Anticoagulation for CRRT

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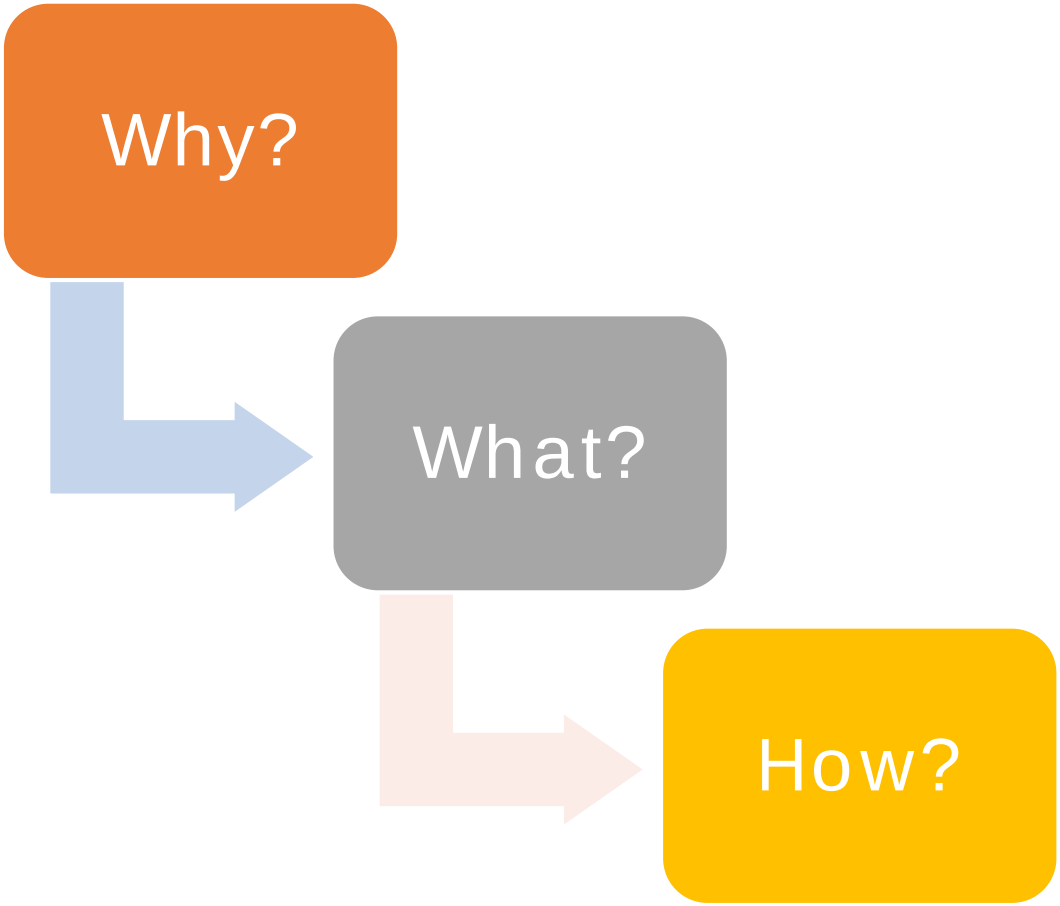
- DISCLOSURE INFORMATION

- Ravindra L Mehta MD
- Speaker
- I had a personal financial relationship with commercial entities during the last two years :

- Specify names of commercial company
- Baxter, Ardea, AM Pharma, GSK, CSL- Behring, Grifols, Astute Inc. Fresenius-Kabi, Ferring Research, Johnson and Johnson, Regulus, Akebia, Intercept, Quark
- Grants: iSAEC; Relypsa, Fresenius-Kabi; Fresenius, Grifols

- *ai sensi dell'art. 3.3 sul Conflitto di Interessi del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009, per conto del Provider New Progress Service srl*

Anticoagulation for CRRT



CRRT Circuit

Maintaining the CRRT circuit is crucial for delivering CRRT effectively

- Dose Delivery
- Labor
- Resources

ORIGINAL

Continuous is not continuous: the incidence and impact of circuit "down-time" on uraemic control during continuous veno-venous haemofiltration

Observational, single center

48 patients

CVVH 2 L/h

260 filters

Anticoagulation per protocol

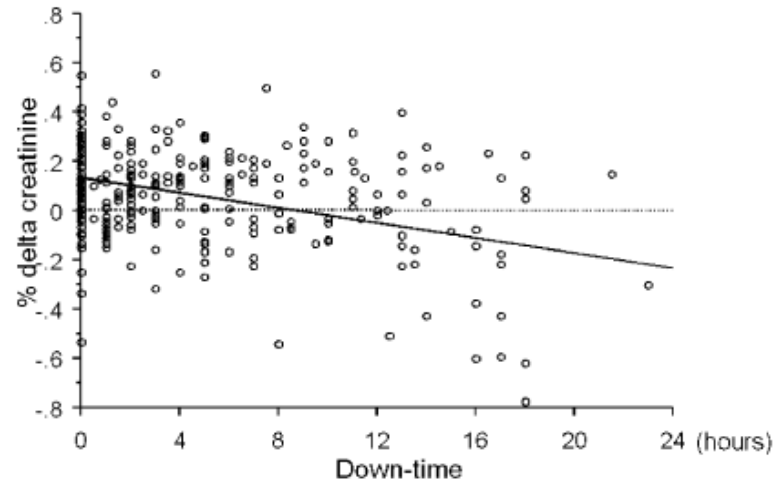
- -INR > 2.5
- -APTT < 60 s
- -Platelets > 150,000 mm3
- -active bleeding
- -post-op (24 h)

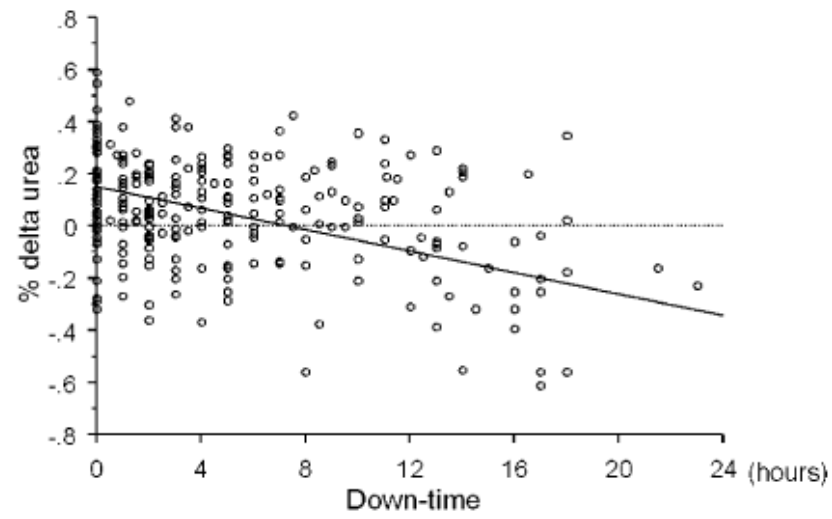
Median filter life 15 h (8.9-26.1)

Median down time 3 h (1-8.3)

- -heparin used 4.0 h vs. no heparin 3.5 h
- -Filter clotting (77.6%)

