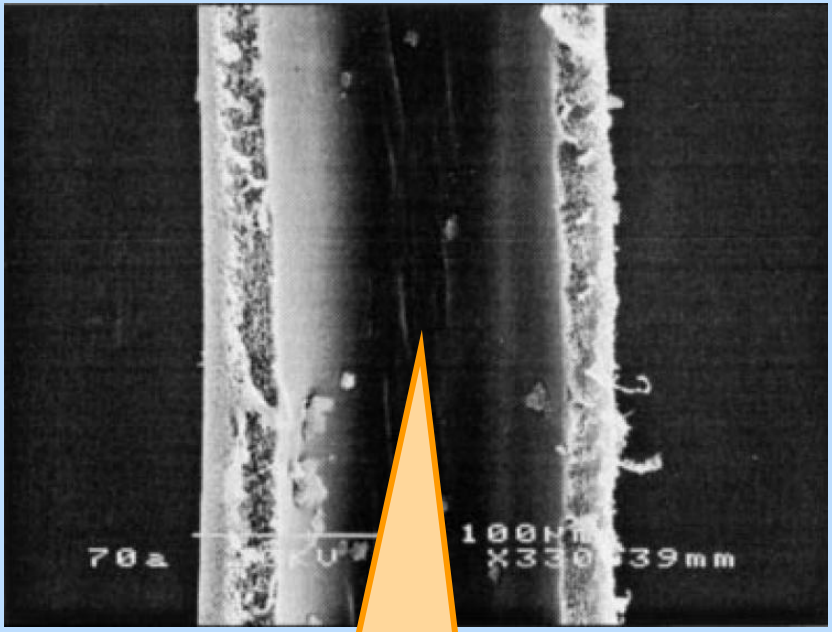
Scanning Electron Micrograph
Polysulfone Dialyzer Hollow Fiber

Heparin



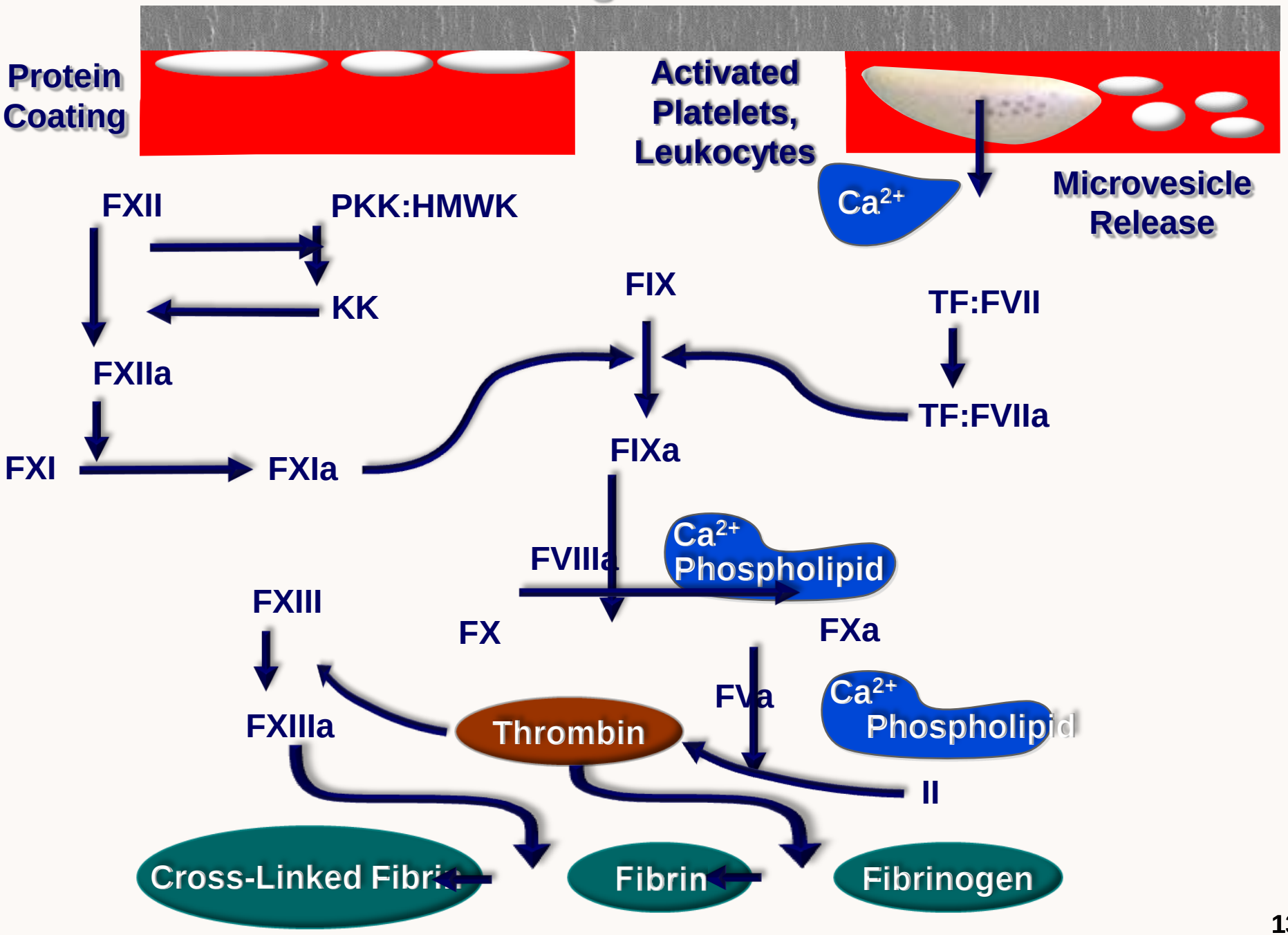
Clotted Fiber

Citrate



Clean Fiber

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


Foreign Surface
Protein Coating
Activated Platelets, Leukocytes
Ca2+
Microvesicle Release
FXII
PKK:HMWK
KK
FXIIa
FXI
FXIa
FIX
FIXa
TF:FVII
TF:FVIIa
FVIIIa
Ca2+ Phospholipid
FX
FXa
FXIII
FXIIIa
Thrombin
FVa
Ca2+ Phospholipid
II
Cross-Linked Fibrin
Fibrin
Fibrinogen

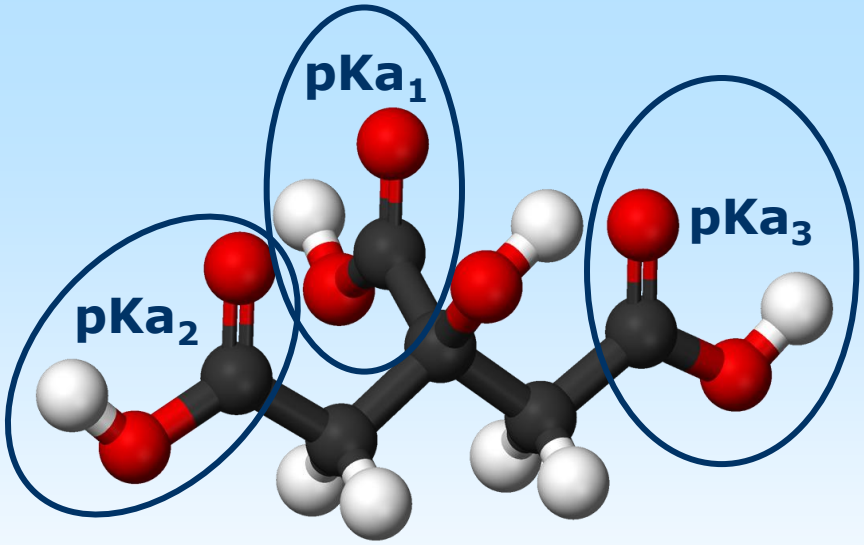
Dialyzer After Saline Rinse Back

10 hours of dialysis with RCA at QB=200 ml/min

5.3.2.2: For anticoagulation in CRRT, we suggest using regional citrate anticoagulation rather than heparin in patients who do not have contraindications for citrate. (2B)

Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney inter., Suppl. 2012; 2: 1–138.