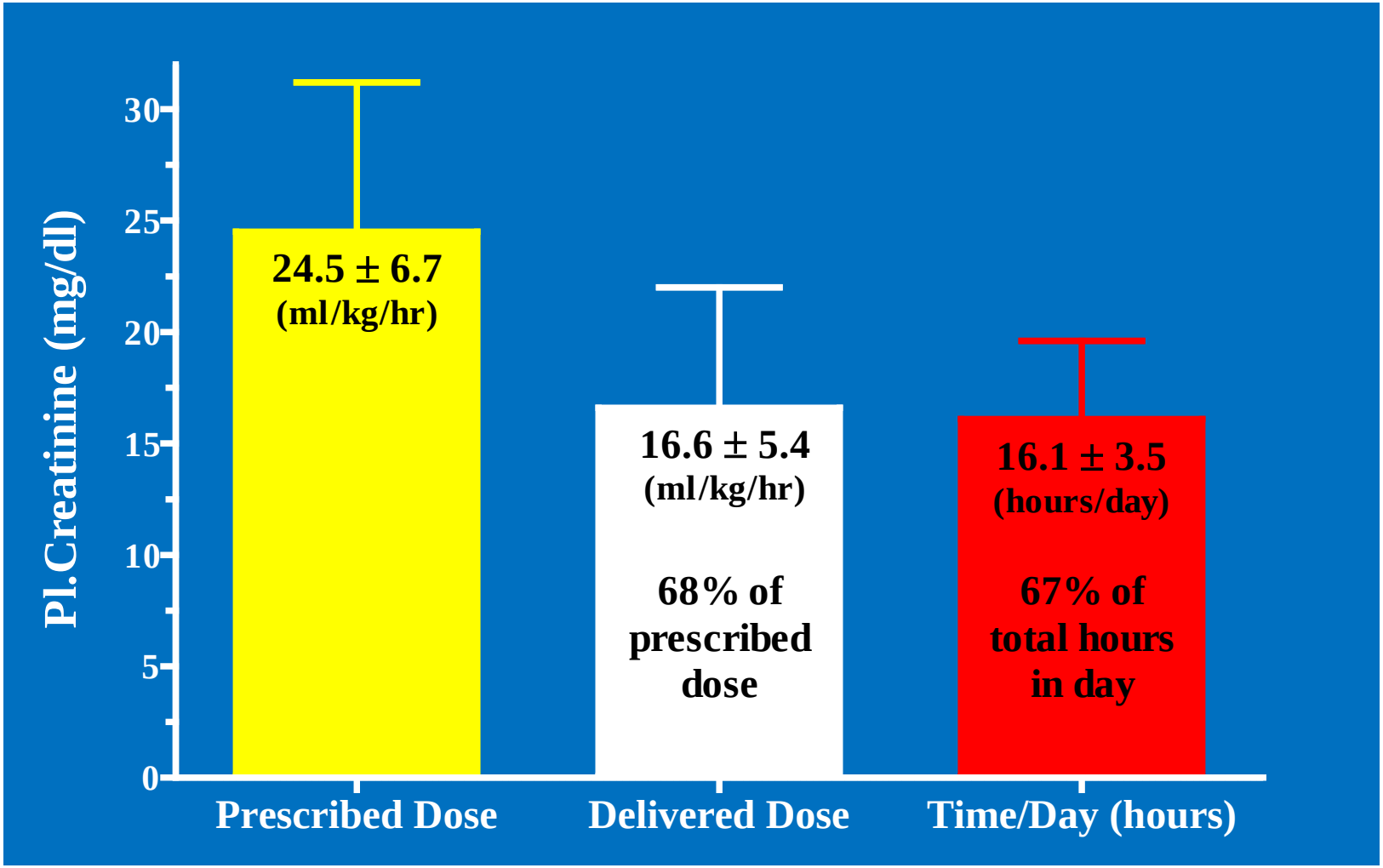
At least 16/24 h needed → Urea and Cr





Uchino S et al. Intensive Care Med; 2003

CRRT Prescription vs. Delivery



Venkataraman et al, *J Crit Care, 2002*

Prescribed vs. Delivered

Reference	Dialysis Modality	Prescribed	Delivered	% of Delivered Dose
Evanson et al. 1998	IHD	Kt/V 1.25±0.47	Kt/V 1.04±0.49	83.5%
Evanson et al. 1999	IHD	Kt/V 1.11±0.32	spKt/V 0.9±60.33 eKt/V 0.8±40.28 dpKt/V 0.84±0.30	86.4 – 75.5%
Venkataraman et al. 2002	CRRT	24.5±6.7 mL/Kg/h	16.6±5.4 mL/Kg/h	68%
Tolwani et al. 2008	CRRT	Standard 20 mL/Kg/h High 35 mL/Kg/h	17 mL/Kg/h 29 mL/Kg/h	85% 82%
Vesconi 2009 et al.	CRRT	34.3 mL/Kg/h	27.1 mL/Kg/h	79%

Effluent Volume in Continuous Renal Replacement Therapy Overestimates the Delivered Dose of Dialysis

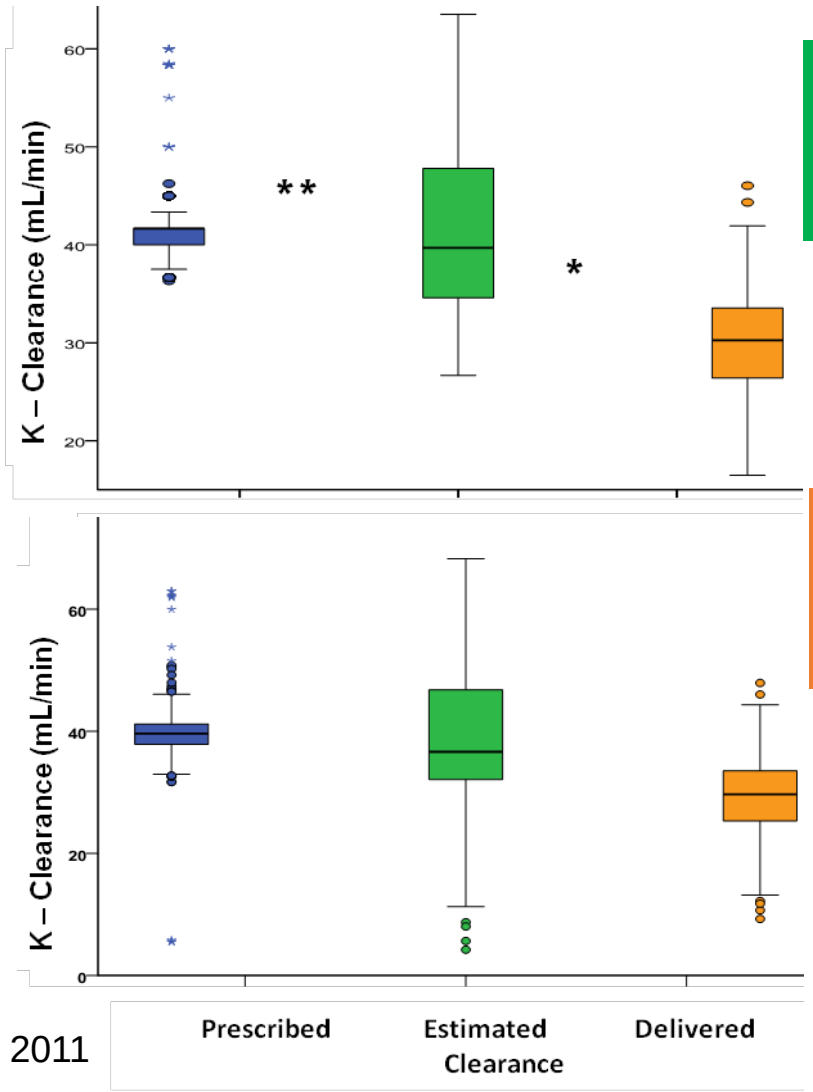
Rolando Claure-Del Granado,* Etienne Macedo,* Glenn M. Chertow,† Sharon Soroko,* Jonathan Himmelfarb,‡ T. Alp Ikizler,§ Emil P. Paganini,‖ and Ravindra L. Mehta*

Data from 52 critically ill patients, AKI requiring dialysis (Pre-dilution CVVHDF)

Regional citrate anticoagulation.

Filter efficacy was assessed by calculating FUN/BUN ratios q12 hr.

Prescribed urea clearance (K, ml/min) - Effluent volume rate = Qd (ml/min) + Qr (ml/min) + Qnet (ml/min)



K Estimated = Effluent volume adjusted for effective time of

K delivered = FUN (mg/dl)/BUN (mg/dl)] x effluent volume rate (ml/min)

Claure-Del Granado et al. CJASN, 2011

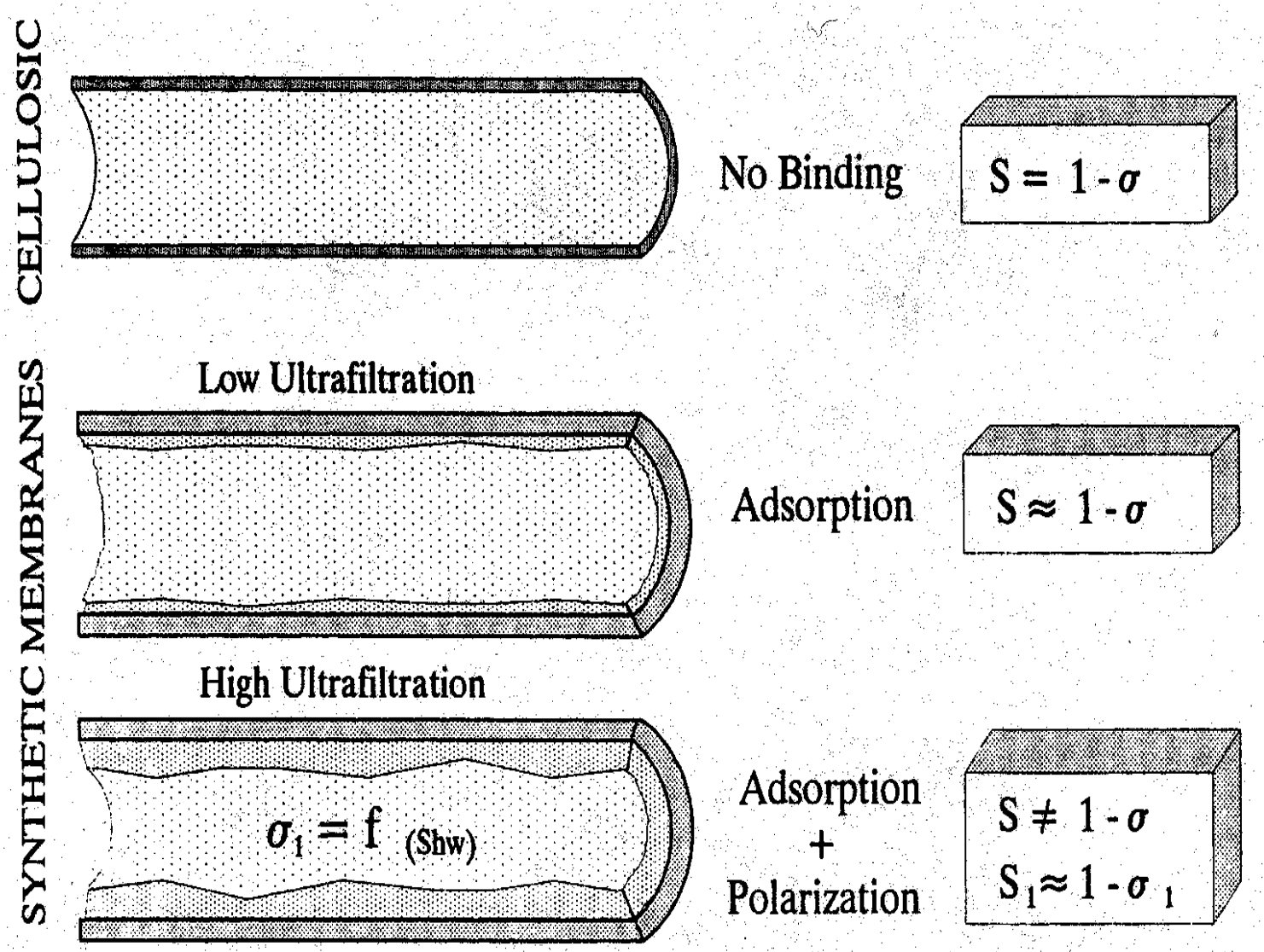
Reasons for Discontinuing CRRT and Filter efficacy

Table 3. Reasons for stopping CRRT

Reasons	Number of Filters	Percentage (%)	FUN/BUN Ratio
Factors affecting treatment time without affecting filter function			
D/C for surgical procedures	10	6.3	0.93 (0.92 to 0.99)
D/C for medical procedures	9	5.7	1.0 (0.95 to 1)
routine filter changes	16	10.1	0.95 (0.84 to 1.0)
machine problems	8	5.0	0.97 (0.85 to 1.0)
transition to IHD	17	10.7	0.96 (0.82 to 0.97)
venous access clot	6	3.8	0.97 (0.96 to 0.98)
physician decision	10	6.3	0.98 (0.94 to 1)
patient or family decision	11	6.9	0.96 (0.94 to 1)
patient recovery	6	3.8	0.95 (0.92 to 0.99)
death	3	1.9	0.98 (0.87 to 1.0)
access change	9	5.7	0.9 (0.87 to 0.95)
Factors affecting filter function			
filter clotted	41	25.8	0.89 (0.83 to 0.94)
filter leak	1	0.63	0.745
low-sieving concentration polarization	12	7.5	0.86 (0.79 to 1.0)

Claure-Del Granado et al. CJASN, 2011

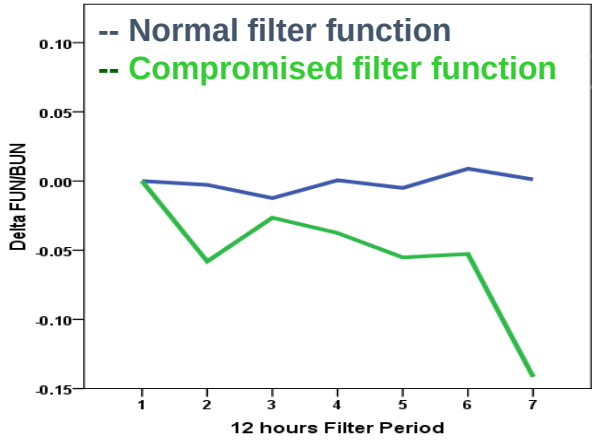
Mechanisms of Blood Membrane Interactions in Dialysis

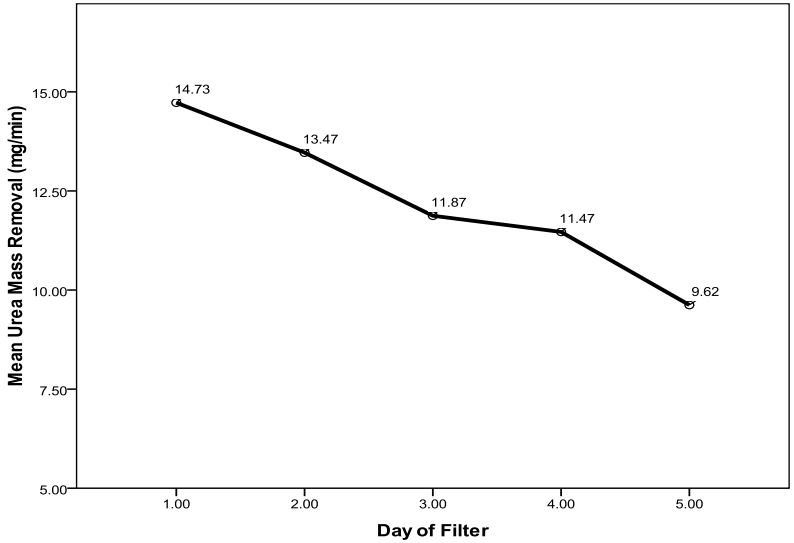


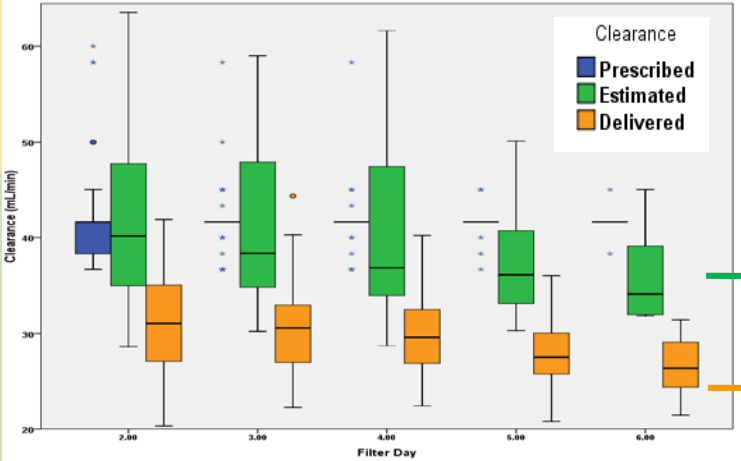
Modified from Ronco et al NDT 1998, 13

Dialysis or Blood side Measurements for Dialysis Dose Determination in Continuous Renal Replacement Therapies?

Rolando Claure-Del Granado, MD[1], Etienne Macedo, MD[1], Sharon Soroko, MS[1], Glenn M. Chertow, MD, MPH[2], Jonathan Himmelfarb, MD[3], T. Alp Ikizler, MD[4], Emil P. Paganini, MD[5], Ravindra L Mehta, MD[1].
Program to Improve Care in Acute Renal Disease (PICARD) study







84 | 58 | 37 | 19 | 7

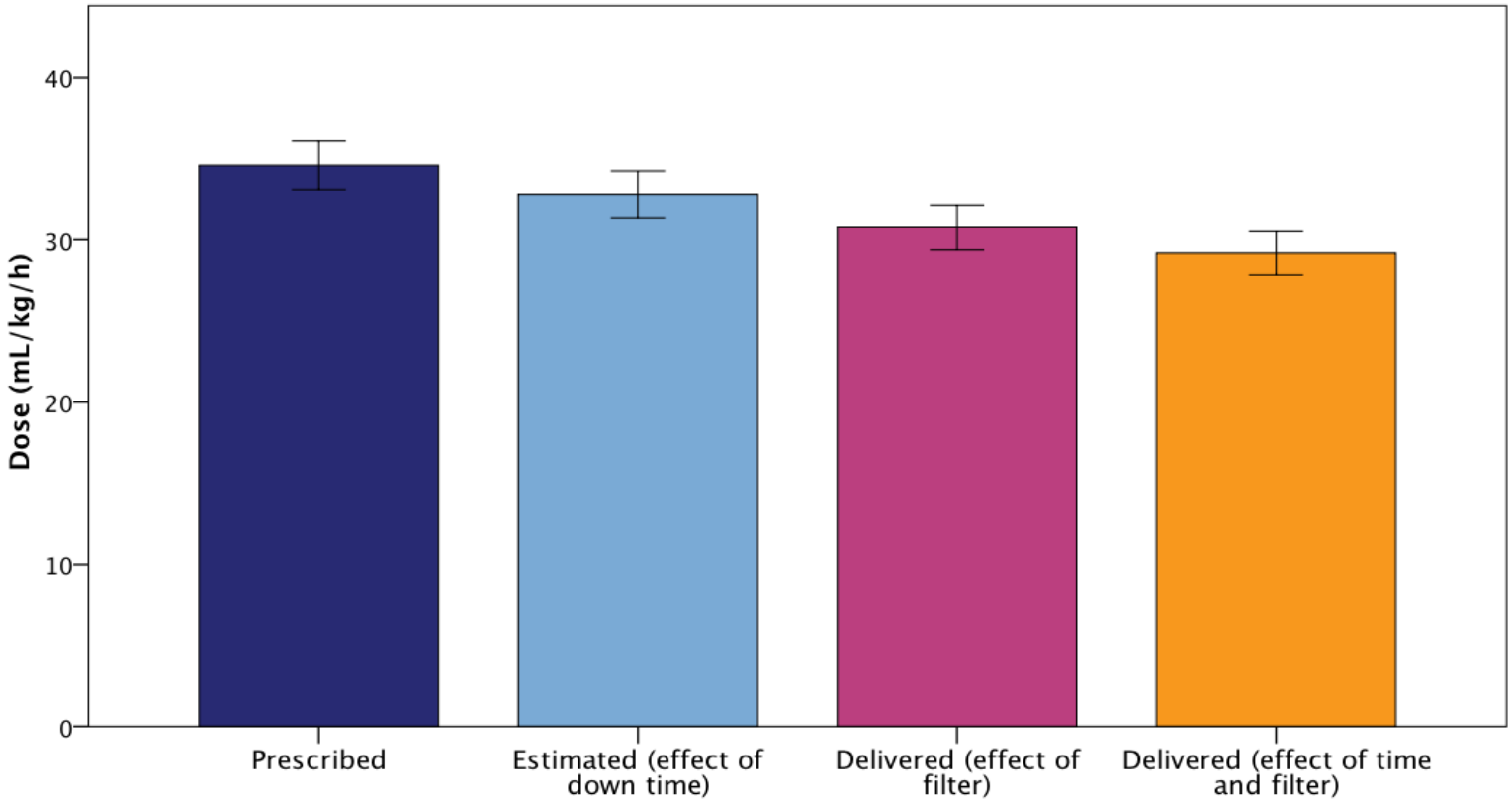
Time effect

Filter efficacy effect

Filter duration effect

ASN Abstract, 2009

The Impact of Down-Time and Filter Efficacy on Delivered Dose of CRRT



Ronco et al. Lancet 356:26-30, 2000
Mehta et al. Kidney Int 60:1154-1163, 2001
Uchino et al. Intensive Care Med 29:575-578, 2000
Kumar et al. IJAO 27:371-379, 2004