Citric Acid / Citrate
Fundamental Properties



$pKa_1 = 3.09$

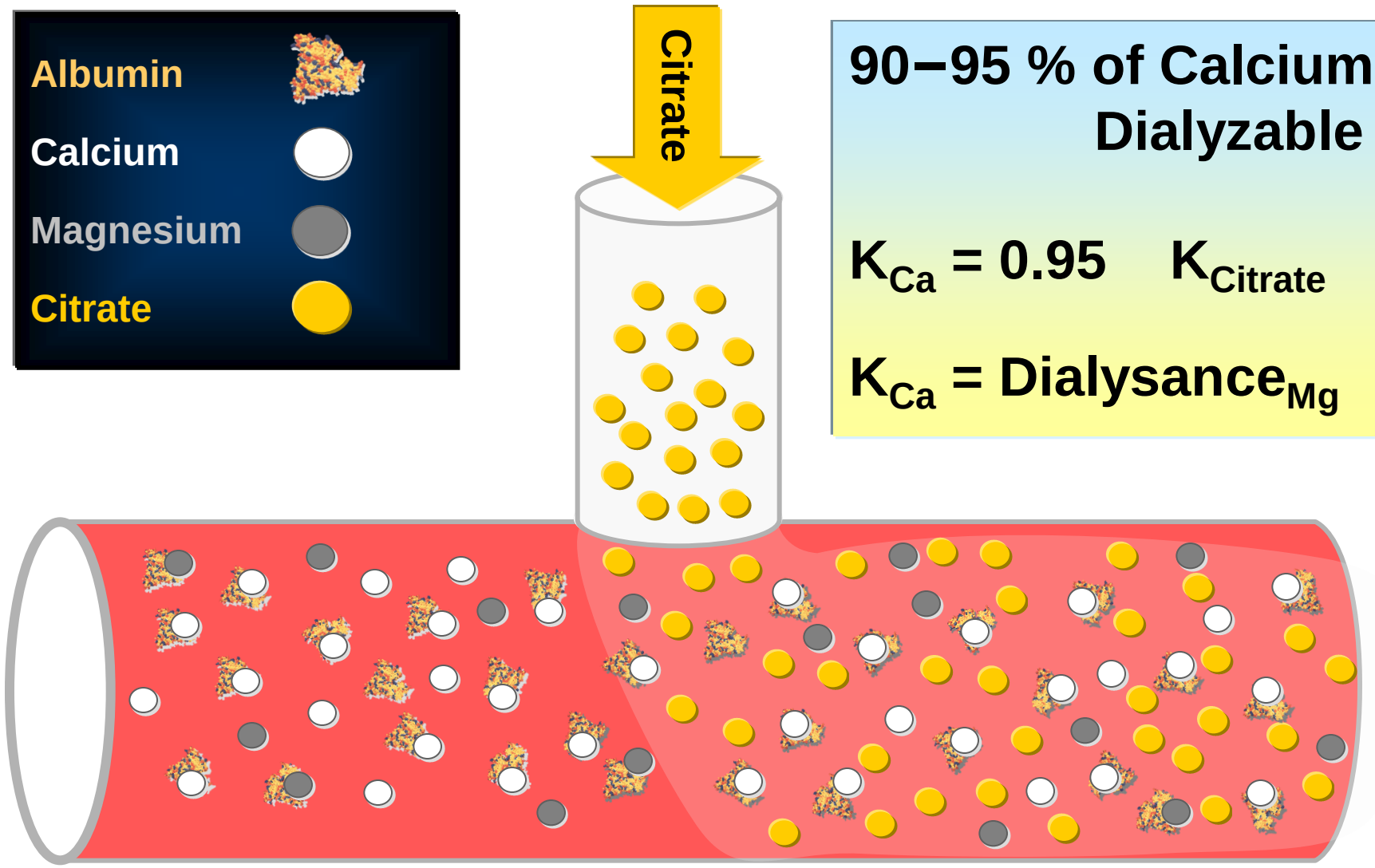
$pKa_2 = 4.75$

$pKa_3 = 5.41$

- **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

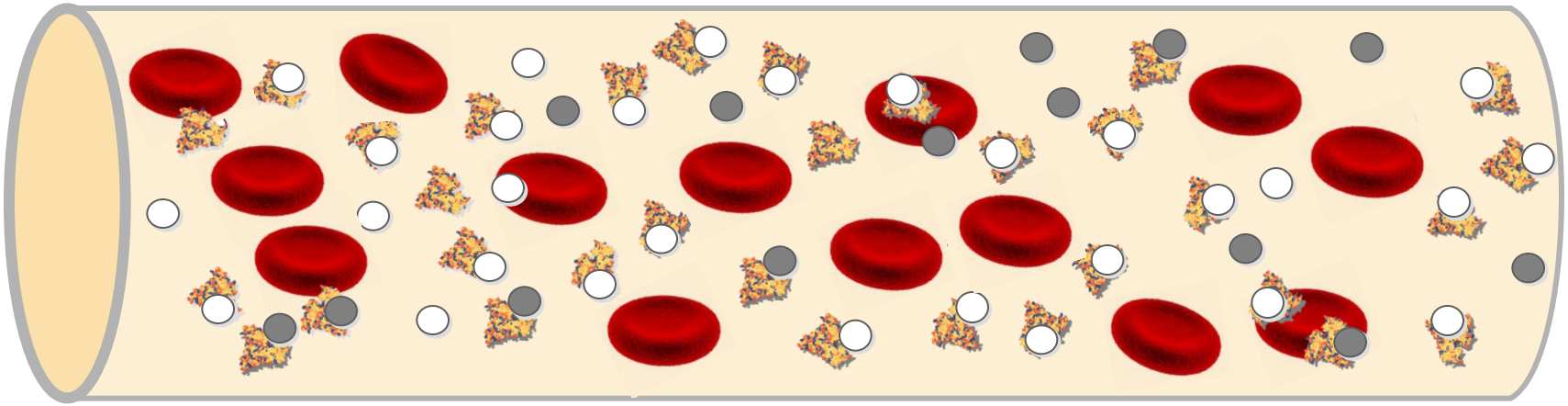


90–95 % of Calcium Dialyzable

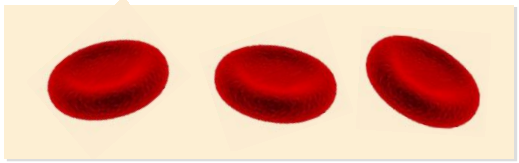
$K_{Ca} = 0.95$ $K_{Citrate}$

$K_{Ca} = Dialysance_{Mg}$

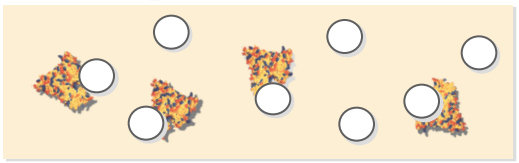
Hematocrit Defines Circuit Plasma Flow



More Red Cells



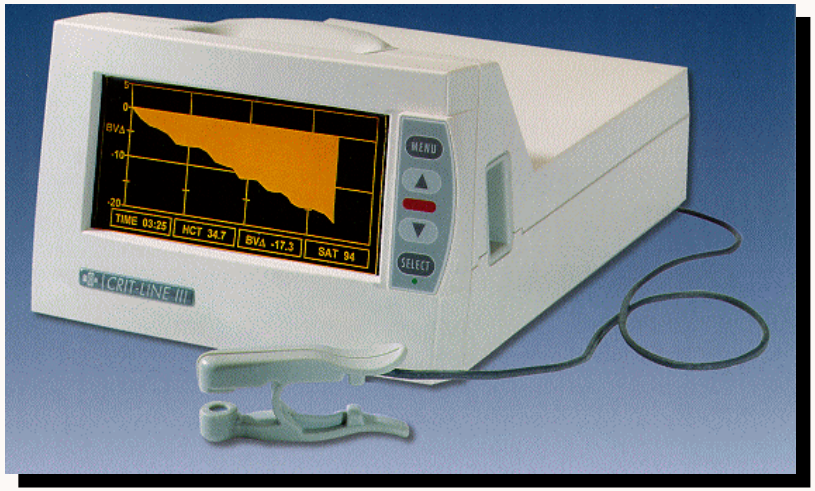
Less plasma flow



Less Ca-Free Plasma to Restore to Target Total Ca

Decrease Ca Infusion Rate

Optical Hemoglobin Monitor



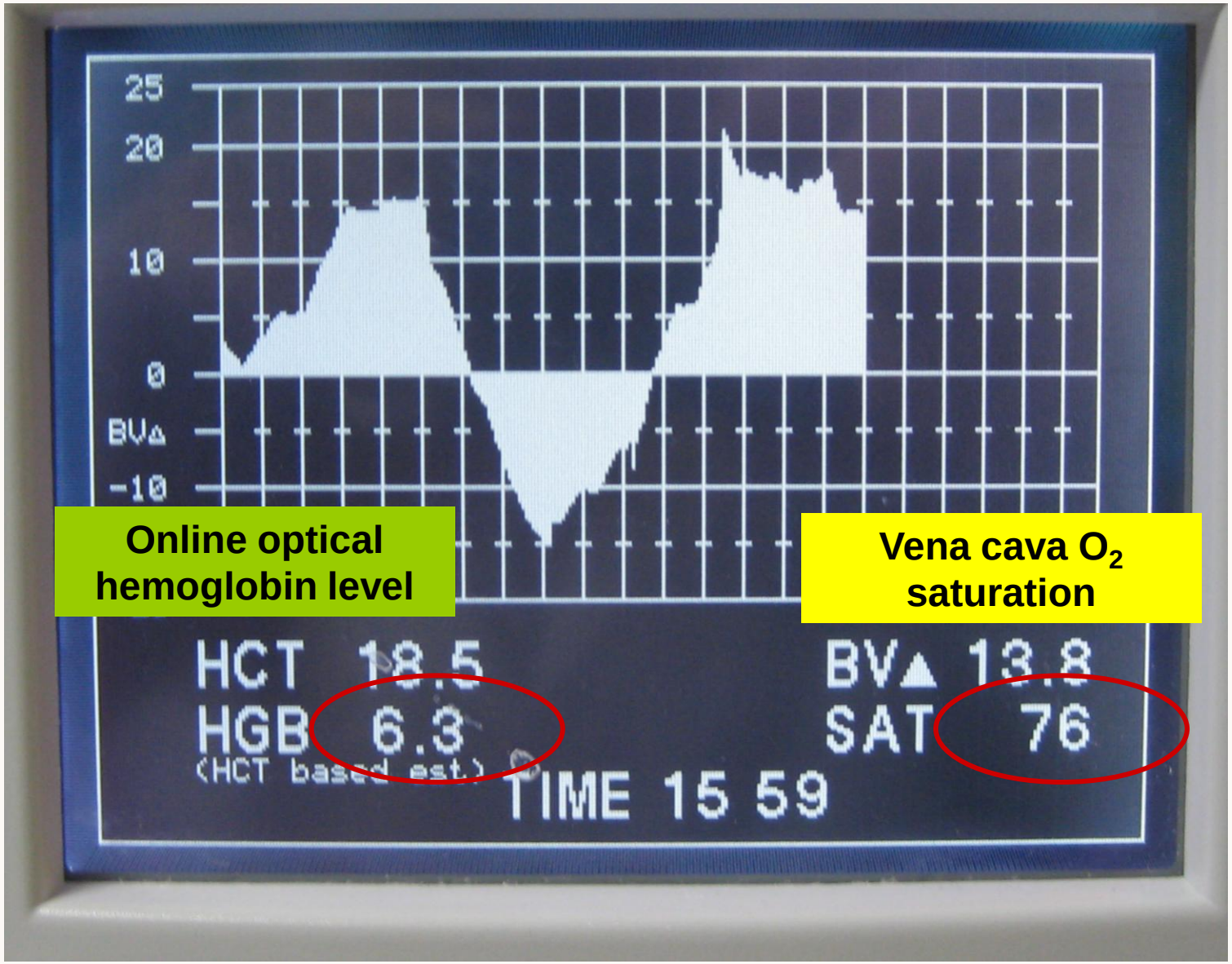
- Probe clips on blood circuit
- No-contact technology
  - Light absorption based
- Measures hematocrit
- Measures O_2 saturation

©Fresenius

©Fresenius

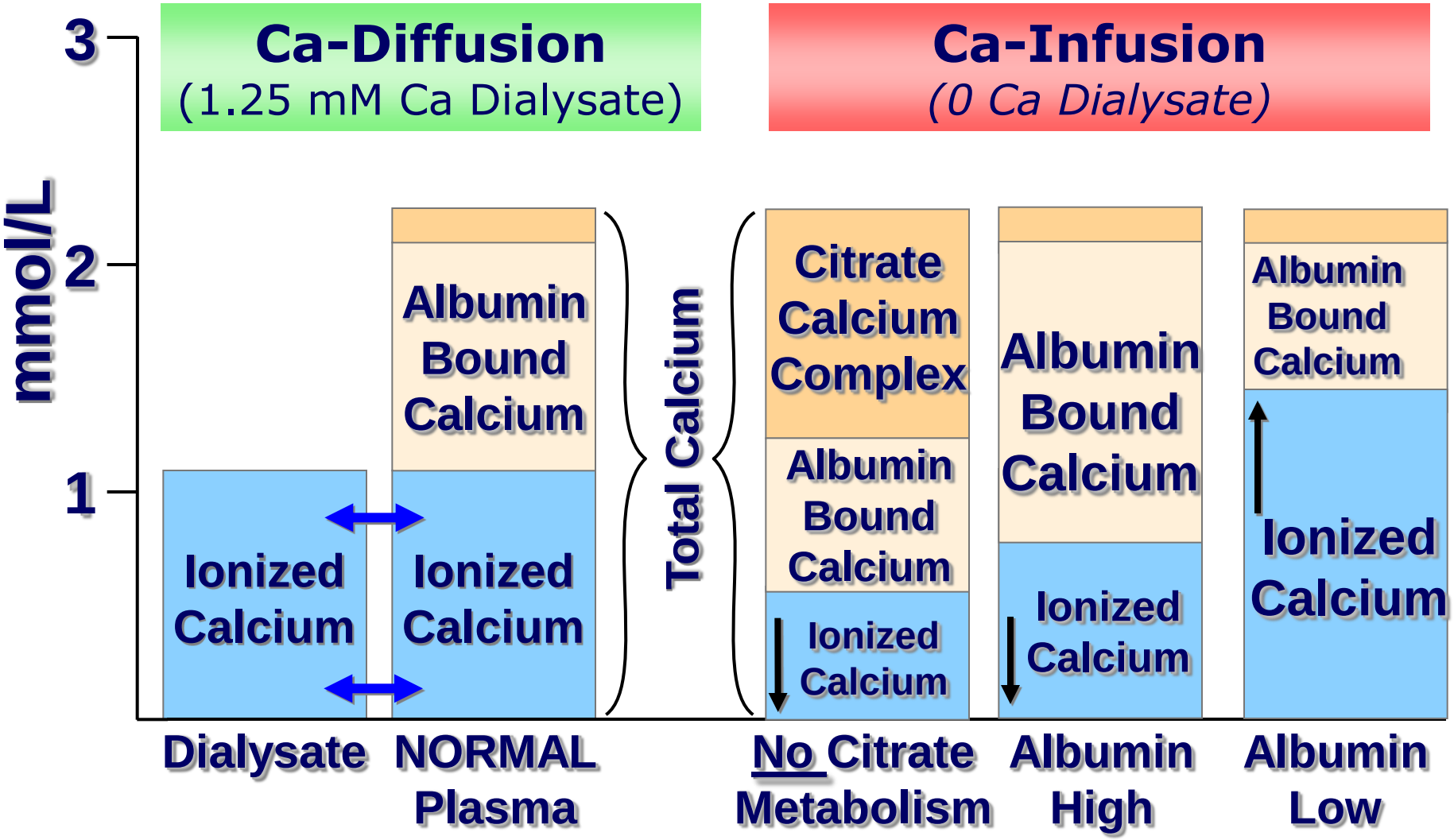
Hemametrics Crit-Line III TQA™—
Online Hematocrit and O_2 saturation Sensor

Hematocrit Monitor Screen



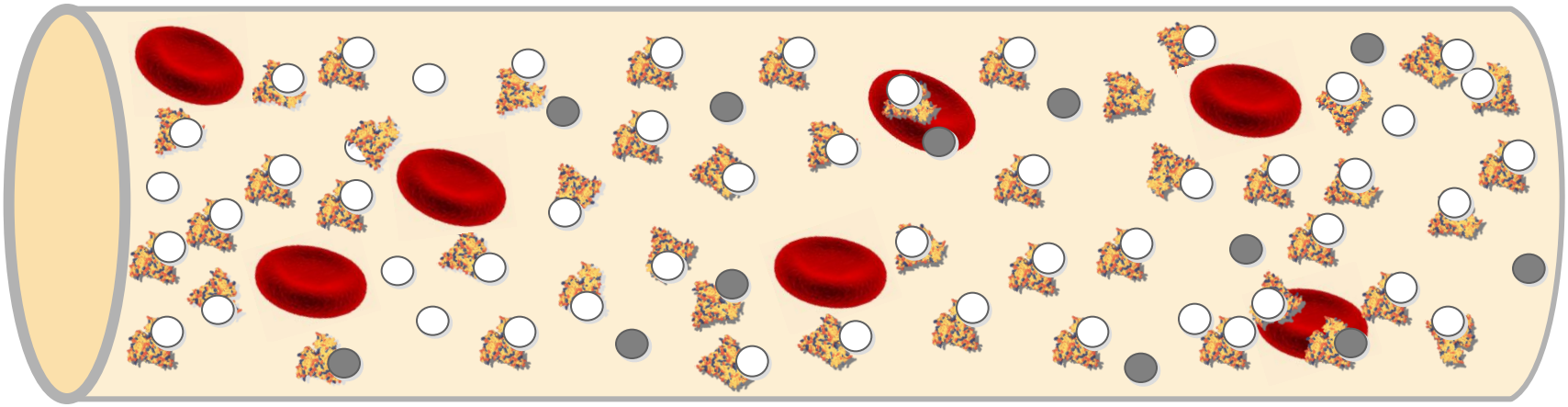
Plasma Ionized & Total Ca

Effect of Citrate and Albumin Levels



Modified from: Davenport A , Tolwani A NDT Plus 2009;2:439-447

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 SLED (ml/hr)

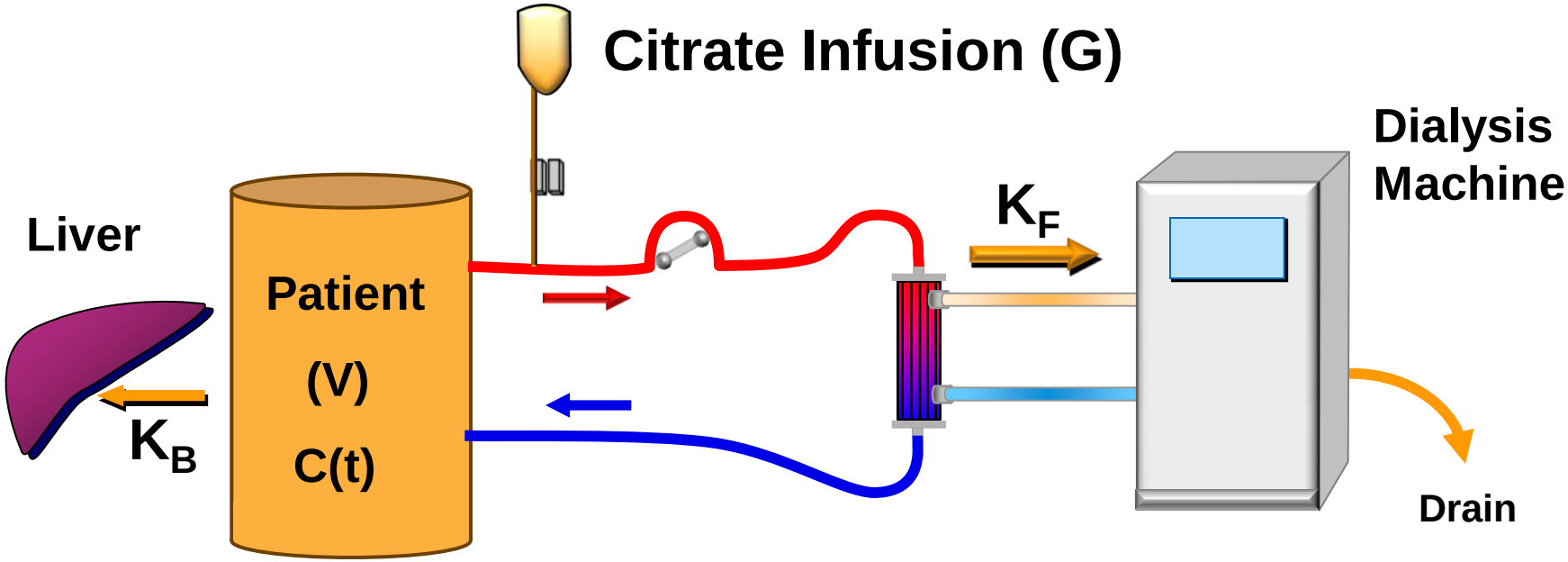
Ca/Mg solution (10 gm CaCl2 + 2 gm MgCl2 in 0.5 L 0.9% saline)

Hgb 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	34	33	32	30	29	28	26	25	24	22
0.8-1.2	36	35	33	32	31	29	28	26	25	24
1.3-1.7	38	37	35	34	32	31	29	28	26	25
1.8-2.2	40					32	31	29	28	26
2.3-2.7	42		**39**		**36**	34	32	31	29	27
2.8-3.2	44					36	34	32	30	29
3.3-3.7	46					37	36	34	32	30
3.8-4.2	48	47	45	43	41	39	37	35	33	31
4.3-4.7	50	48	47	45	43	41	39	37	35	33
4.8-5.2	52	50	48	46	44	42	40	38	36	34
5.3-5.7	54	52	50	48	46	44	42	40	37	35

Starting Value | New Value

Citrate Kinetic Modeling

Patient with Volume (V) and Citrate Concentration C(t)



Mass Balance Equation

$$V \frac{dC}{dt} = G - C(K_F + K_B)$$

Szamosfalvi B et al: United States Patent Application 20080015487

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

Single-Pool, Fixed Volume Citrate Kinetic Modeling

$$C(t) = C(0) \cdot e^{-\left[(K_F + K_B) \cdot \frac{t}{V}\right]} + \left(\frac{G}{K_F + K_B}\right)\left(1 - e^{-\left[(K_F + K_B) \cdot \frac{t}{V}\right]}\right)$$

C(t) = Citrate in systemic plasma (mmol/L)

K_F = Filter plasma K_{Cit} (L/h) = QP E_{Cit}

K_B = Body plasma K_{Cit} (L/h)

t = time from start of modeling (h)

V = V_D Citrate = Extra Cellular Fluid Space (L)

G = Citrate Load (mmol/h) = QP C_{Inf} $(1-E_{Cit})$

Citrate Measured Versus Model Predicted Levels In ESRD

	ESRD
C_0	0.1
V_0	22
G	24
K_B	19

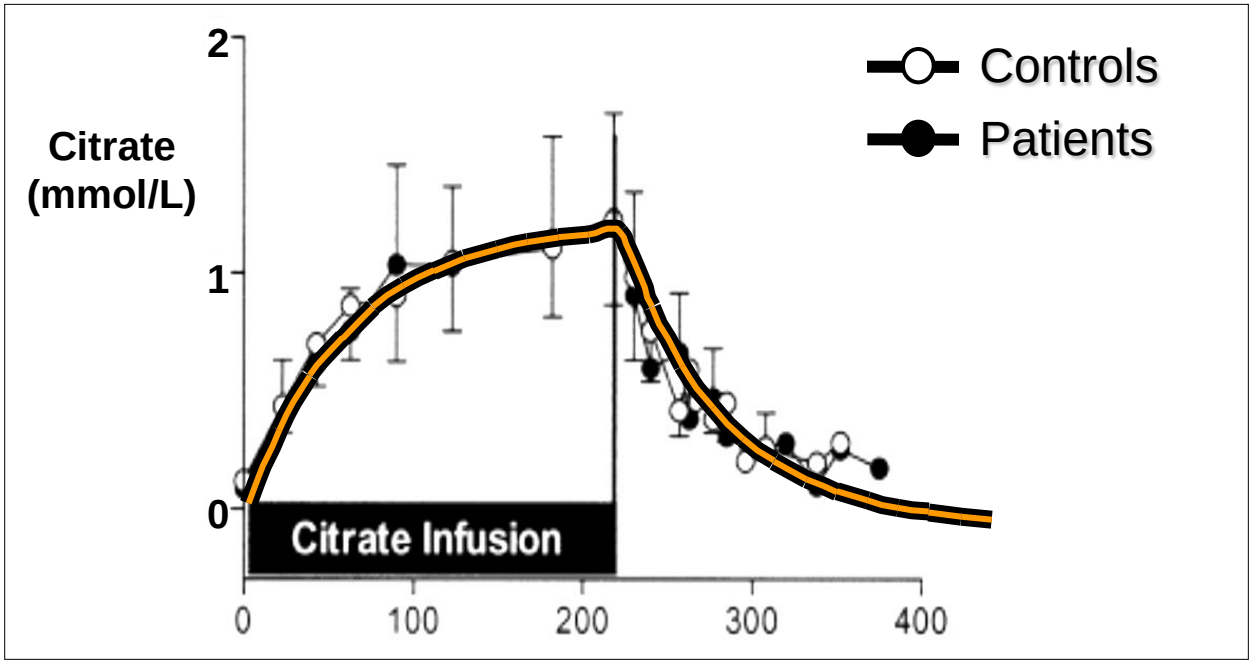


Table 2. Citrate Pharmacokinetics

	Patients With Renal Failure (n = 7)	Control Subjects (n = 11)
Baseline citrate (mmol/L)	0.09 ± 0.03	0.12 ± 0.03
Maximum citrate (mmol/L)	1.24 ± 0.42	1.19 ± 0.33
Time to maximum concentration (min)	212 ± 18	196 ± 31
AUC (mmol × min/L)	265 ± 85	270 ± 76
Citrate half-life (min)	49 ± 14	59 ± 14
Clearance (L/min)	0.31 ± 0.06	0.35 ± 0.11