J Am Soc Nephrol 21: F-FC172, 2010

Anticoagulation in CRRT
Goals

Maintain patency of extracorporeal circuit

- Prevent clotting of filter and circuit
- Maintain efficacy of solute and fluid removal

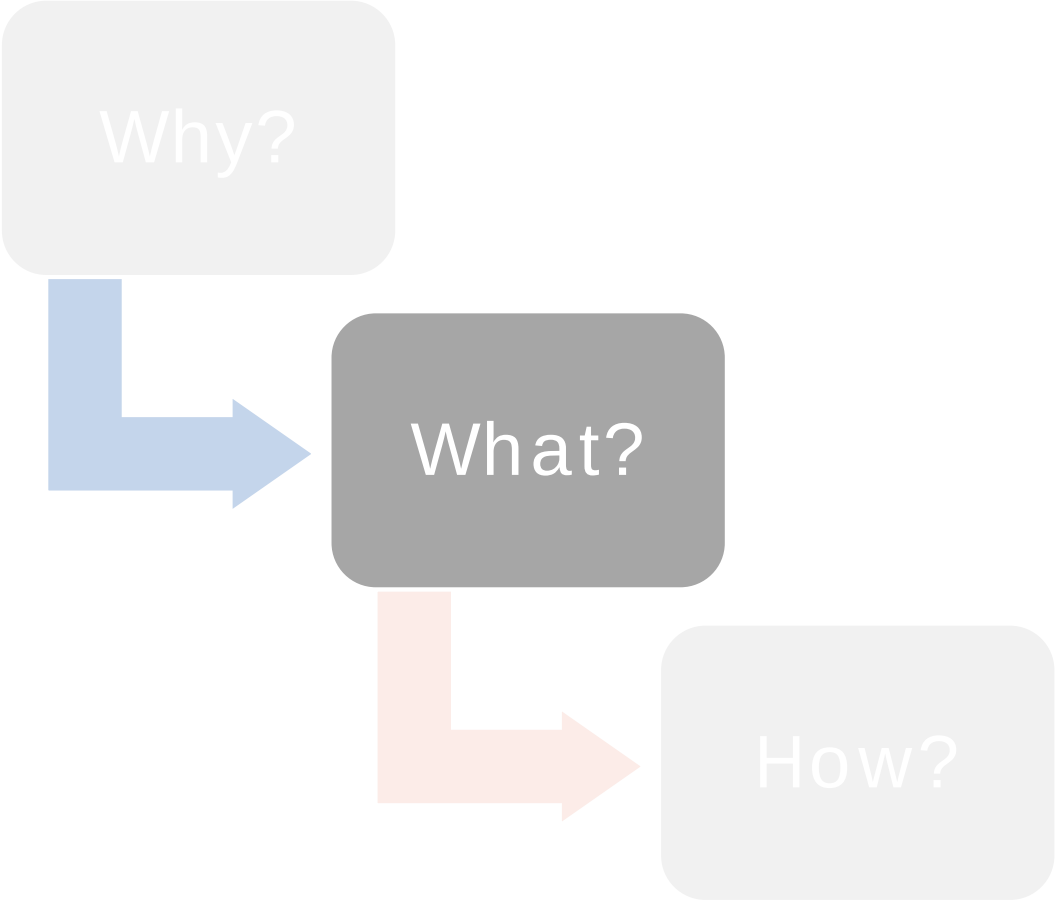
Avoid systemic anticoagulation

- Bleeding
- Alterations in coagulation parameters
- Platelet dysfunction

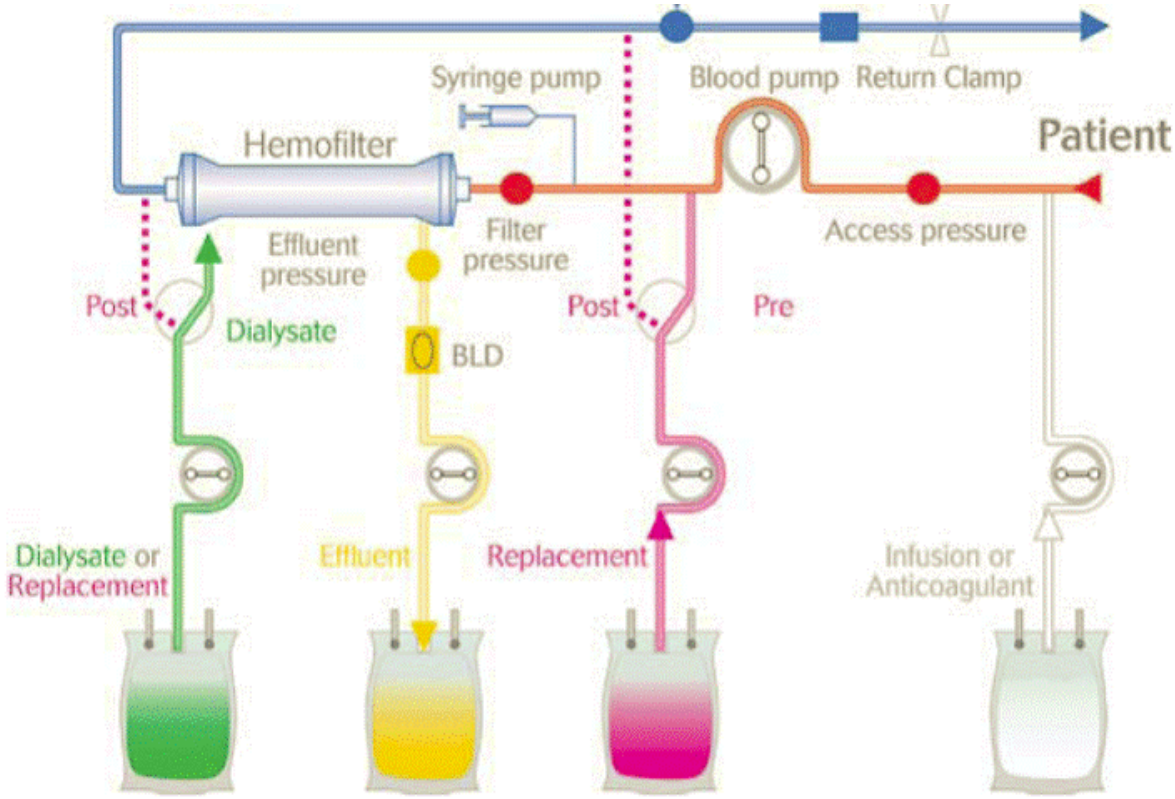
Provide an inert surface for blood membrane interaction

- Minimize activation of complement and cytokine cascade
- Reduce cellular activation
- Inhibit concentration repolarization
- Facilitate transfer of charged molecules

Anticoagulation for CRRT



Hydraulic Circuit for PrismaFlex



Prismaflex Disposable Set: Specifications

Sets	Surface Area (m^2)	BFR (ml/min)	DFR (ml/hr)	Priming Volume (ml)	Blood Volume (ml)	Max Filtration Capacity (ml/hr)
M60*	0.6	50-180	0-4000	1000	93	4000-pre 3000-post 2000-pbp
M100	0.9	75-400	0-8000	1000	152	8000-pre 6000-post 4000-pbp
HF1000	1.15	75-400	0-8000	1000	165	
HF1400	1.4	75-400	0-8000	2000	186	