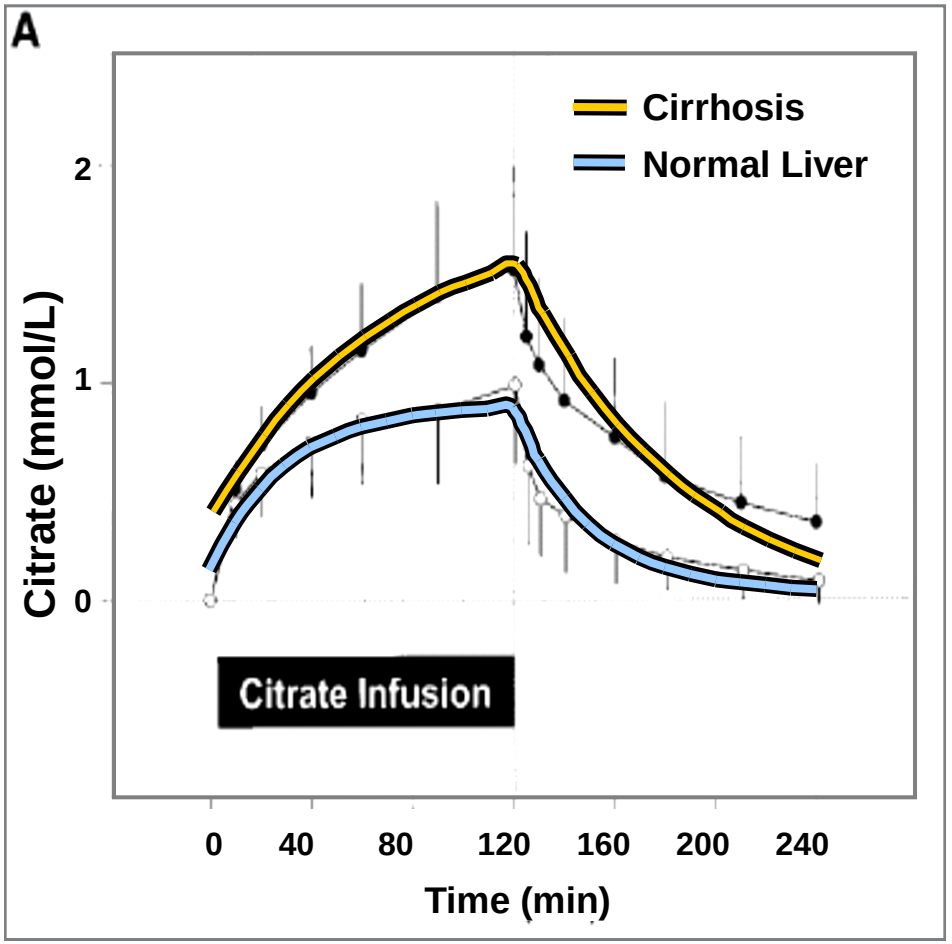
Adapted from Bauer *et al*, Am J Kidney Dis 46:903-907

Measured vs Modeled Citrate Levels

Normal vs Reduced Liver Function

	Cirrhotic Patients	Control Group	*p* Value
Total dose, mmol	77 ± 21	72 ± 10	.40
$C_{baseline}$, mmol/L	0.51 ± 0.13	0.06 ± 0.13	<.001
C_{max}, mmol/L	1.60 ± 0.50	1.01 ± 0.39	.007
T_{max}, mins	115 ± 12	114 ± 16	.93
AUC, mmol × min/L	282 ± 130	131 ± 68	<.001
$t_{1/2}$, mins	69 ± 33	36 ± 18	.001
Vd_z	27 ± 9	29 ± 10	.52
Vd_{ss}	23 ± 6	21 ± 6	.34
Clearance, mL/min	340 ± 185	710 ± 397	.002

	Cirrhosis	Normal
C_0	0.5	0.1
V	23	21
G	38	36
KB	20	43

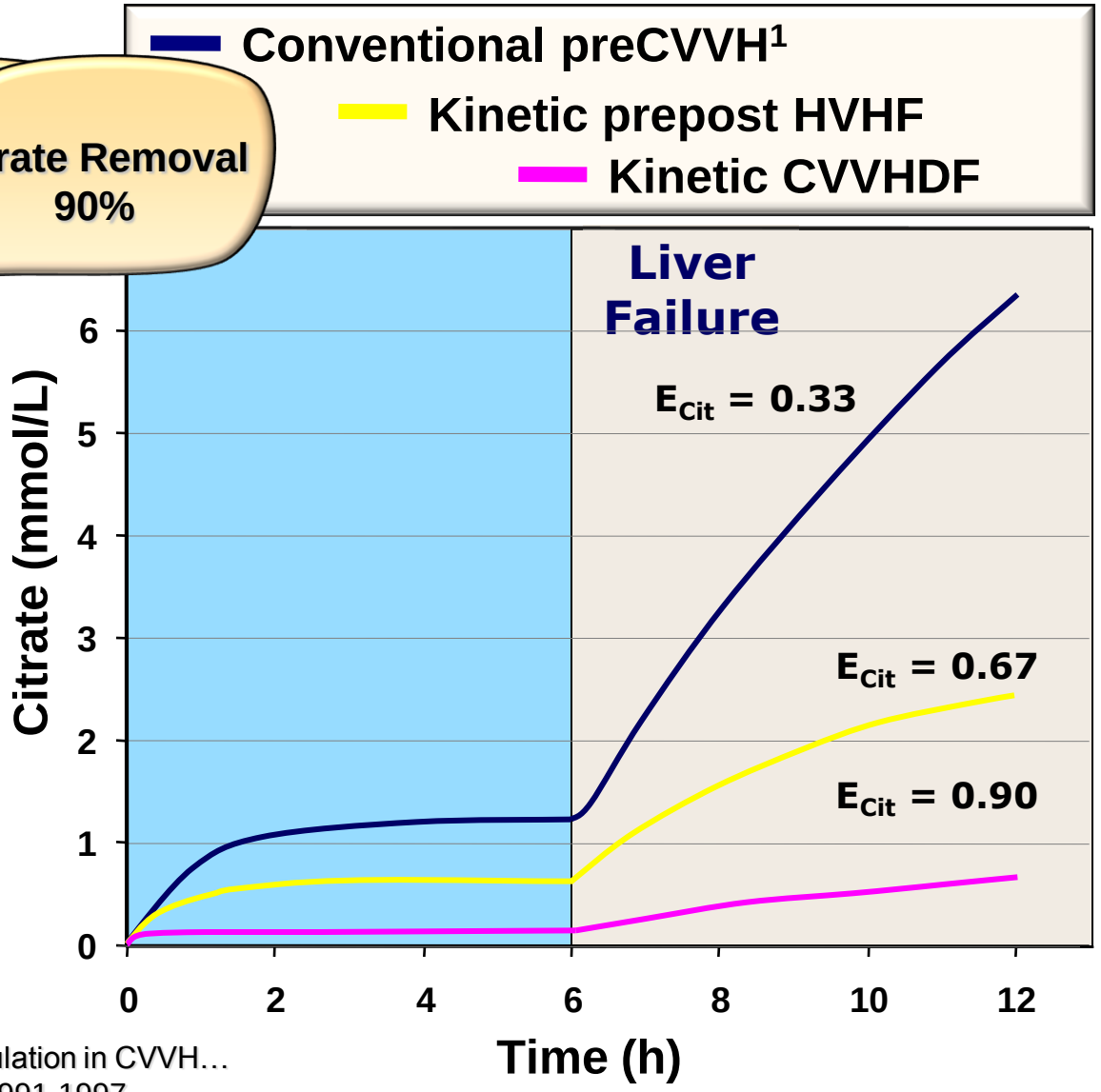


	Cirrhotic Patients	Control Group	P
Clearance mL/min	340 ± 185	710 ± 397	0.002

Kinetic Analysis of Traditional CRRT with RCA

Systemic Citrate Kinetic Modeling Pre- and Post Liver Failure

Kinetic	Citrate	Citrate	Citrate Removal 90%
Q_P			
C_{Inf}	6.5	5.7	7
E_{Cit}	0.33	0.67	0.9
C_0	0.1	0.1	0.1
V_0	21	21	21
G	26	15	2.3
K_f	2	5.4	2.9
K_b	18	18	18
K_{bs}	0	0	0



1. Palsson et al.: Regional citrate anticoagulation in CVVH… Kidney International, Vol 55 (1999), pp 1991-1997.

Conventional RCA Dangers

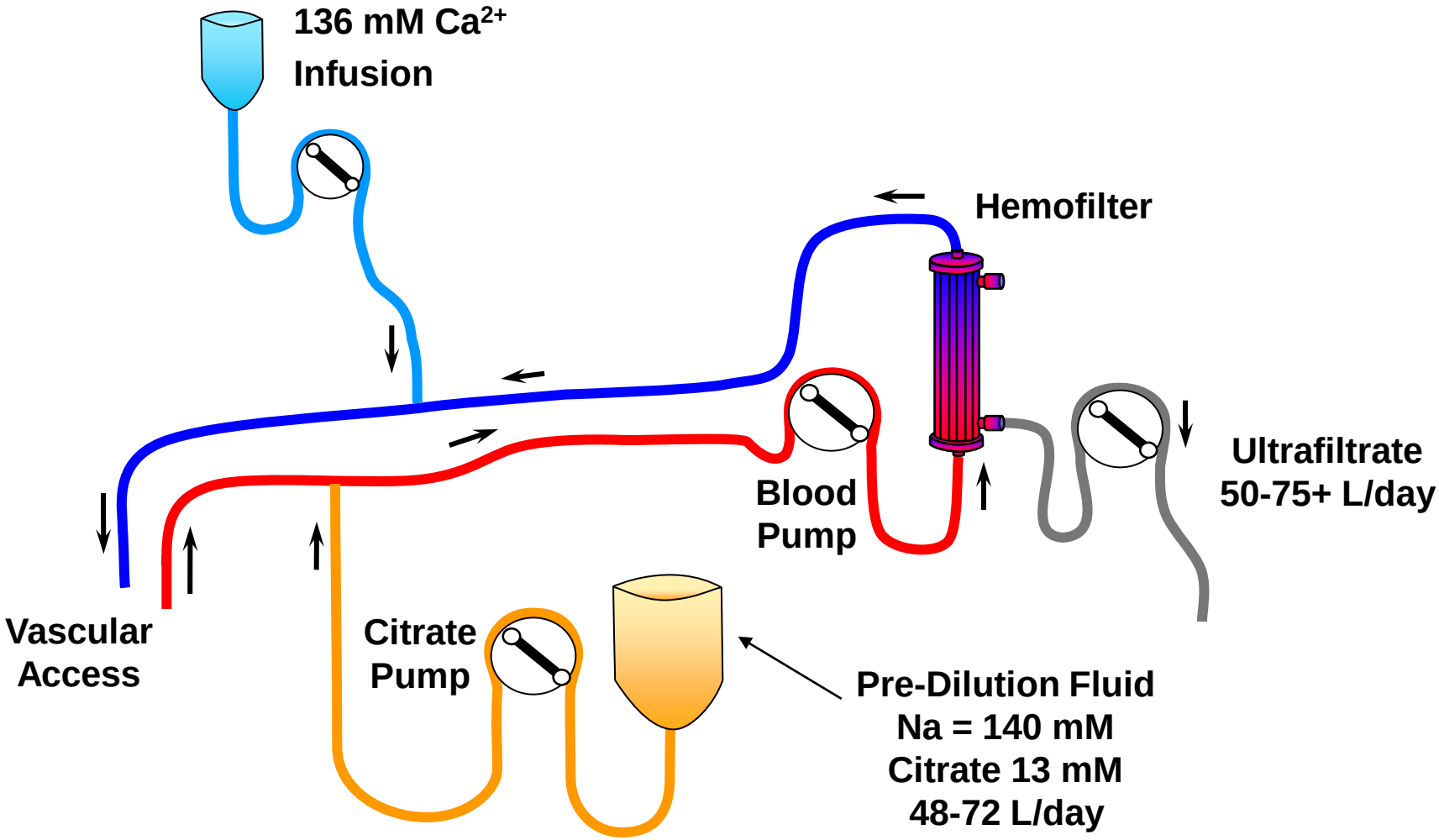
1. Labs change rapidly, ie, faster than Q6H

Ex: iCa may fall from 1.0 mM to <0.6 in 2–3 h, if citrate metabolism is impaired

2. Labs change due to disease, citrate metabolism and CRRT, precluding a cause-specific response

Ex: The iCa may fall due to tissue sequestration, citrate accumulation or net Ca loss with the CRRT

Isolated Pre-Dilution CVVH



1. Aman et al.:Metabolic effects of citrate- vs bicarbonate-based substitution fluid in continuous venovenous hemofiltration: A prospective sequential cohort study. Journal of Critical Care (2010) 25, 120–127
2. Palsson et al.: Regional citrate anticoagulation in continuous venovenous hemofiltration in critically ill patients with a high risk of bleeding. Kidney International, Vol 55 (1999), pp 1991-1997.

Kinetic Analysis Of Conventional RCA for Pre-Dilution CVVH

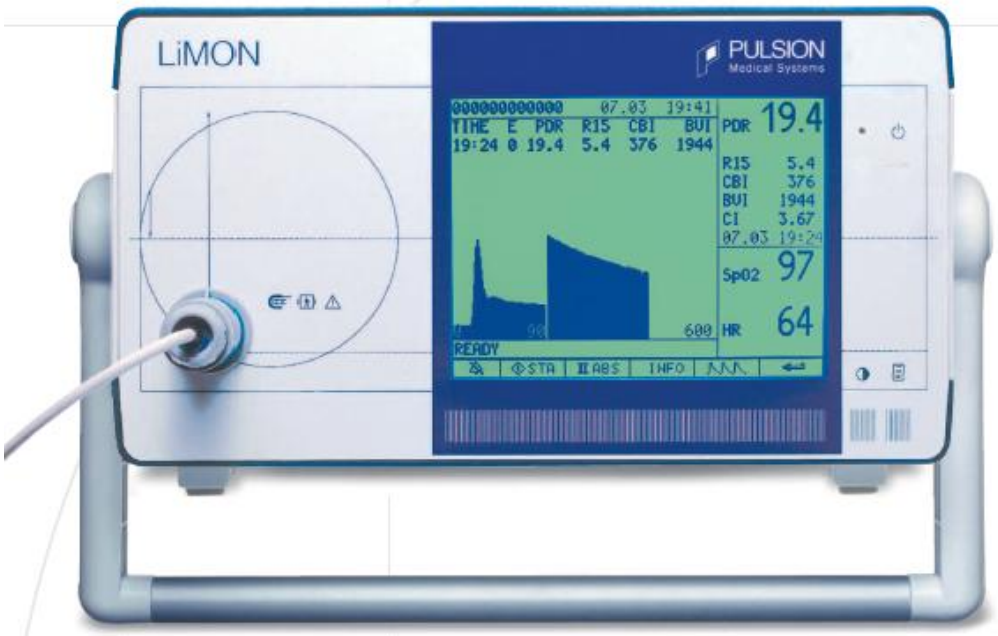
Prescribed Flows	
(Hct	30 %)
QB	150 ml/min
QP	6 L/h
QPre	3 L/h
QCa	30-50 ml/h

Kinetic Parameters	
Cinf =	6.5 mM
Ecit =	**0.33**
Cmax ≤	13 mM
C Load, G =	26 mmol/h
K_{urea} =	2.3 L/h
G/K_{urea} =	**11.3 mmol/L**

Kinetic Analysis of Conventional RCA for Pre-Dilution CVVH

- **Na^+** mass balance neutral at serum **$Na^+ \approx 140$ mM**
- **HCO_3^-** mass balance restored by citrate metabolism; no metabolic alkalosis
- Maximum possible systemic citrate level **13 mM!**
- **Systemic plasma iCa^{2+}, iMg^{2+} and $HCO3^-$ cannot be maintained when citrate metabolism is impaired**

Commercial Liver Monitor



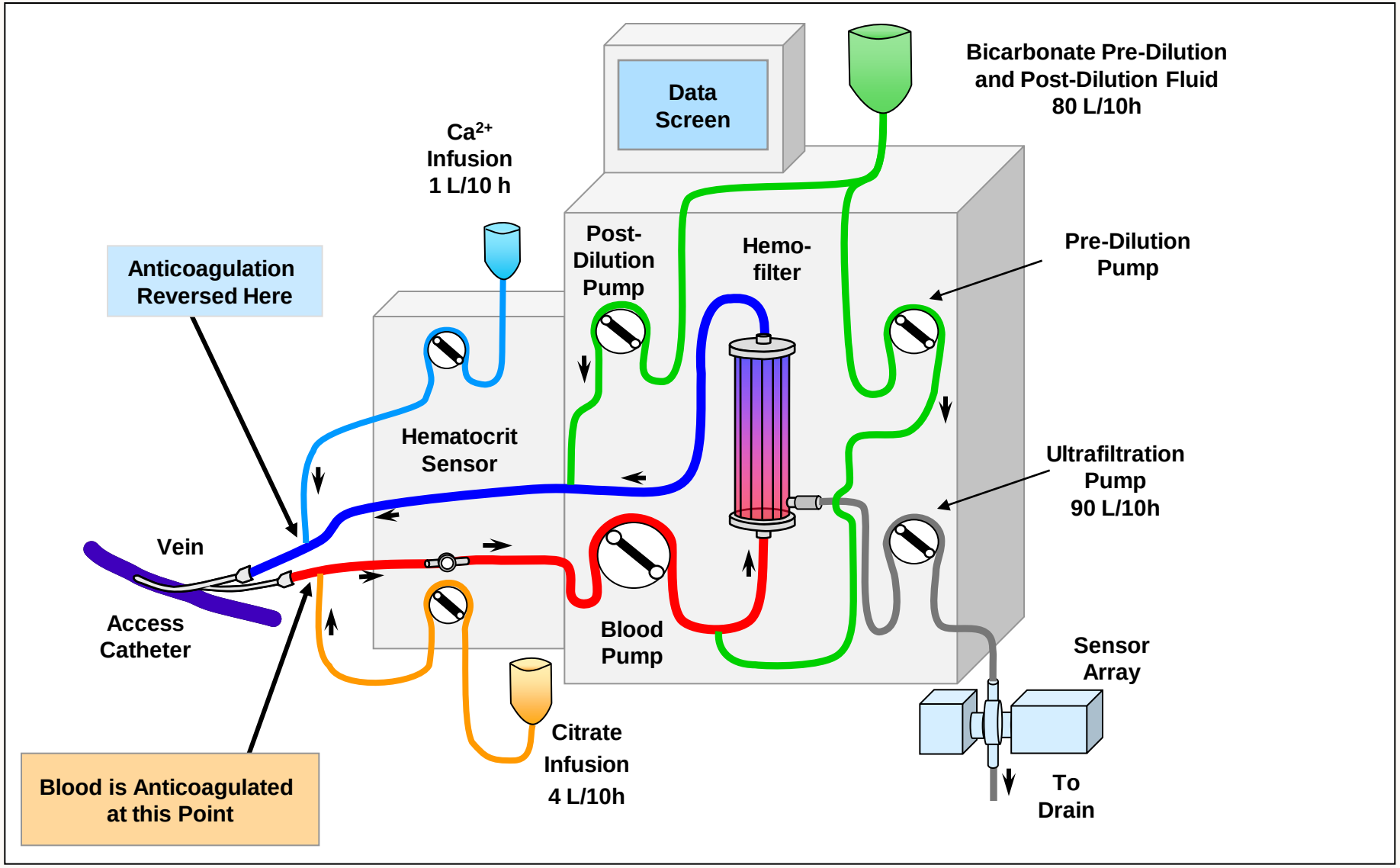
©www.pulsion.de (accessed June 10, 2012)

- ✔ Global liver function from the elimination of the diagnostic drug ICG-PULSION: Plasma Disappearance Rate (PDR), Retention Rate after 15 min (R15) and Blood Clearance of ICG (CB)
- ✔ Circulating Blood Volume (BV)

- **Measures indocyanine green (ICG) clearance (CB)**
- **ICG CB correlates: ICU survival[1,2] and [citrate level][3]**

1. Kimura S, et al: Indocyanine green elimination rate detects hepatocellular dysfunction early in septic shock and correlates with survival. Crit Care Med. 29:1159-63, 2001
2. Sakka S, et al: Prognostic Value of the Indocyanine Green Plasma Disappearance Rate in Critically Ill Patients. Chest 122: 1715-20, 2002
3. Link et al: Total to ionized calcium ratio predicts mortality in CRRT with citrate anticoagulation in critically ill patients. Critical Care 2012, 16:R97 doi:10.1186/cc11363

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



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

ACD-A — Acid

- **Used most often**
- **Provides acidic circuit pH**
- **Plasma $\Delta Na^+ \approx +3$ mEq**
- **Plasma $\Delta HCO3^- \approx -3$ mEq**

4%-TSC — Basic

- **Used rarely, briefly**
- **Acidemic patients ($pH < 7.1$ or $HCO_3^- < 10$)**
- **Plasma $\Delta Na^+ \approx +9$ mEq**
- **Plasma $\Delta HCO3^- \approx 0$ mEq**

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 100 ml/min $\longrightarrow$ Q_{Cit} 200 ml/h if 4%-TSC is used)

Commercial Bicarbonate Fluids

Na^+	(130) **140**	**mM**
K^+	2	mM
HCO_3^-	(25) **35**	**mM**
Mg^{2+}	0.75	mM
Cl^-	108.5	mM
Ca^{2+}	0	mM
Dextrose	5.5	mM

Na^+	(130) **140**	**mM**
K^+	4	mM
HCO_{3-}	(25) **35**	**mM**
Mg^{2+}	0.75	mM
Cl^-	110.5	mM
Ca^{2+}	0	mM
Dextrose	5.5	mM

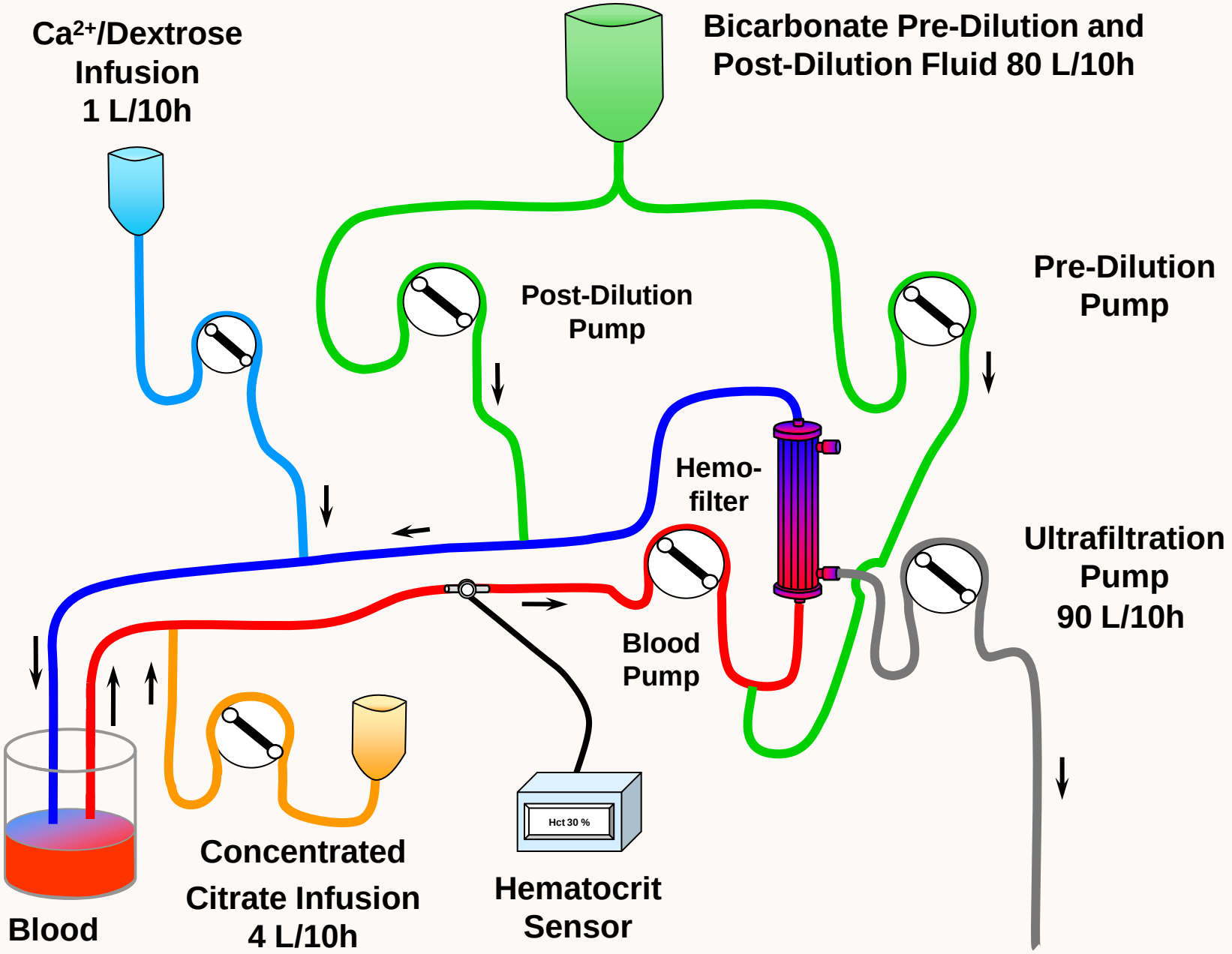
- High Mg^{2+}; little Mg^{2+} supplementation needed
- Ca^{2+} infusion without dextrose
- Sodium-phosphate supplementation required[1]

1. Troyanov et al: Phosphate addition to hemodiafiltration solutions during continuous renal replacement therapy. Intensive Care Med (2004) 30:1662–1665

Ca^{2+}/Mg^{2+} Solution

For ACD-A		
Ca^{2+}	136	mM
Na^{+}	126	mM
Mg^{2+}	20	mM
Cl^{-}	438	mM

- Ca infusion does not impact Na and dextrose mass balance
- Mg content helps restore magnesium mass balance
- At QB of 80 ml/min, QCa = 40-50 ml/h


Ca2+/Dextrose
Infusion
1 L/10h
Bicarbonate Pre-Dilution and
Post-Dilution Fluid 80 L/10h
Post-Dilution
Pump
Pre-Dilution
Pump
Hemo-
filter
Ultrafiltration
Pump
90 L/10h
Blood
Pump
Hct 30 %
Concentrated
Citrate Infusion
4 L/10h
Hematocrit
Sensor
Blood

Kinetic Analysis of RCA for Pre- and Post-Dilution HVHF

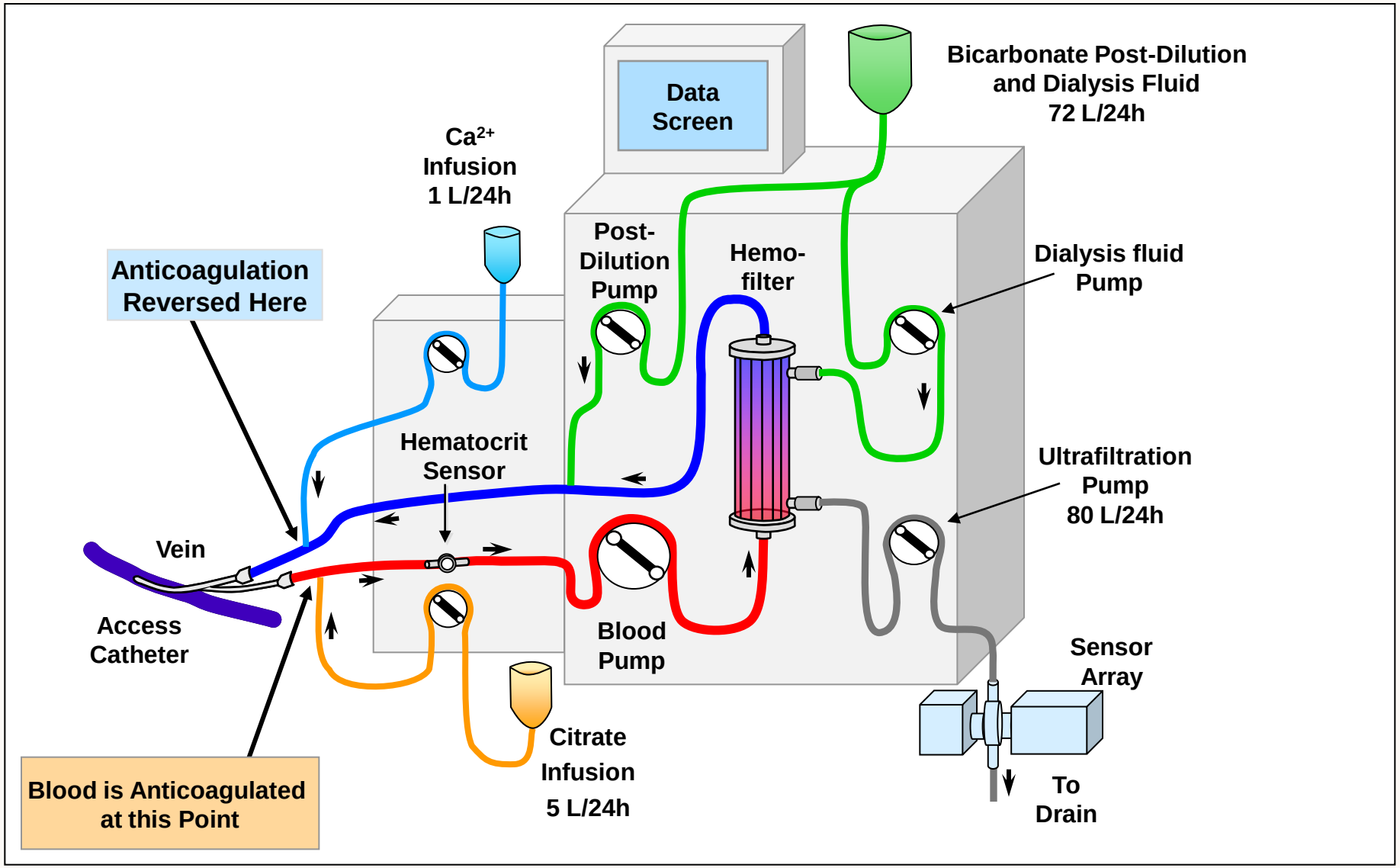
Prescribed Flows	
(Hct	30 %)
QB	200 ml/min
QP	8 L/h
QCit	400 ml/min
QPre	4.1 L/h
QPost	3.9 L/h
QCa	100 ml/h

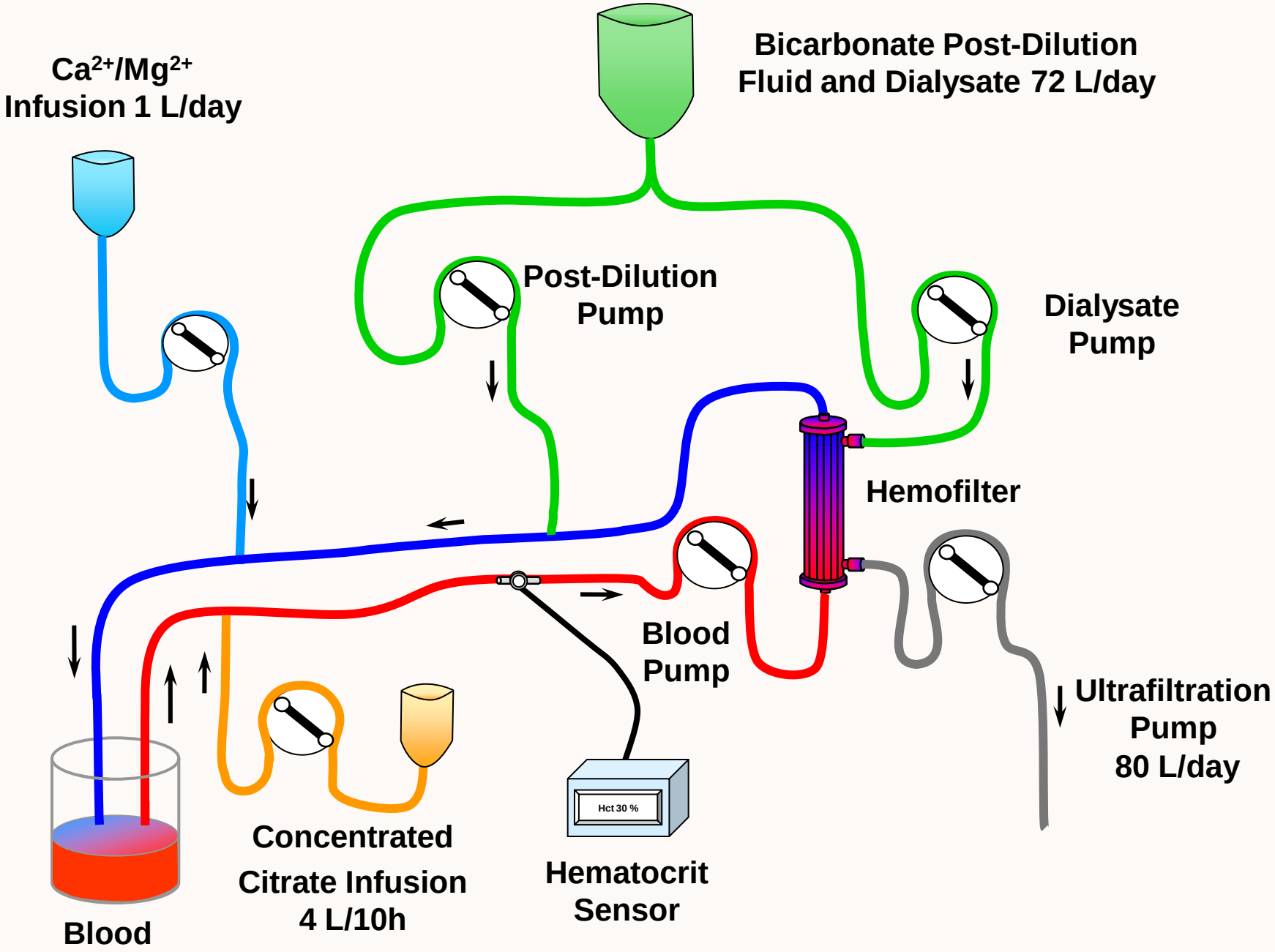
Kinetic Parameters	
Cinf =	5.7 mM
Ecit =	**0.67**
Cmax ≤	3 mM
C Load, G =	16 mmol/h
K_{urea} =	6.3 L/h
G/K_{urea} =	**2.5 mmol/L**