*Indicated for patients >11kg

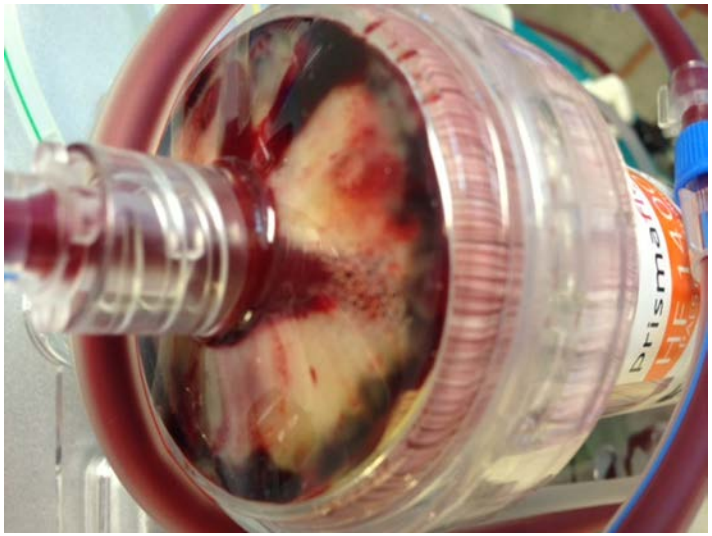
Clotting of Filter and Circuit

Vascular Access

Circuit Factors

- Connectology
- Filtration Fraction
- De-aeration chamber

Insufficient Anticoagulation



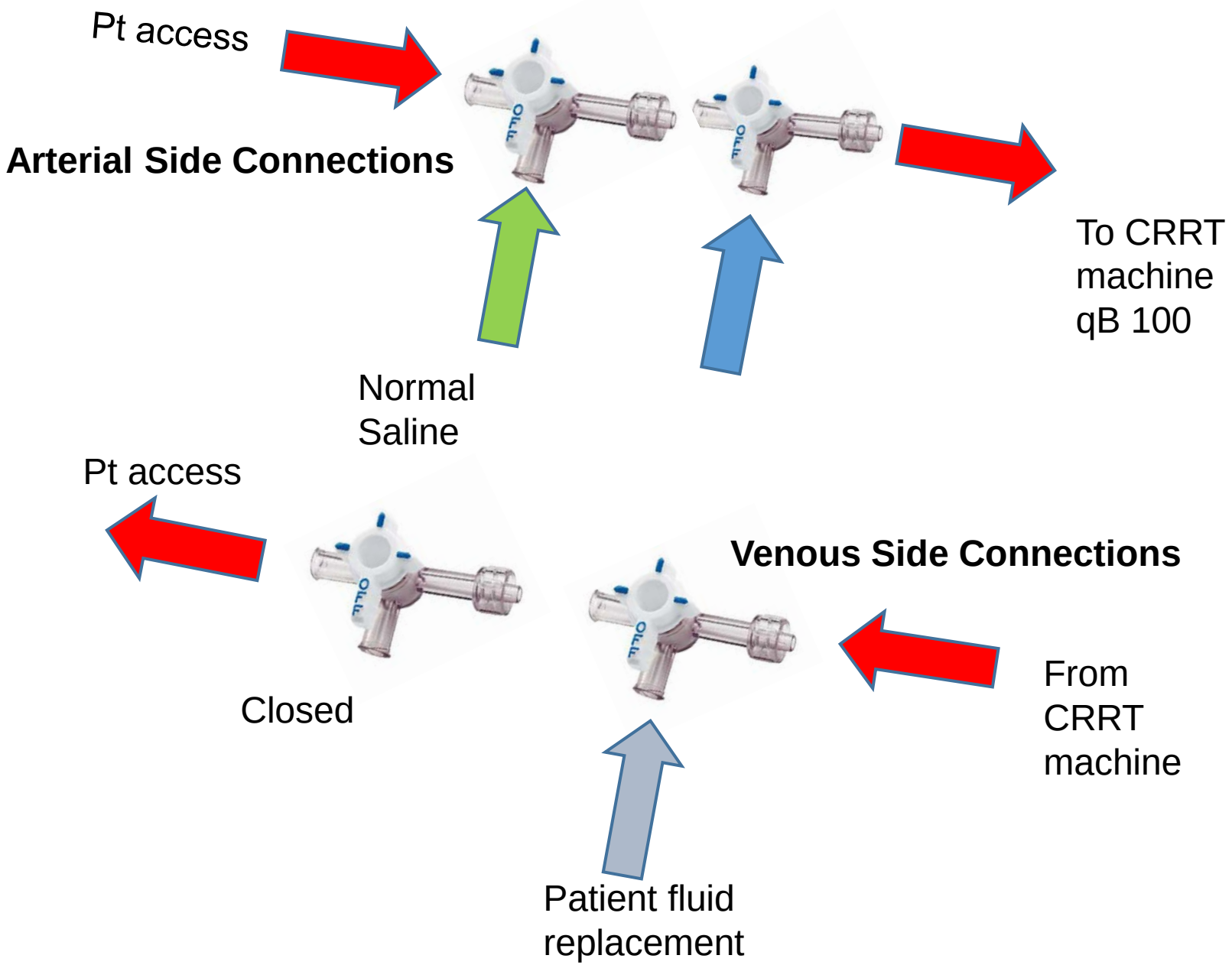
Access Issues Influencing Dialysis Delivery
Prevention and management of catheter dysfunction

Choice of the dialysis catheters	
Materials	Silicone or polyurethane catheter
	Heparin coated catheters are not recommended
Diameters	12- to 16-French (4–5 mm)
Length	For the upper sites: at least 15 cm to obtain right atrium placement for soft DC, superior vena cava for rigid DC
	For the lower sites: probably at least 24 cm
Lumens	Dual lumen catheter
	Two single-lumen catheters less easy to place but at least as accurate as dual lumen catheters
Tunnelization	Lower rate of DC dysfunctions but placement more difficult
Choice of the insertion site	
	Femoral and right jugular sites better than left jugular site
	Right internal jugular site should be preferred in intermittent hemodialysis if Q_B has to be higher than 200 ml/min
	Subclavian sites to be avoided
	Ultrasound guidance especially for jugular sites
	Preserve vascular network

Positioning of the catheter	
Upper sites	Tips of the catheter placed next to the right atrium in the superior vena cava
	Check chest radiography
Lower sites	Tips of the catheter placed in the inferior vena cava
During renal replacement therapy (RRT)	
Flush	Use saline solution flushes before and after every RRT session
Pressure	Check pressure greater than −250 mmHg on the inflow site
	Check pressure <250 mmHg on the outflow site
Lock	Anticoagulant lock, i.e., heparin after every RRT
Clamp	Careful clamp closing after every RRT
In case of dysfunction	
Patient	Try to change patient position
Flush	Try to flush catheter lumens with saline solutions
Catheter	Try to rotate the catheter
Lumens	Try to reverse catheter lumens. Prolonged port reversal not recommended due to recirculation which compromises efficacy
Locks	Fibrinolytic locks are not evaluated and are not yet recommended
Dose of RRT	Check previous KT/V in case of intermittent hemodialysis session and consider catheter replacement
Education of the team	