Kinetic Analysis of RCA for Pre- and Post-Dilution HVHF

- **Na^+** mass balance neutral at serum **$Na^+ \approx 140$**
- **HCO_3^-** mass balance neutral at **$HCO_3^- \approx 25–30$**
- Use 35 mM HCO_3^- fluid in severe liver failure
- **Ca** infusion dosed to maintain systemic **iCa ≥ 1.25**
- Filter performance does not need to be monitored since only convective clearance is used

RCA for 24-hour Post-Dilution CVVHDF




Ca2+/Mg2+
Infusion 1 L/day
Bicarbonate Post-Dilution
Fluid and Dialysate 72 L/day
Post-Dilution
Pump
Dialysate
Pump
Hemofilter
Blood
Pump
Ultrafiltration
Pump
80 L/day
Hct 30 %
Concentrated
Citrate Infusion
4 L/10h
Hematocrit
Sensor
Blood

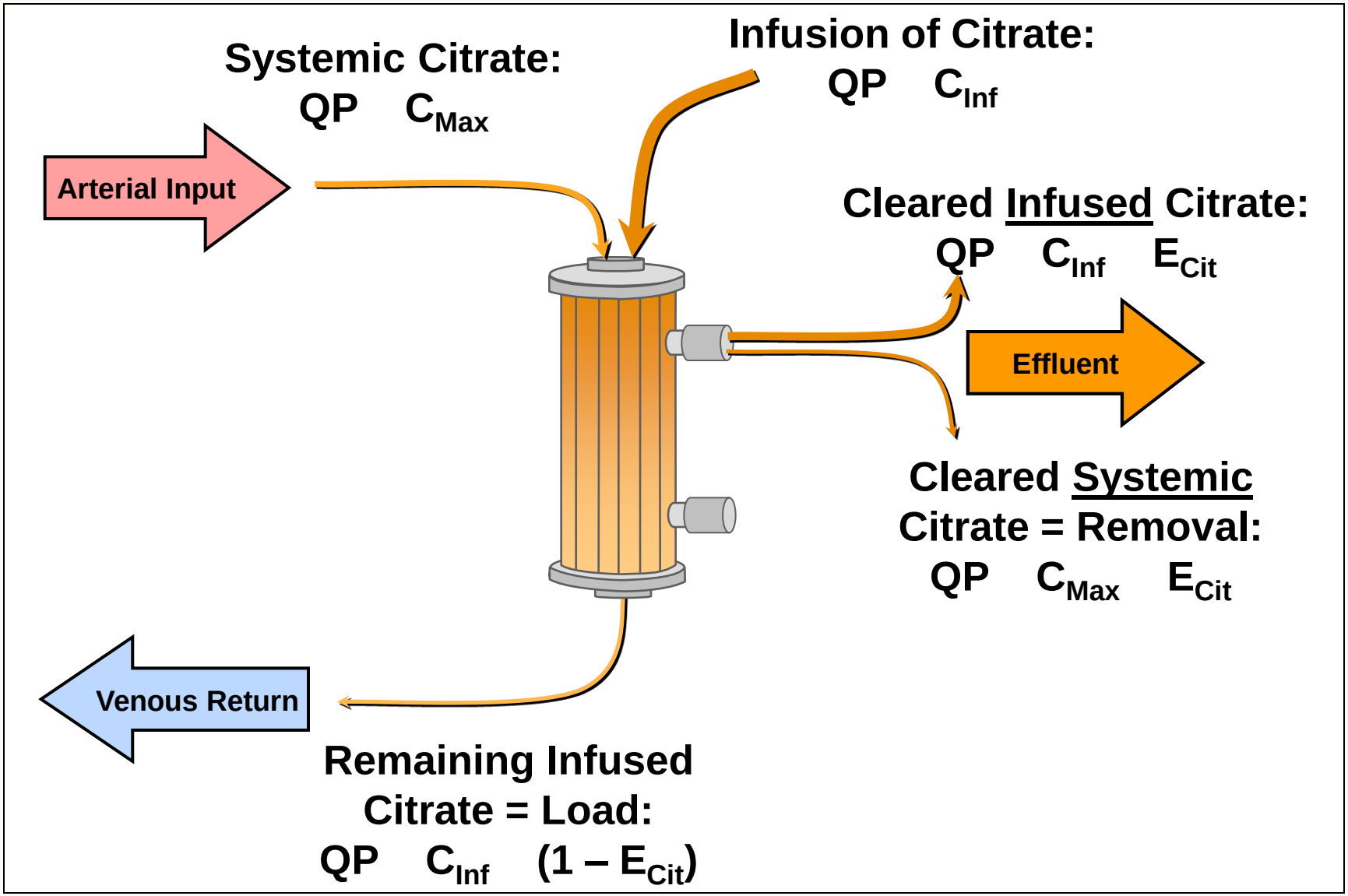
Kinetic Analysis of RCA for Post-Dilution CVVHDF

Prescribed Flows	
(Hct	30 %)
QB	80 ml/min
QP	3.2 L/h
QCit	200 ml/min
QPost	0.8 L/h
QD	2.4 L/h
QCa	≈45 ml/h

Kinetic Parameters	
Cinf =	7 mM
Ecit =	**0.9**
Cmax ≤	1 mM
C Load, G =	2.3 mmol/h
K_{urea} =	3.3 L/h
G/K_{urea} =	**0.7 mmol/L**

Citrate Fluxes In The Dialyser

Absent Body Metabolism



Maximum Systemic Citrate Level (C_{Max})

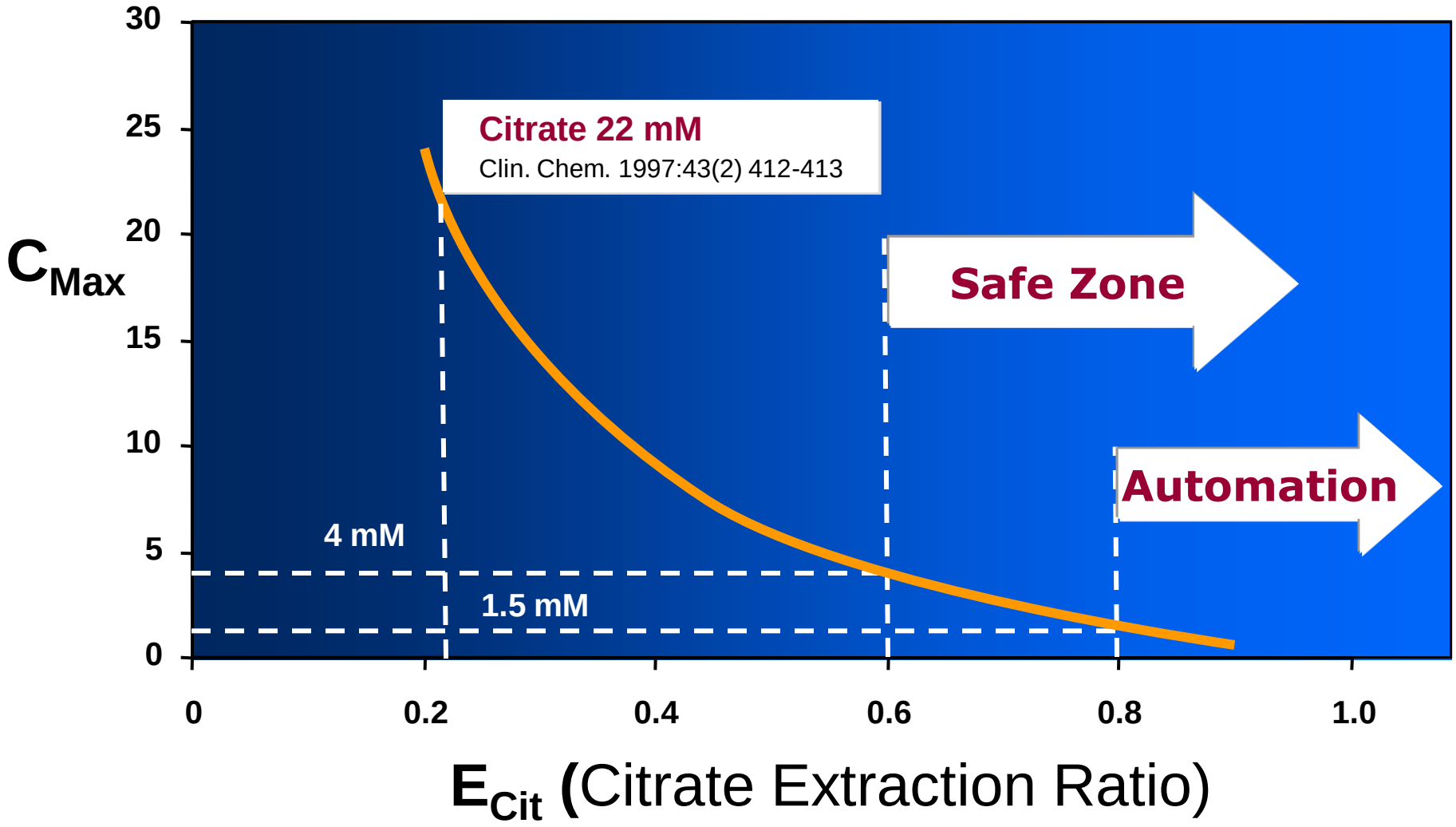
Steady State

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

C_{Inf}: constant

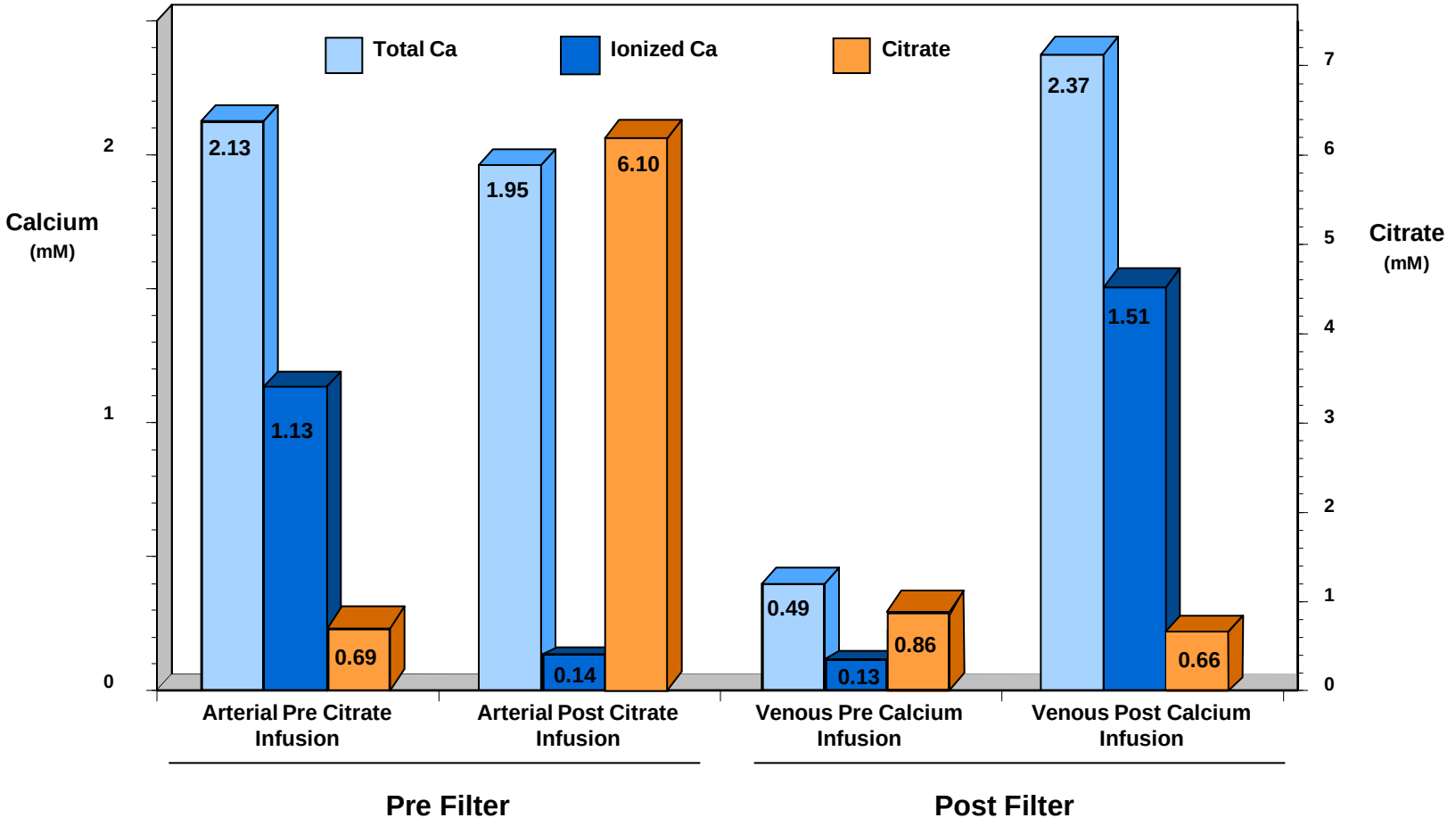
Szamosfalvi B et al: United States Patent Application 20080015487

Relationship of C_{Max} to E_{Cit}



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).

CVVHDF Chemistry Data

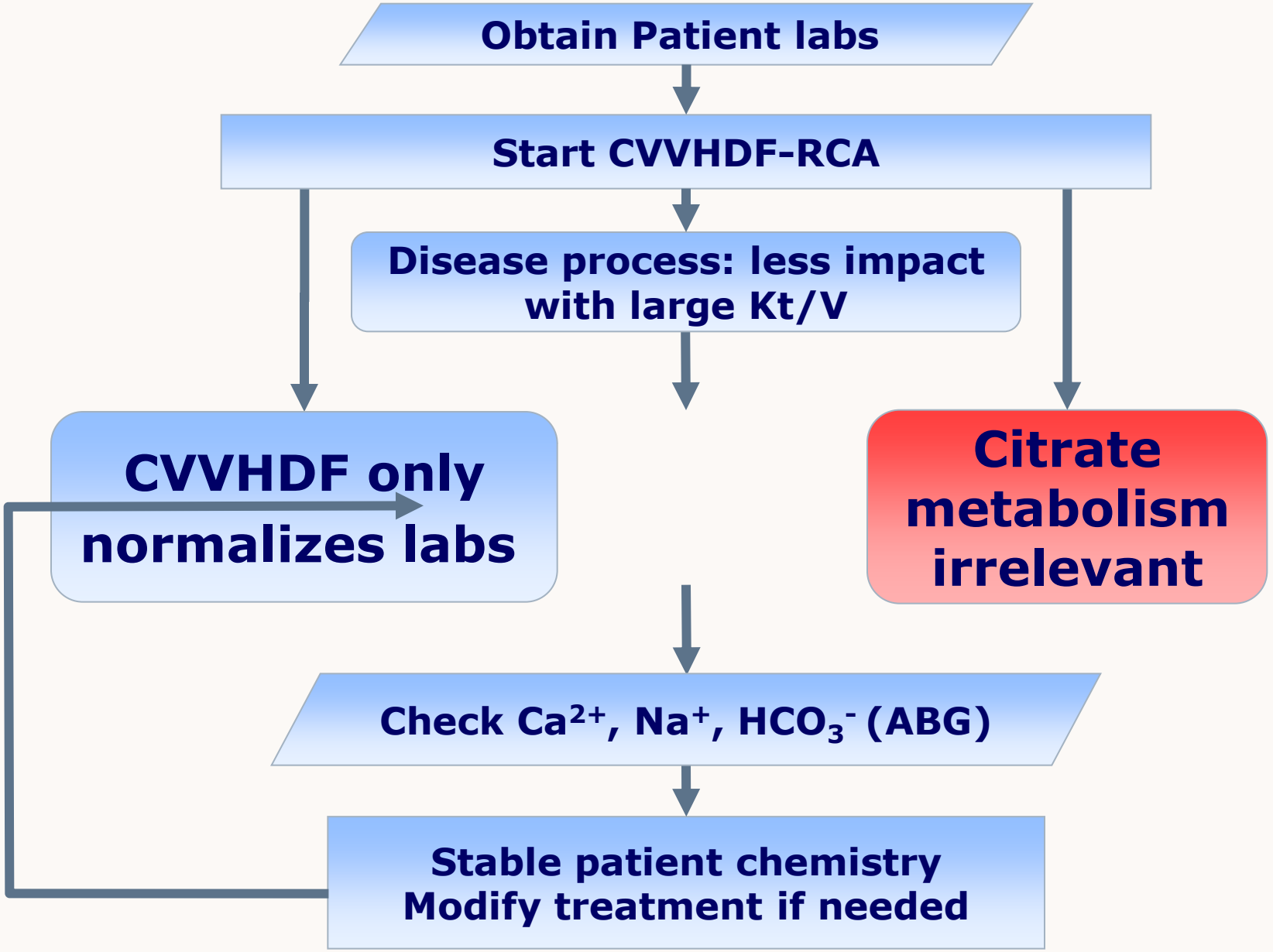
	Alb (g/dL)	Total Ca (mM)	Ionized Ca (mM)	Citrate (mM)	Mg (mg/dL)	P (mg/dL)	Na (mM)	K (mM)	Cl (mM)	CO_2 (mM)	GLU (mg/dL)
Arterial Pre-Citrate Infusion	2.7	2.13	1.13	0.69	1.9	4.2	138	2.6	105	26	87
Arterial Post-Citrate Infusion	2.3	1.95	0.14	6.10	1.9	4.1	139	2.4	96	22	197
Venous Pre-Ca / Mg Infusion	3.4	0.49	0.13	0.86	2.0	3.0	136	2.6	102	26	58
Venous Post-Ca / Mg Infusion	2.4	2.37	1.51	0.66	1.9	2.7	138	2.5	105	27	89
Fresh Dialysate	0	0.27 (0)	Low (0)	0	2.2	2.0	142	2.6	107	35	Low (0)
Filter Effluent	0	1.8	0.15	4.08	1.9	3.3	142	2.4	102	26	179

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).

Kinetic Analysis of RCA for Post-Dilution CVVHDF

- **Na^+** mass balance neutral at serum **$Na^+ \approx 138$**
- **HCO_3^-** mass balance neutral at serum **$HCO_3^- \approx 26$**
- **Ca** infusion dosed to maintain systemic **iCa ≥ 1.1**
- The filter performance must be monitored since diffusive clearance is used

Safe CVVHDF-RCA Operation



What is the biggest disadvantage of traditional CRRT?

Problems with traditional CRRT

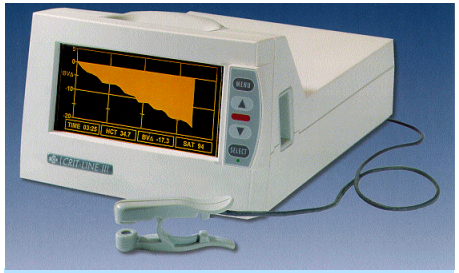
1. Cumbersome despite improved machines:
   - Scale-based balancing of > 50 liters effluent
   - Frequent clotting complications
   - Cannot use fistula or graft access
2. Very expensive compared to dialysis:
   - Custom blood circuits and filters
   - Pre-packaged replacement fluid
   - Nurse time if 1:1 nurse: patient ratio is needed
3. Lack of consensus on best approach:
   - CVVH versus CVVHDF versus CVVHD
   - Optimal replacement fluid compositions
   - Optimal anticoagulation strategy

Future Directions

Hemodynamic Monitoring: Triple Lumen Dialysis Catheter and Arterial Catheter

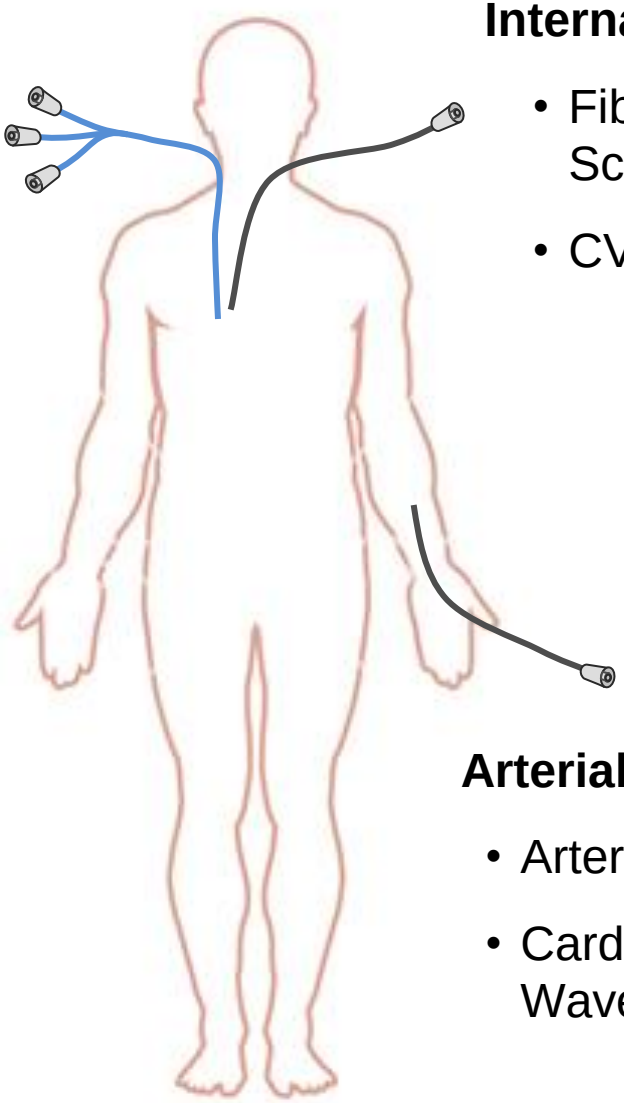
Triple Lumen Dialysis Catheter

- Continuous $ScVO_2$ monitor
- CVP



- Measures Hemoglobin
- Measures O_2 Saturation

Crit-Line III,
Hemametrics, LLC
(acquired by Fresenius)



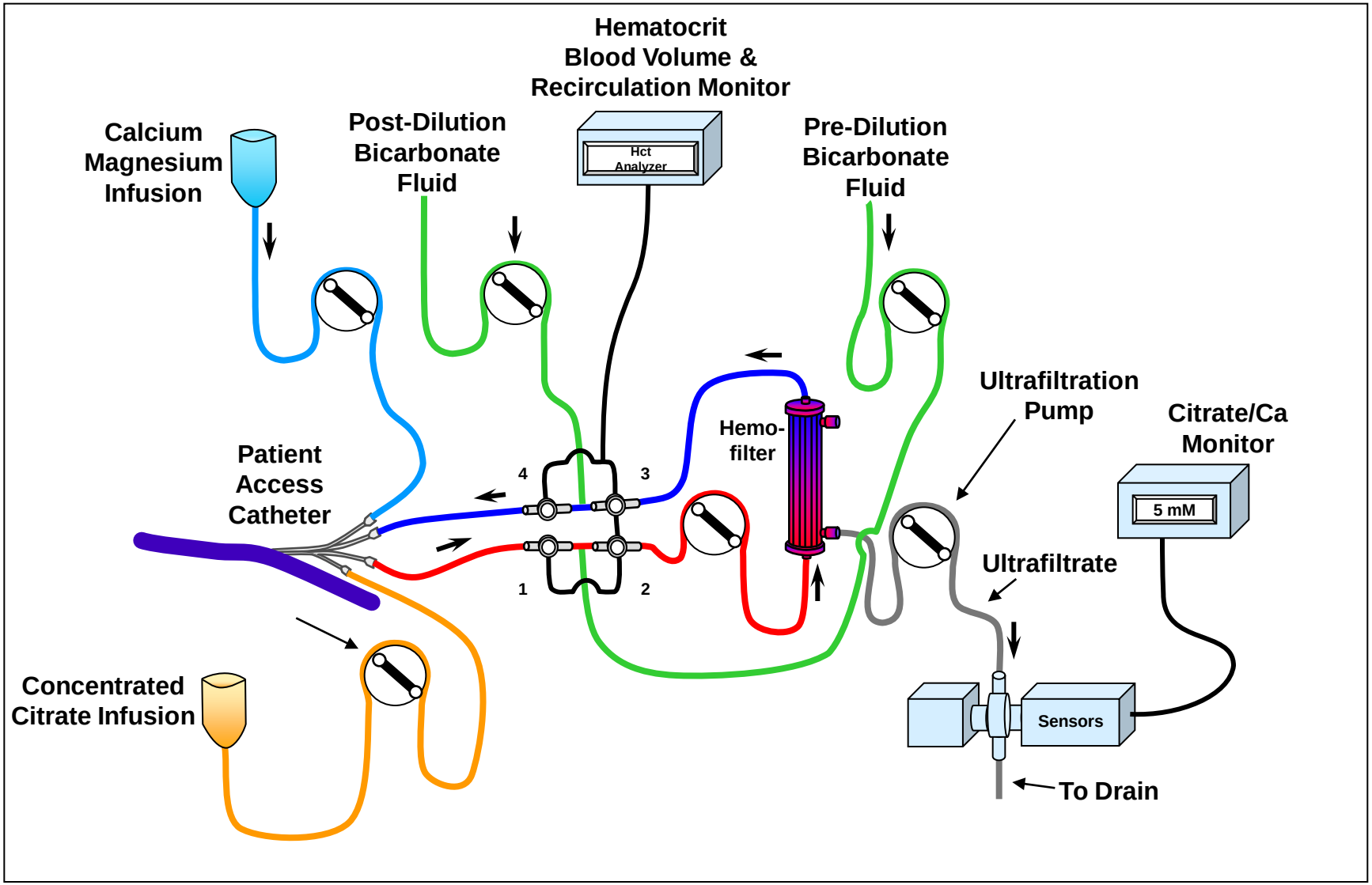
Internal Jugular (IJ) Catheter

- Fiber optic Continuous $ScVO_2$
- CVP

Arterial Line

- Arterial Pressure Monitoring
- Cardiac Output: Arterial Pulse Waveform Analysis

Proposed 6-pump Renal Replacement Therapy System With Effluent Citrate- and Calcium Sensor



Szamosfalvi B et al: United States Patent Application 20080015487

Effluent Solute Sensing Requirements

- Measure/know the circuit delivered blood flow
- Measure/know the circuit delivered plasma flow
- Avoid blood clotting and biofouling completely
- Measure dialysance of solute of interest
- Measure access recirculation
- Know flow rate and composition of all fluids

THE SYSTEMIC SOLUTE LEVEL IS CALCULATED!

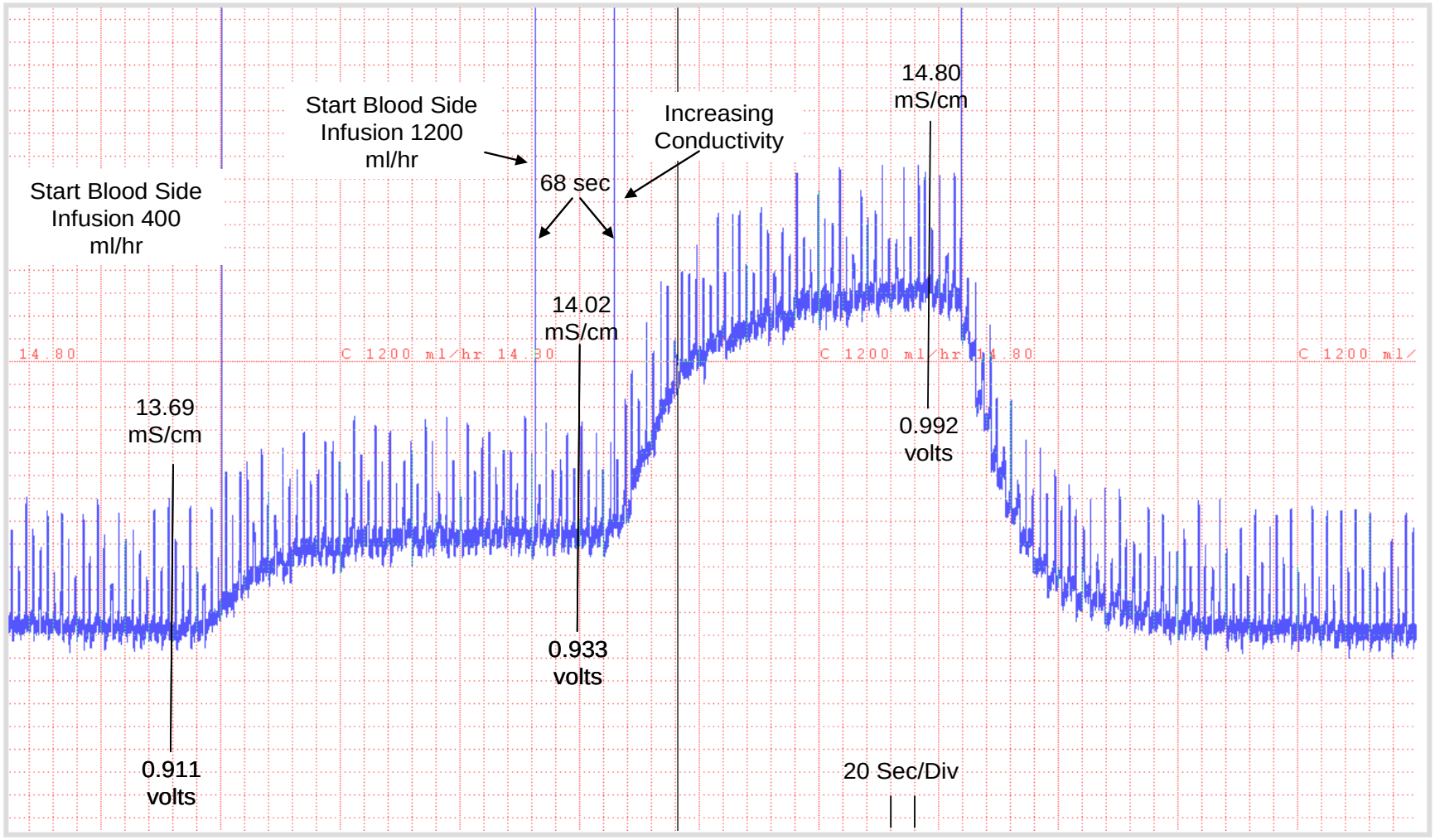
1. Szamosfalvi et al.: System And Method For Delivery Of Regional Citrate Anticoagulation To Extracorporeal Blood Circuits US Patent 8133194

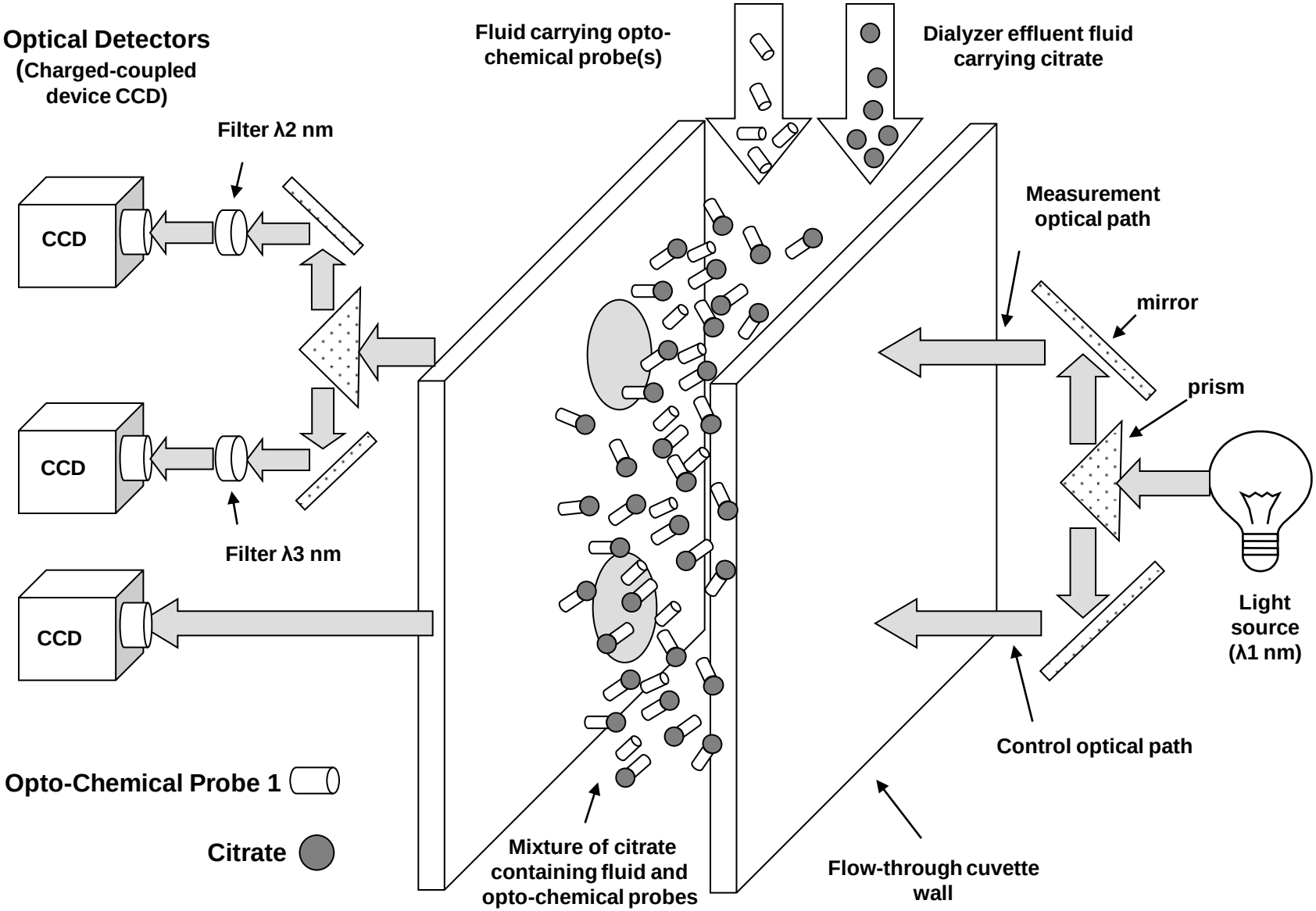
Citrate 4% and 14.7% Na infusion in blood side. Conductivity in drain circuit.