Mrozek et al. Annals of Intensive Care 2012, 2:48

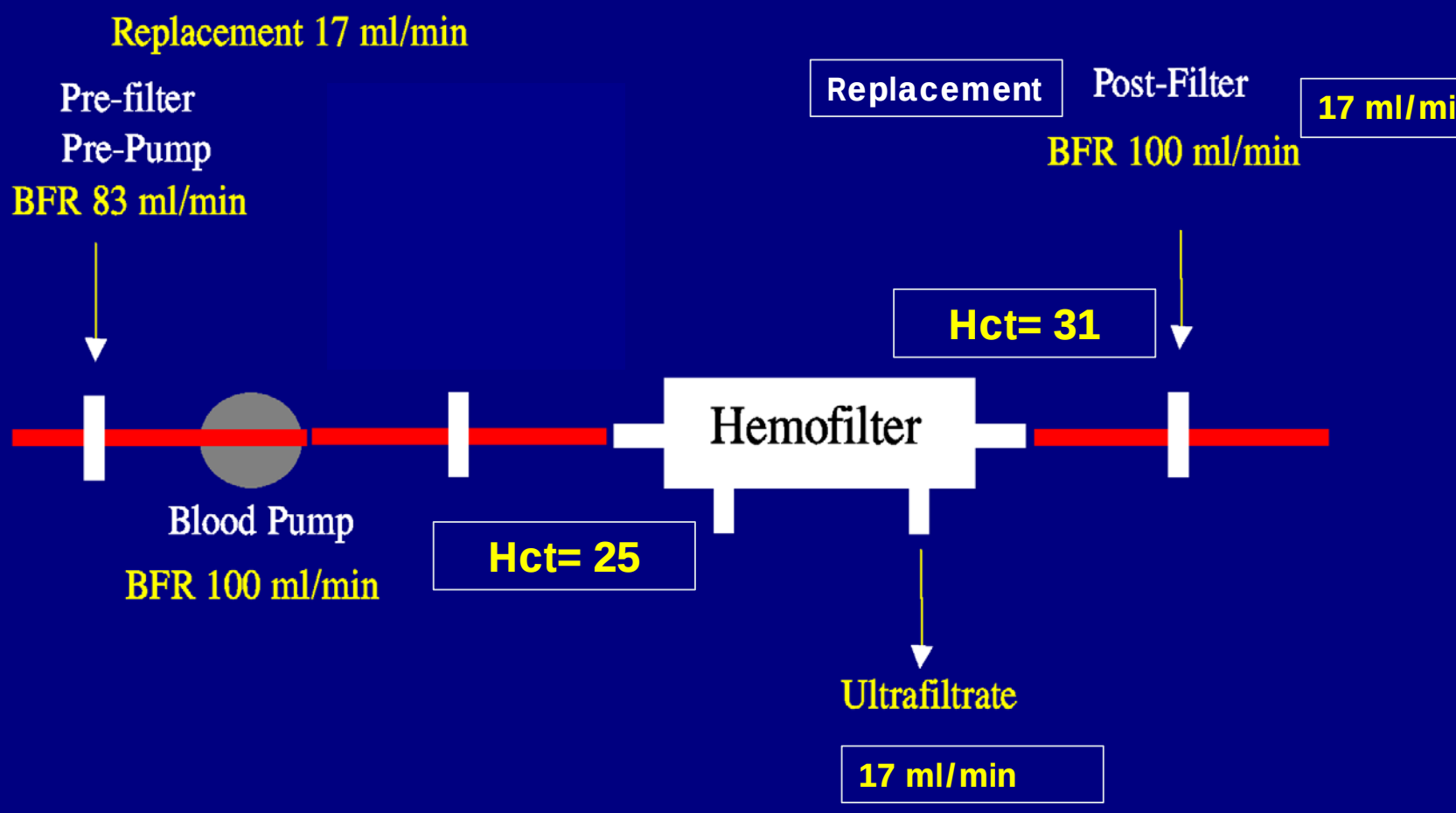
Circuit Connections UCSD



Fluid Management in Continuous Renal Replacement Therapy

Pre-Filter vs Post-Filter Replacement Fluid

Modality: CVVH with UFR 1L/hr



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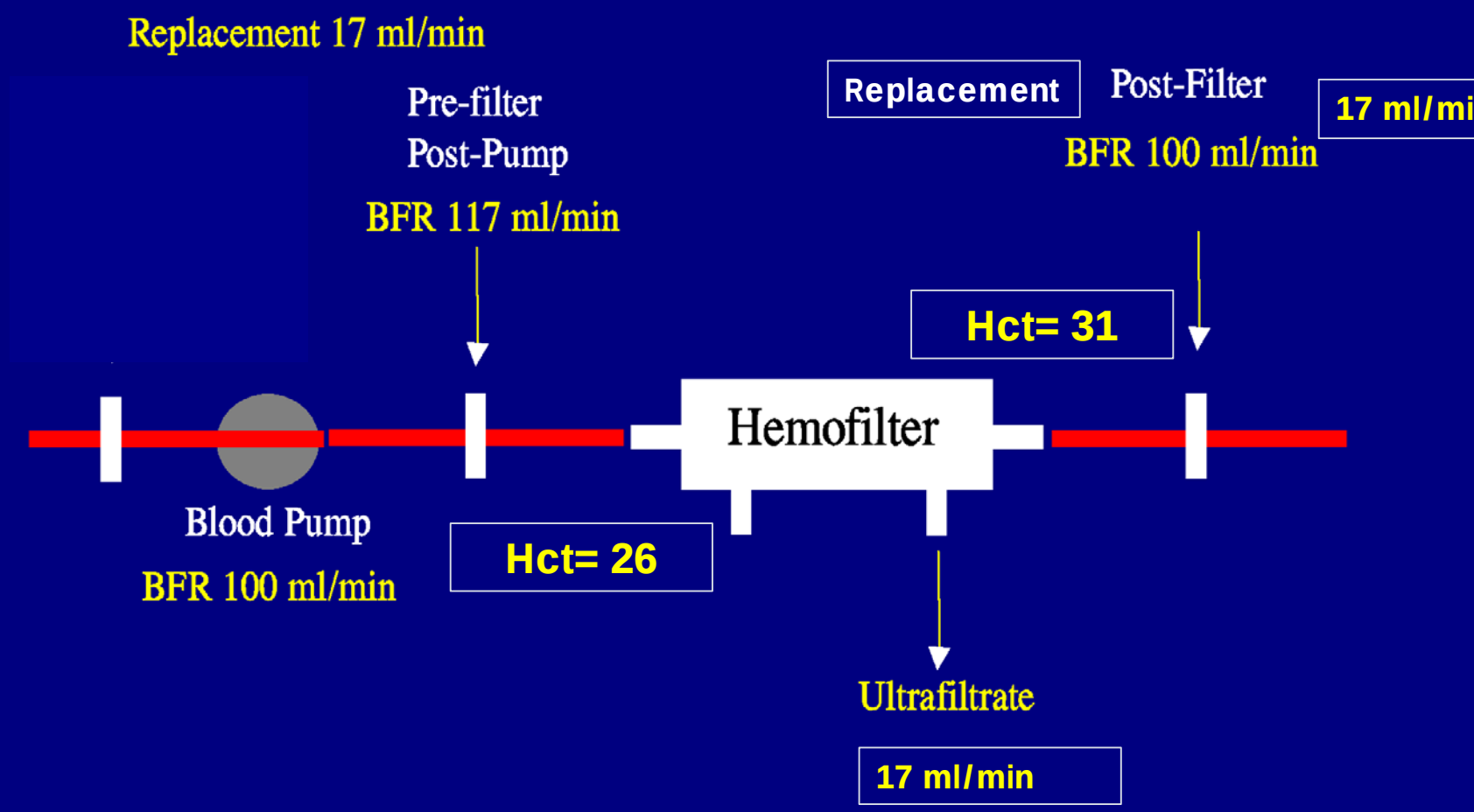


Pre-Dilution vs Post-Dilution CVVH

Filtration fraction (FF) = ultrafiltration rate/ plasma water flow rate

- FF values > 0.20 undesirable due to hemoconcentration-related effects on filter performance
  - major limitation of post-dilution CVVH
  - dependent on blood flow rate (Q_B) and hematocrit (Hct)

$$FF = \frac{\text{UF rate (ml/min)}}{\text{plasma flow rate } (Q_P) \text{ (ml/min)}}$$

Table 3. Plasma flow and FF for different Q_Bs, UF rates and Hct

Hct, %	Q_B = 150 ml/min		Q_B = 200 ml/min	
	Q_P	FF	Q_P	FF
UF = 1,000 ml/h				
Hct = 25	112.5	0.15	150	0.11
Hct = 35	97.5	0.17	130	0.13
Hct = 40	90	0.19	120	0.14
UF = 2,000 ml/h				
Hct = 25	112.5	0.30	150	0.22
Hct = 35	97.5	0.34	130	0.26
Hct = 40	90	0.37	120	0.28

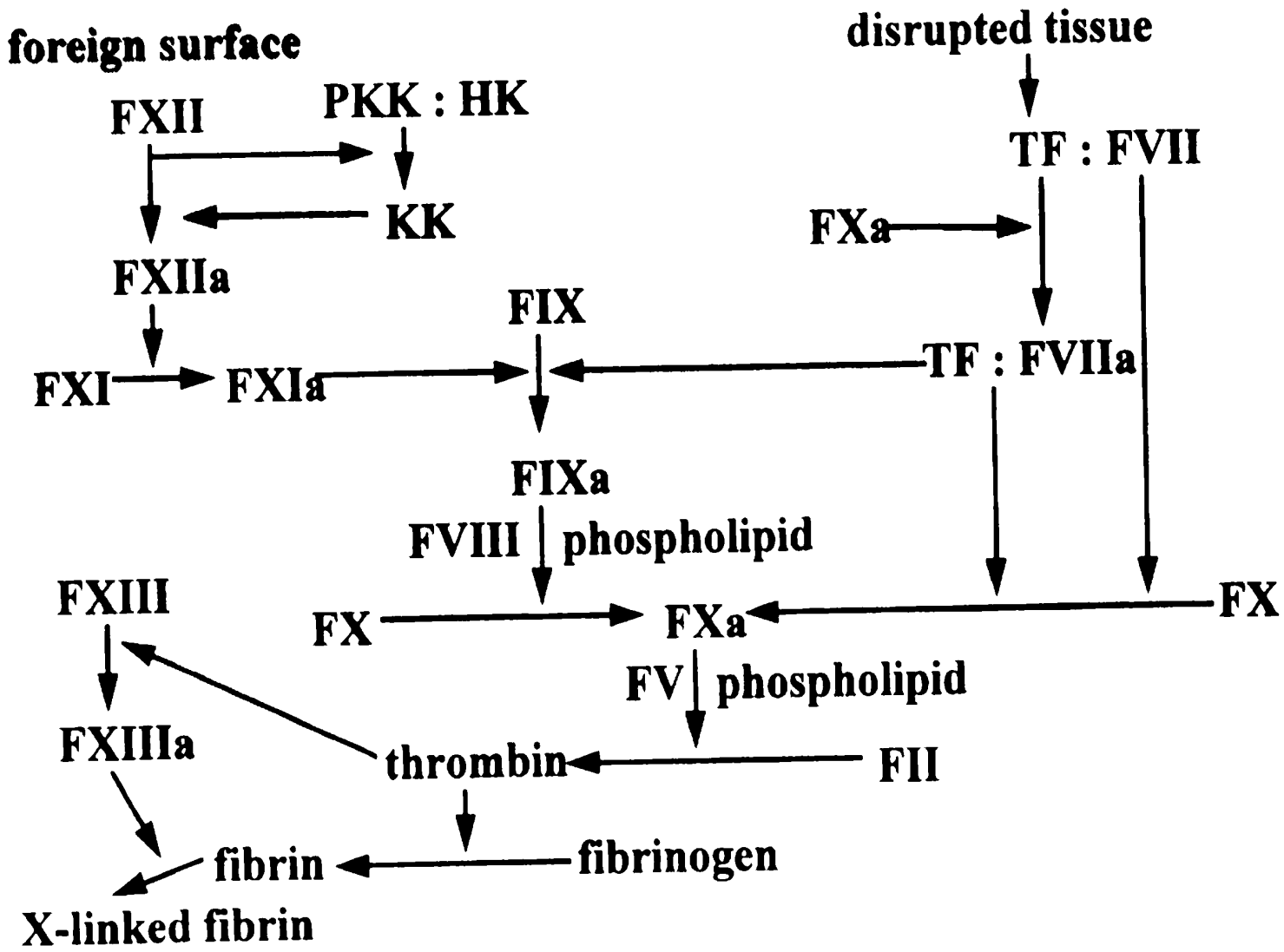
Q_P = Plasma flow rate in ml/min.

Circuit Considerations

DEAERATION CHAMBER

Manages air in the return line, the deaeration chamber provides a unique conveyance path that works like a vortex to propel all air out of the blood. Post-filter replacement solution is added into the deaeration chamber on top of the blood. Using a minimum of 200 to 500 ml/hr of post filter replacement will prevent air/blood interface. This is recommended to minimize clotting and foaming into deaeration chamber.

Coagulation Pathways



Modified from Davenport: Am J Kid Dis: 1997; suppl 4: S20-27

Anticoagulation for CRRT Modalities

Mechanical

- Circuit design (air-blood interface)
- Reduced viscosity (pre-dilution)

Systemic

- Heparin
- Low molecular weight heparin
- Prostacyclin
- Thrombin inhibitors
  - Lepirudin
  - Argatroban
  - Nafomastat mesylate

Regional

- Heparin
- Citrate

Unfractionated Heparin (UFH)

Intrinsic system

XII -> XIIa = Hagemann Factor

XI -> XIa
+ Ca

IX -> IXa
+ VIIIa, Ca

Extrinsic system

VII -> VIIa
+ Ca

- 4.5-6 kDa
- $t_{1/2}$ 2-4 hrs (increased in renal failure)
- Affected by antithrombin deficiency

Antithrombin III

X -> Xa = Prothrombin activator
+ Va, Ca

Prothrombin -> Thrombin

Fibrinogen -> Fibrin + XIIIa -> cross-linked Fibrin

Low molecular weight heparin (LMWH)

Intrinsic system

XII -> XIIa = Hagemann Factor

XI -> XIa + Ca

IX -> IXa + VIIIa, Ca

Antithrombin III

X -> Xa = Prothrombin activator + Va, Ca

Prothrombin -> Thrombin

Extrinsic system

VII -> VIIa + Ca

more active in inhibiting factor Xa, less with factor IIa

half-life up to 10 hours

monitoring: Measurement of anti-Xa activity (0.3 – 0.5 IU/ml)

Fibrinogen -> Fibrin + XIIIa -> cross-linked Fibrin

Citrate

Intrinsic system

XII -> XIIa = Hagemann Factor

XI -> XIa + Ca

IX -> IXa + VIIIa, Ca

X -> Xa = Prothrombin activator + Va, Ca

Prothrombin -> Thrombin

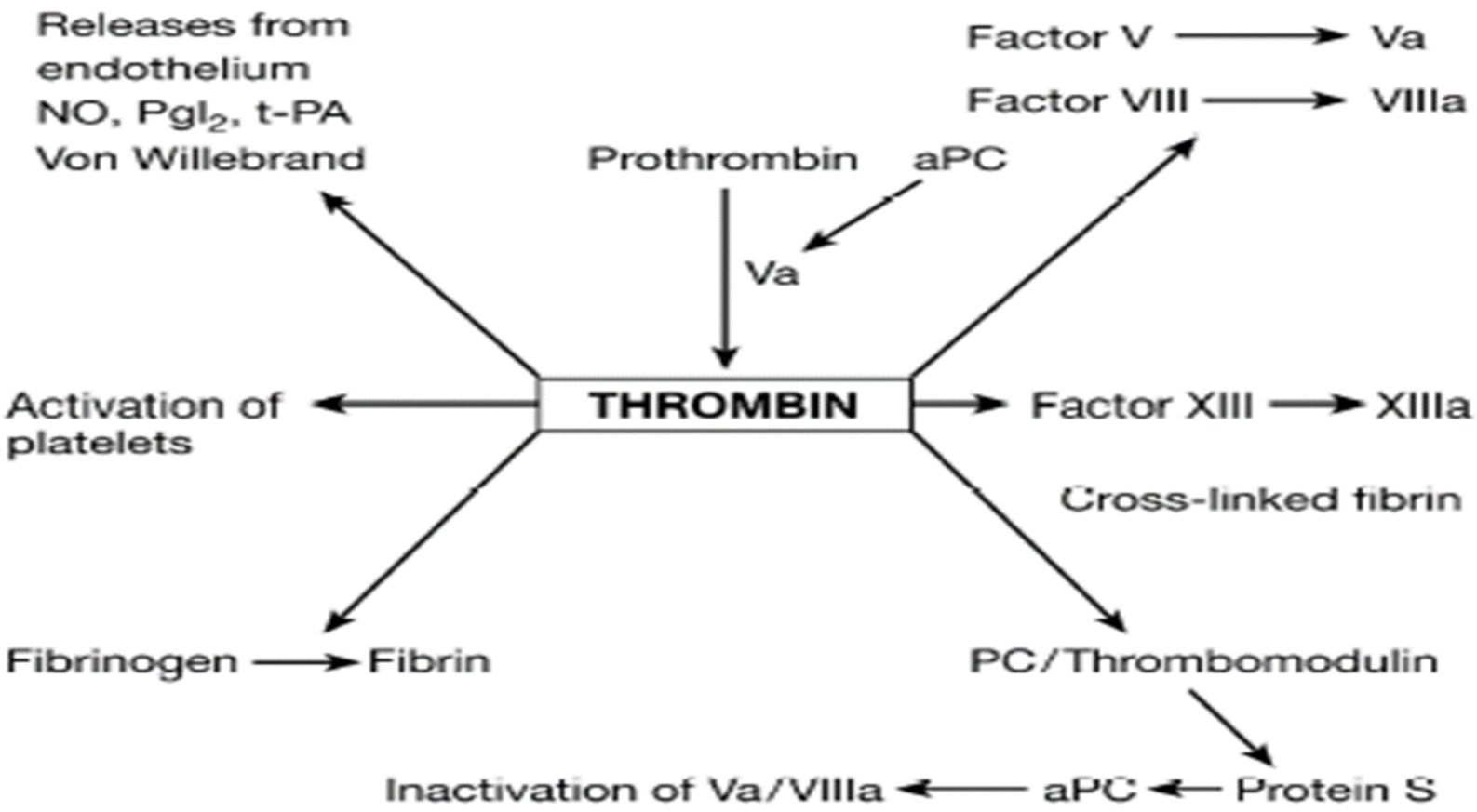
Fibrinogen -> Fibrin + XIIIa -> cross-linked Fibrin

Extrinsic system

VII -> VIIa + Ca

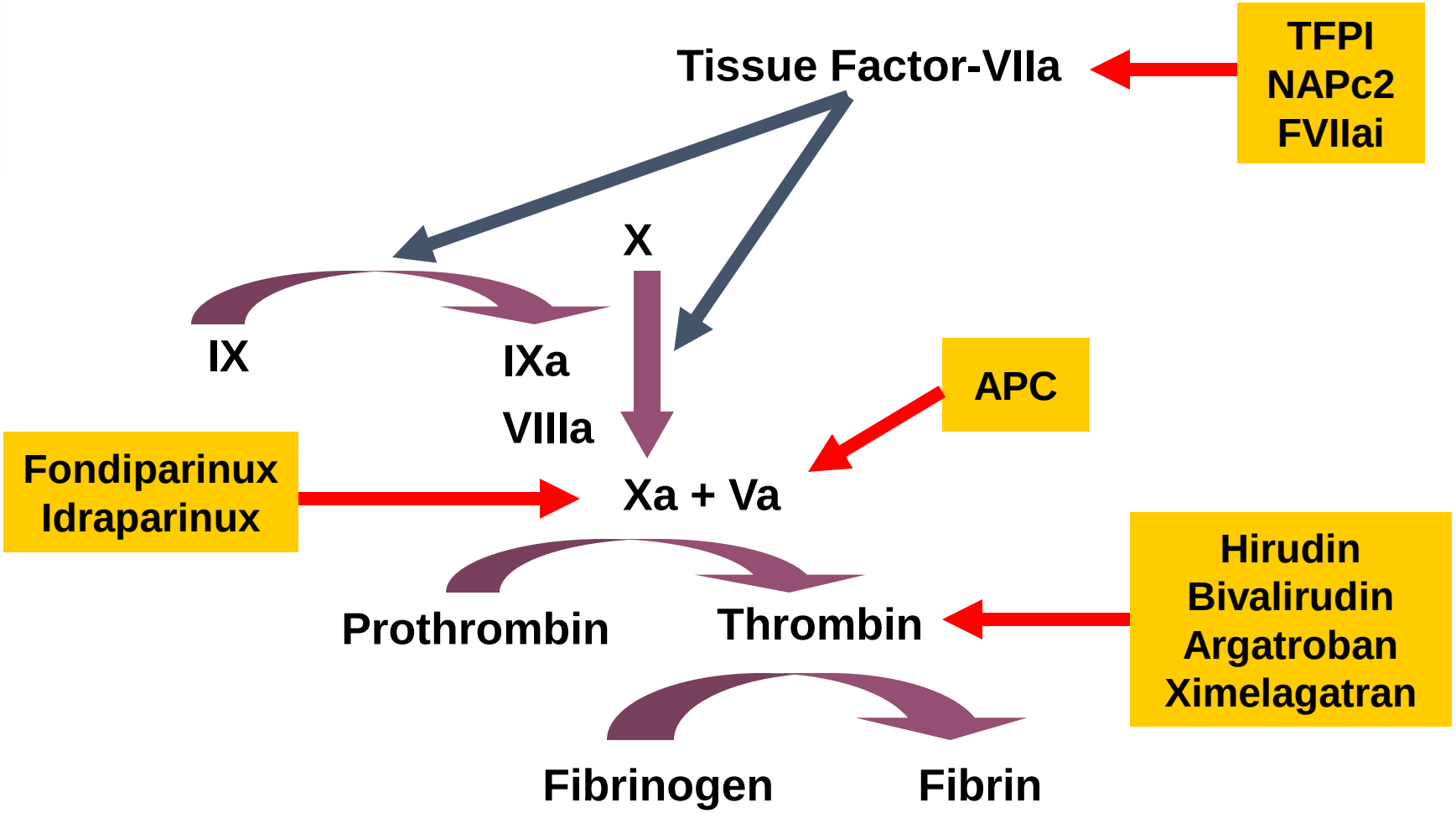
- Chelates free Ca^{+2} in extracorporeal circuit
- Prevents activation of Ca^{+2}-dependent procoagulants
- Anticoagulant effect measured by iCa^{+2}
- Anticoagulation reversed by Ca^{+2} infusion