Blood-side Infusion : 4% Na Citrate & 14.6 % NaCl (total Na = 560 mEq/L)

Dialysate: 140 Na, 2.0 K, 2.5 Ca mM. Conductivity Meter: WTW LF2000.

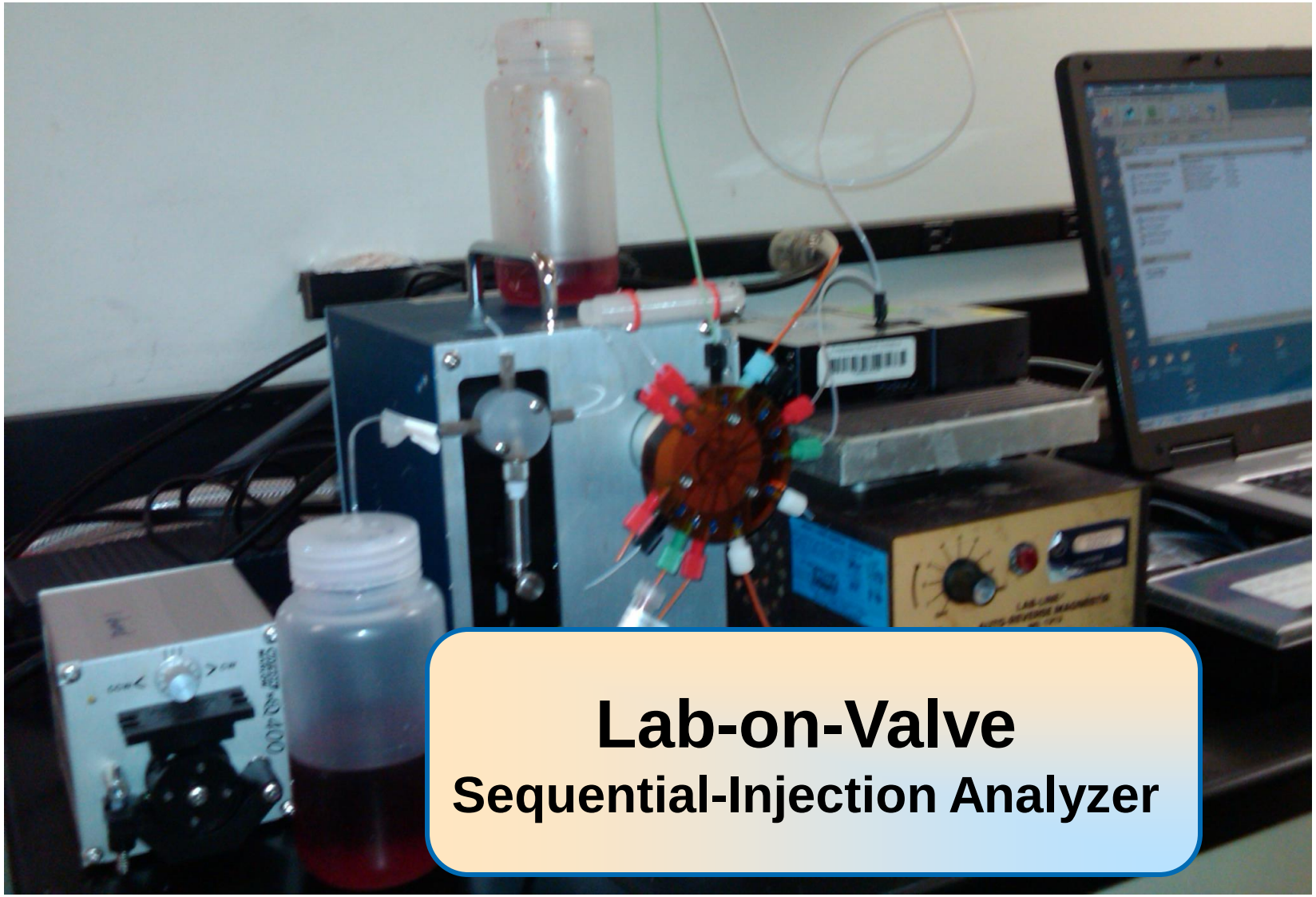
Optiflux 200NR filter, Flows: QB = 200 ml/min, QD =300 ml/min



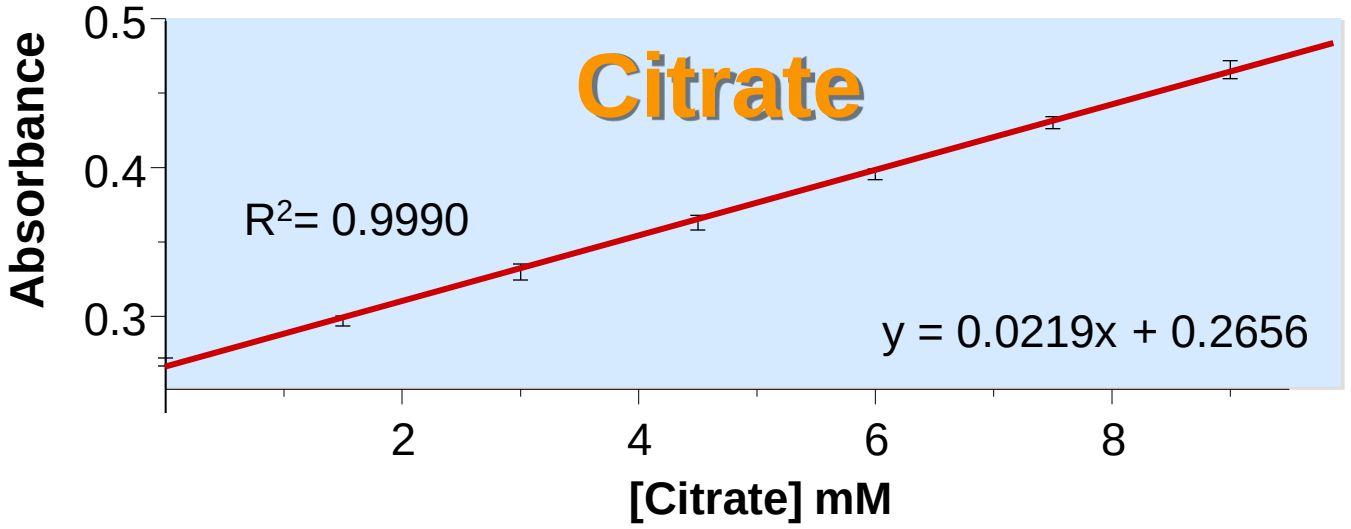


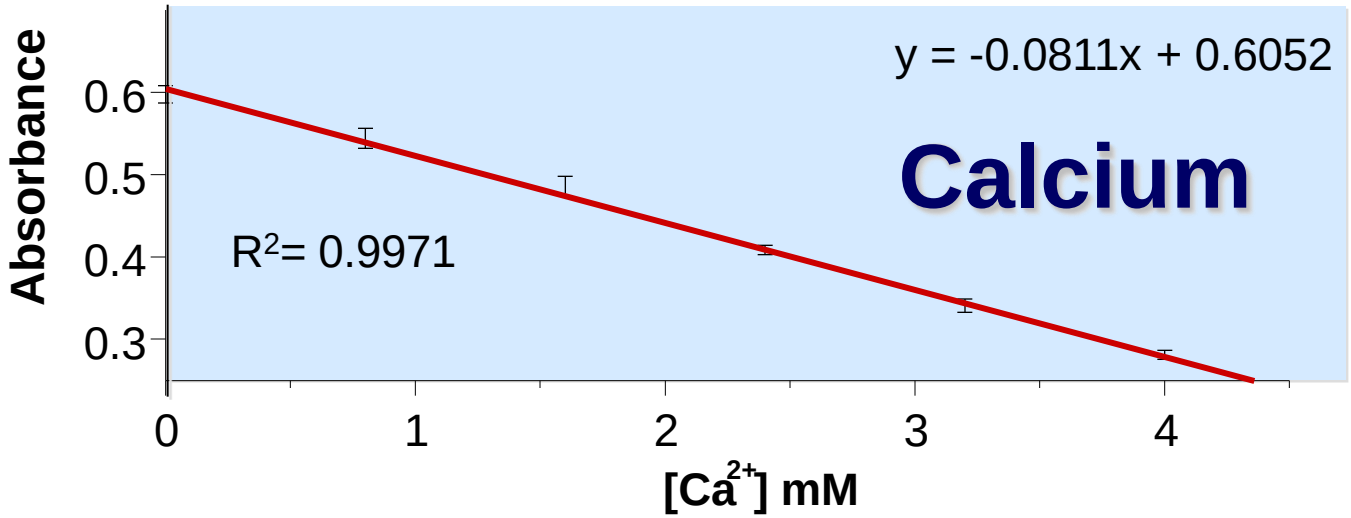
Description of a citrate, calcium and magnesium sensor for use in a continuously flowing fluid circuit. The system mixes the opto-chemical probes and the drain fluid containing citrate, calcium and magnesium before making the optical measurements. Probe binding results in changes in light absorption 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.

System for Measurement of Citrate and Calcium

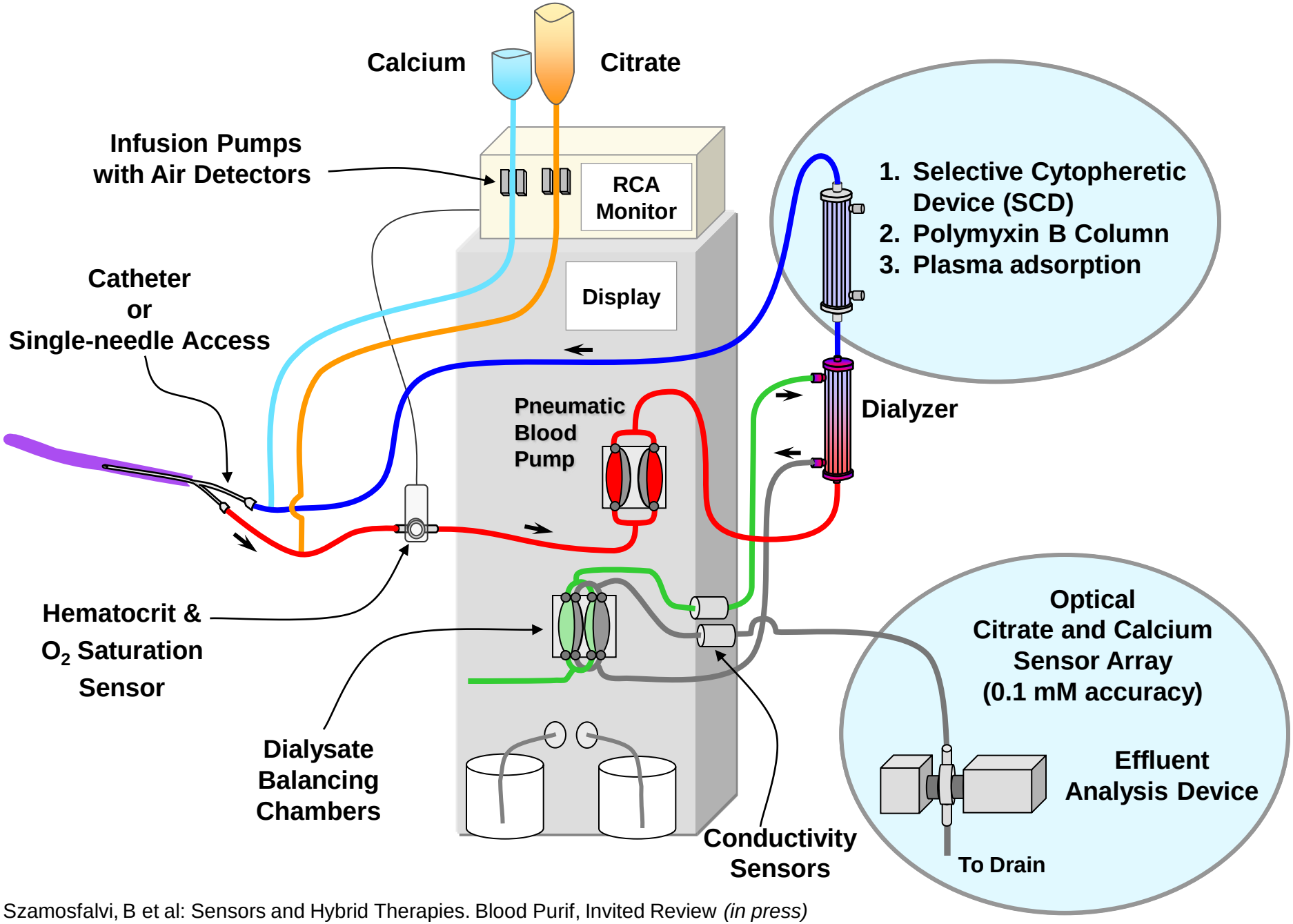


Optical Dialyser Effluent Citrate- and Calcium Sensor

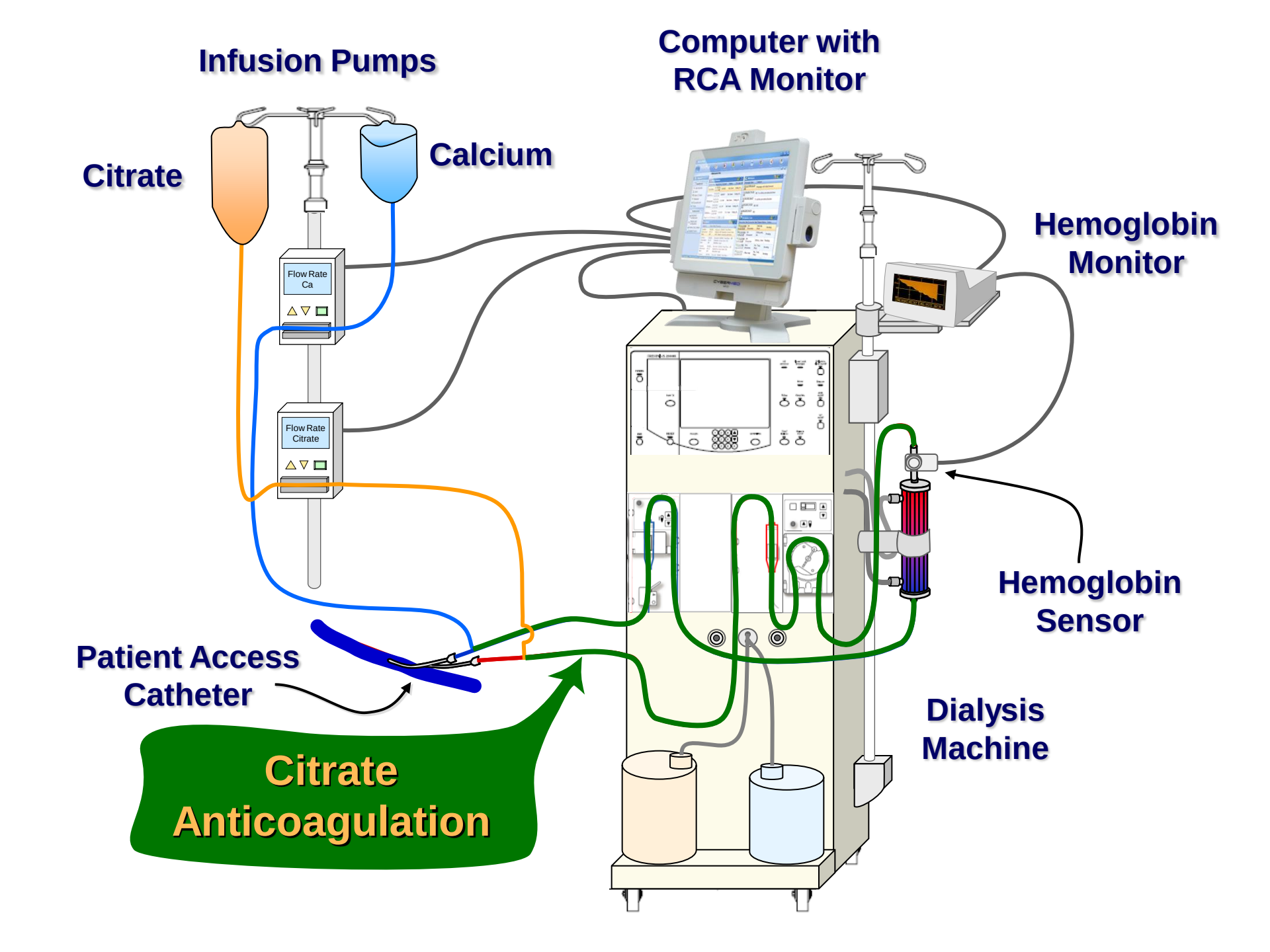


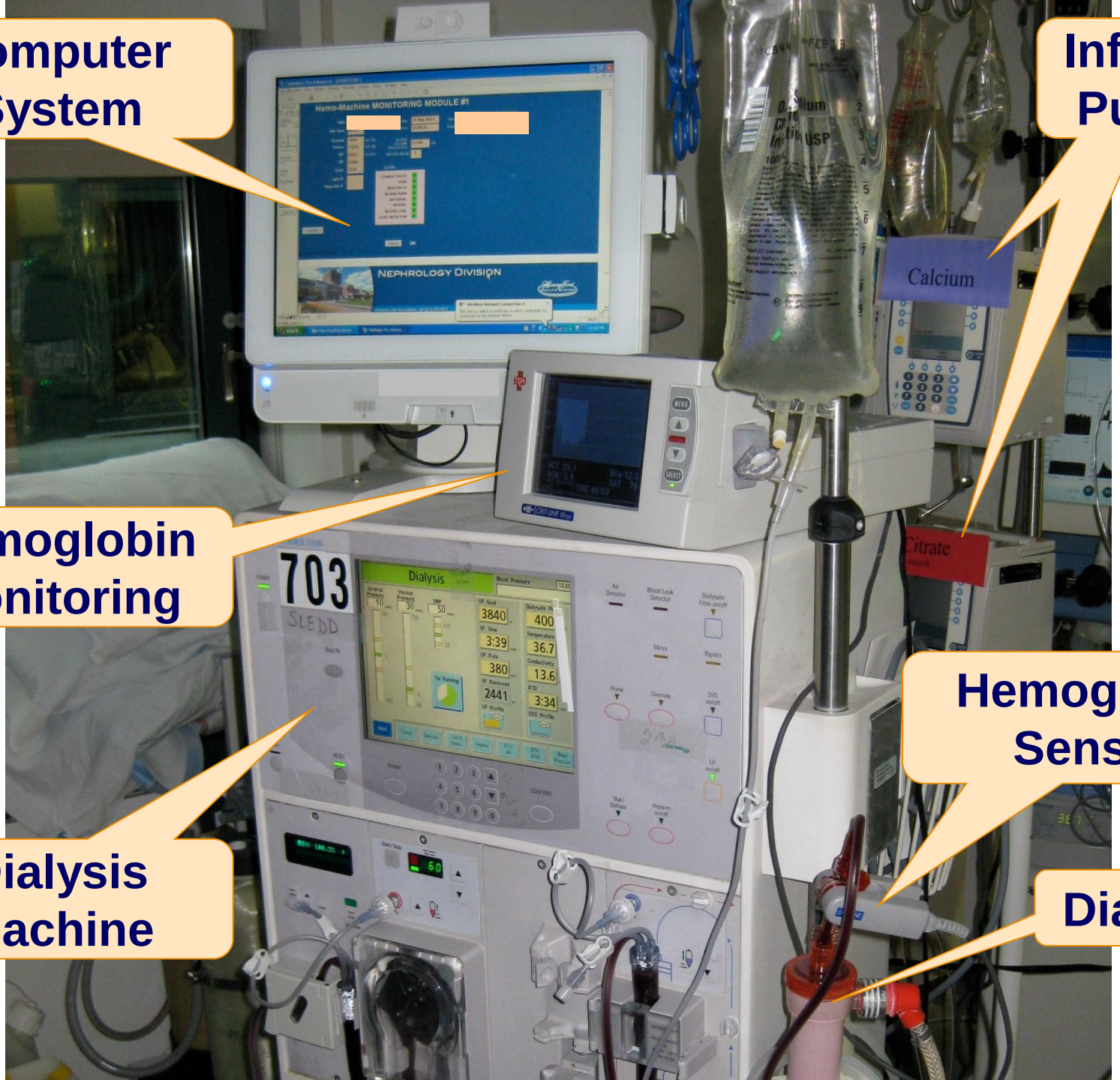


Adapted from Yang, Y. J., B. Szamosfalvi, J. Yee, S. Frinak and E. V. Anslyn (2011). "Development of an online citrate/Ca2+ sensing system for dialysis." Analyst 136(2): 317-320



Szamosfalvi, B et al: Sensors and Hybrid Therapies. Blood Purif, Invited Review *(in press)*


Infusion Pumps
Computer with RCA Monitor
Citrate
Calcium
Flow Rate Ca
Flow Rate Citrate
Hemoglobin Monitor
Hemoglobin Sensor
Patient Access Catheter
Dialysis Machine
Citrate Anticoagulation


Computer System
Infusion Pumps
Hemoglobin Monitoring
Hemoglobin Sensor
Dialysis Machine
Dialyzer
Hemo-Machine MONITORING MODULE #1
NEPHROLOGY DIVISION
Calcium
Citrate
703
Dialysis

Hybrid Renal Support 2012 → Future

Near-automated RCA at low blood flows with online clearance

Hematocrit and central venous O_2 saturation monitoring

Computerized SLED prescribing & telemetry monitoring

Focus: EASE OF USE,
LOW COST for Early Start CRRT

Antibiotic Dosing: based on measurement of online clearance

Improved Biocompatibility

↓ WBC, PLT & complement activation

Ultrapure dialysate, NO acetate

Developing Therapies

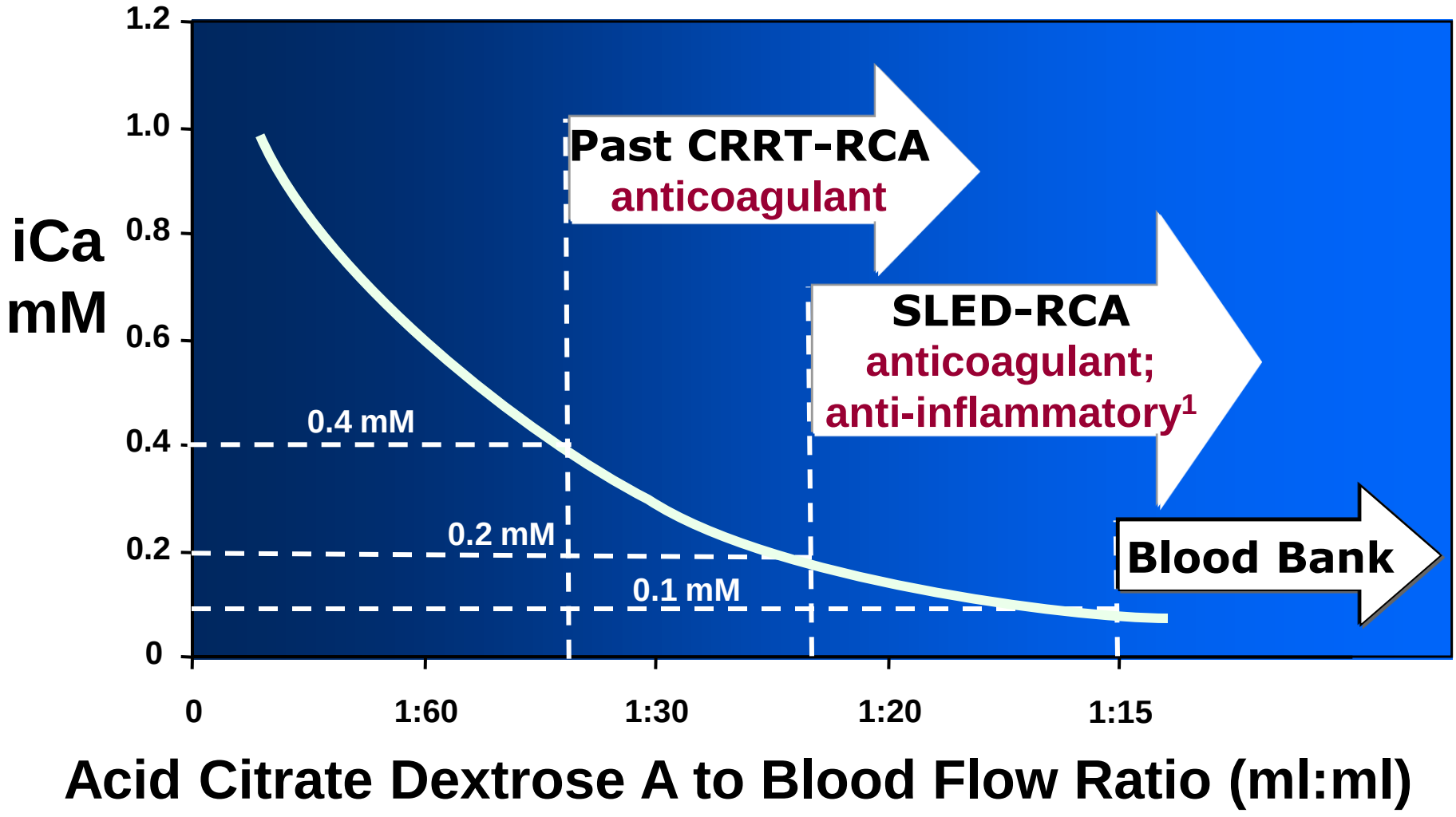
Columns for removal of endotoxin, cytokines, inflammatory cells, protein-bound toxins

OUTCOME:

(?) Improved Survival & Renal Recovery

Circuit Ionized Calcium (iCa):

Citrate:Blood Flow Ratio Defines Effect of RCA



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

Dialyzer After Saline Rinse Back

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

Dialyzer New

Dialyzer After 43 Hours

HFH Cost of 72 hours of CRRT ($)

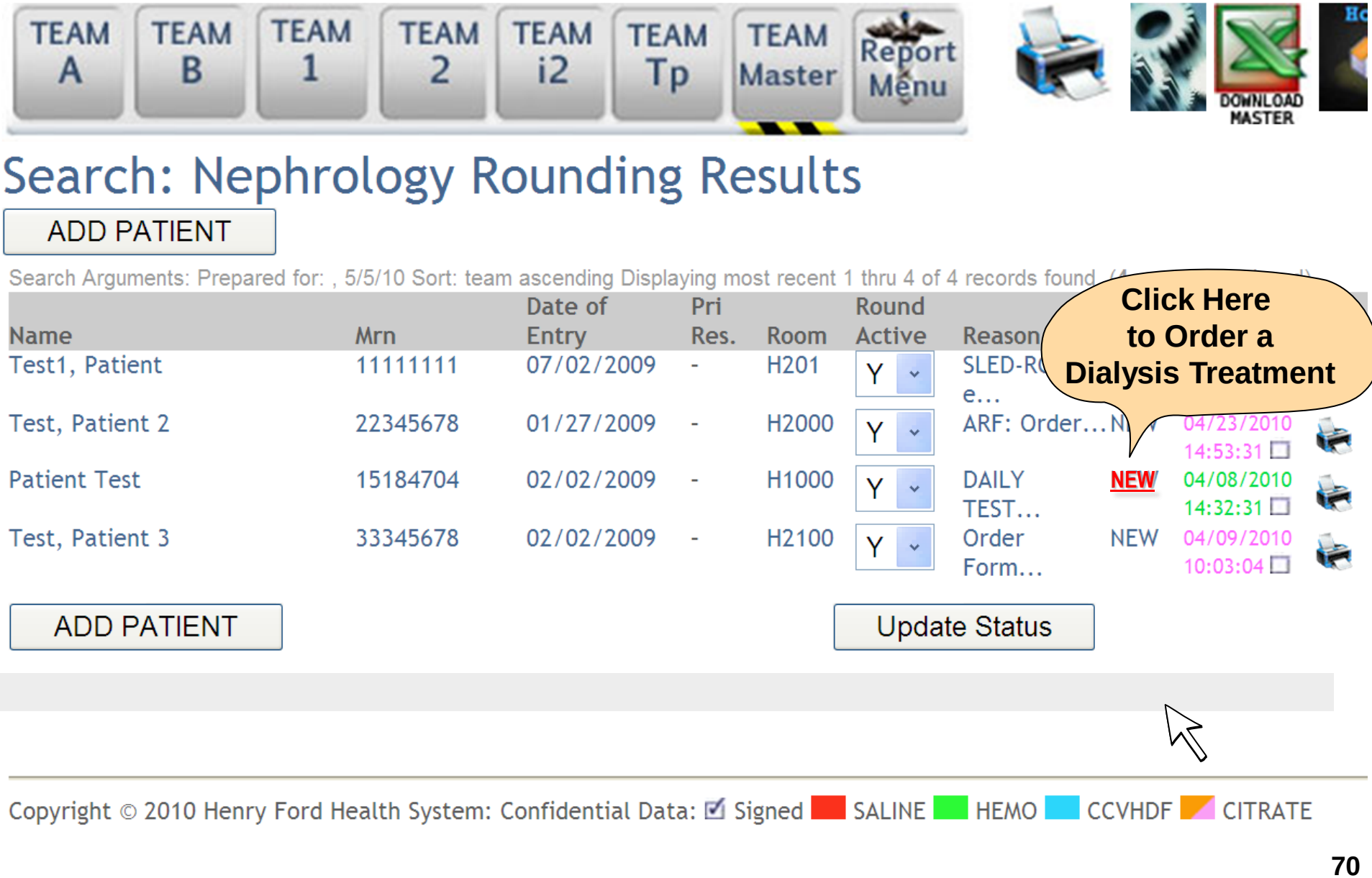
	Traditional CRRT	24-hour SLED-RCA
Filter & Tubing	$300	$45
Fluid/Dialysate	$1000	$50
Citrate/Ca +Lab	$0	$150
Total Cost 72 h	$1,300	$245

SLED-RCA Daily Savings ≈ $350/day/pt

Alarm-Free SLED-RCA provides additional savings by allowing the staff to safely care for more CRRT patients

Scaling Up SLED-RCA: "In The Cloud" Electronic Prescription Generation and Database Archival

Inpatient Rounding List



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:

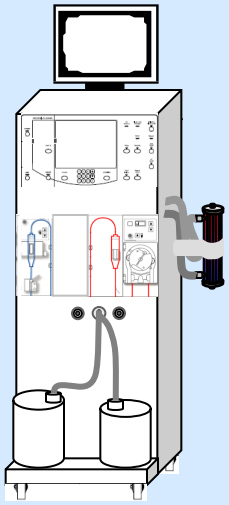
60 y.o male status post CABG 10/12/2010; course complicated by HAP, VDRF and anuric AKI. CRRT was started 10/20/2010.

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

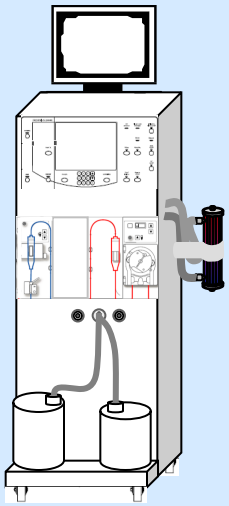
Attending Physician Attestation:

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

Telemetry Data Server

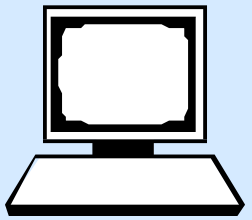


ICU Bedside Dialysis

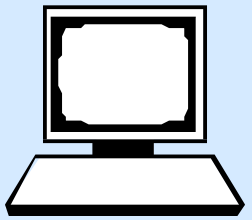


Acute Dialysis Unit

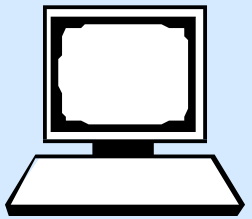
Hospital Electronic Health Record Data Server



Dialysis Unit Nurse's Station



Nephrologist's Office



Hospital Electronic Health Record Client PC

Treatment Telemetry Multiple Choices

HFH “Citrate Group”

- Balazs Szamosfalvi, MD
- Stanley Frinak, MSEE
- Jerry Yee, MD
- Tom Lubkowski
- Gary Zasuwa
- CRRT Technician Team
- ICU Teams
- Greenfield Health System