Thrombin Inhibitors

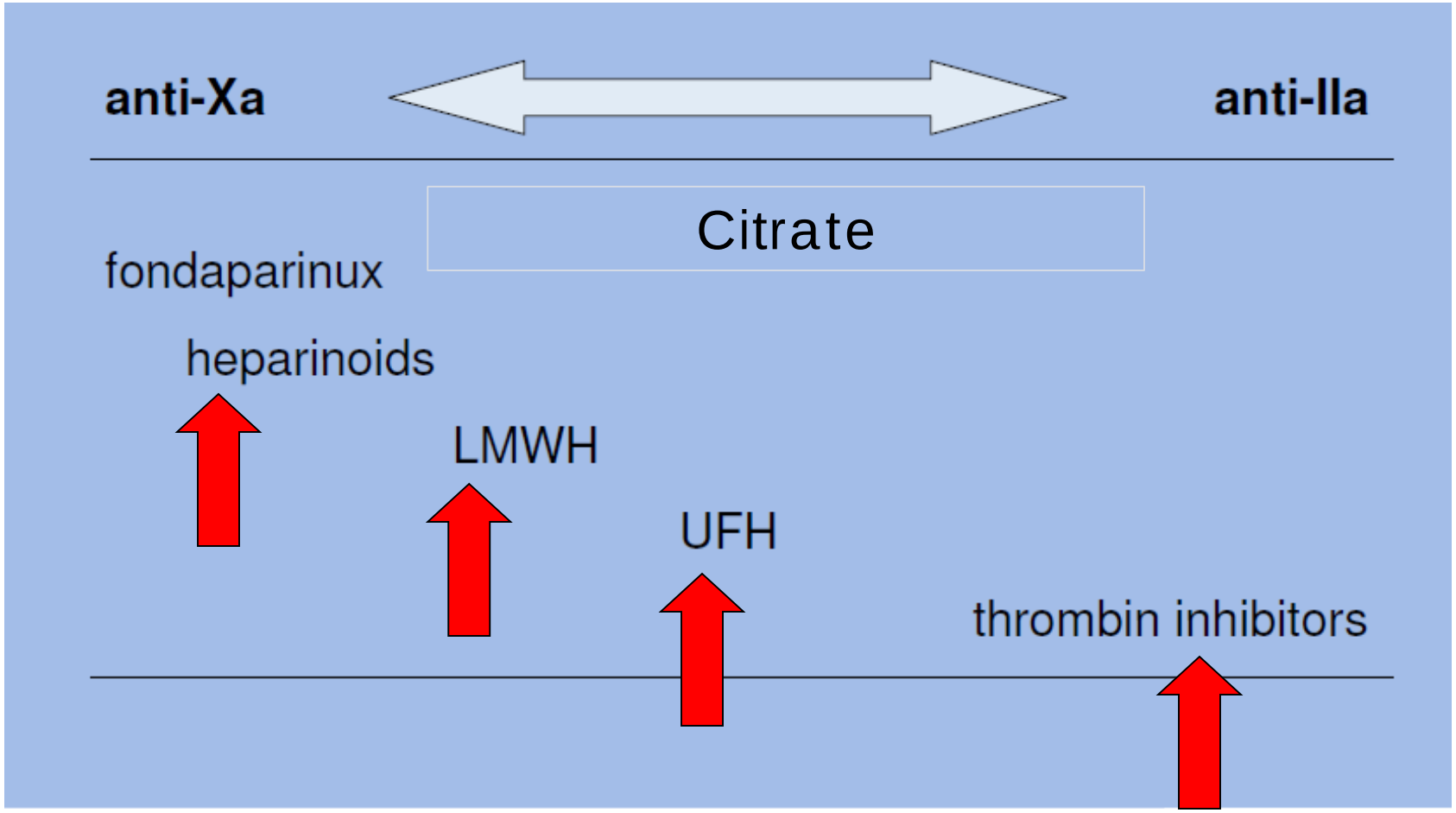


Pravinkumar E et al: British Journal of Anaesthesia 90 (5): 676±85 (2003)

Thrombin Inhibitors



Mechanisms of Anticoagulants



Natural Anticoagulant Pathways

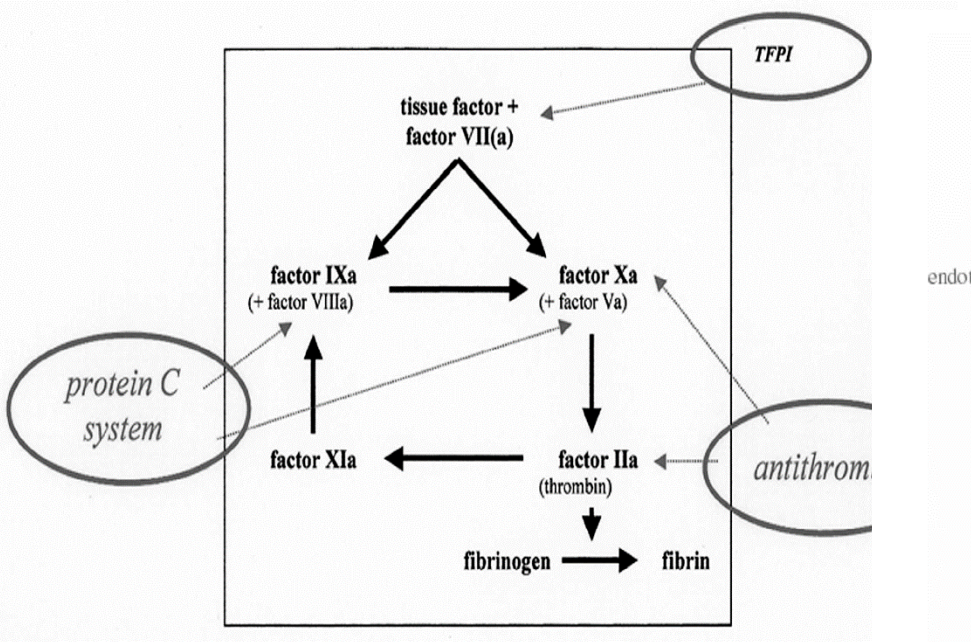
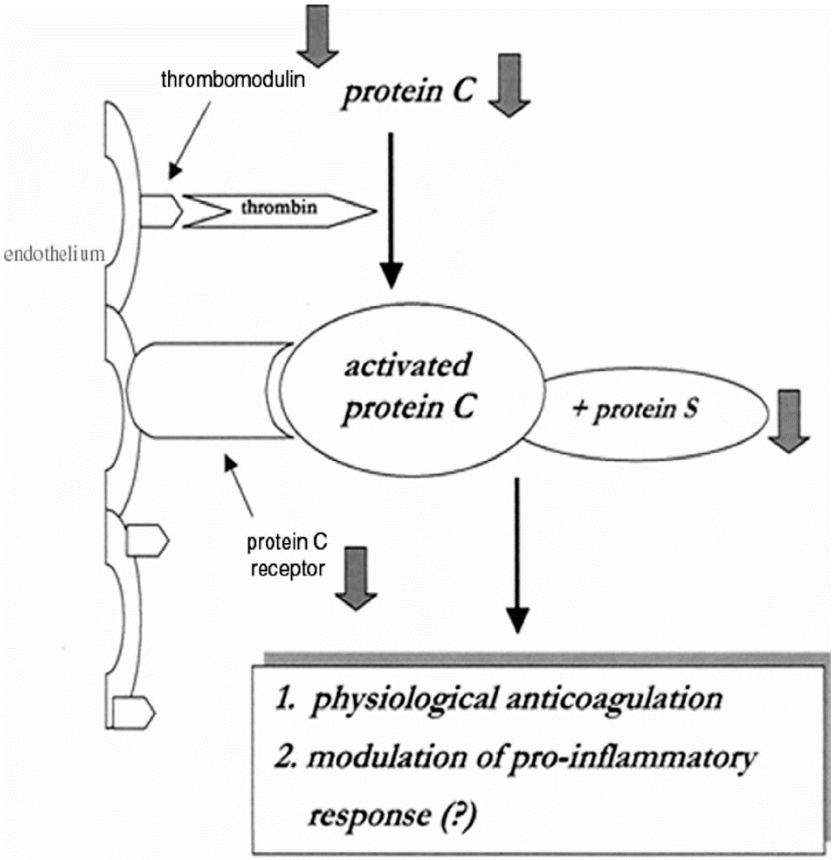


Figure 2. Point of impact of the three major physiological anticoagulant pathways.

Antithrombin is the most important inhibitor of thrombin and factor Xa, activat protein C is able to degrade the essential cofactors Va and VIIIa, and tissue f pathway inhibitor (TFPI) inhibits the tissue factor/factor VIIa complex.



Acquired Deficiency of Natural Anticoagulants

	Protein C	Protein S	ATIII
Liver Disease	++	++	++
DIC	++	++	++
CP Bypass	++	-	?+
Uremia	?	?	?
Pregnancy	-	+	?
Lupus	-	+	++
Nephrotic syndrome	+	+	++
Drugs			
Warfarin	++	++	?
Chemotherapy	++	++	?
Heparin	-	-	++

Antithrombin III deficiency during CVVHD

		ATIII deficiency	Control
Pt characteristics	Apache II	24.9(6)	21.7(4)
	MODS score	2.9(0.8)	2.2(0.8)
Coagulation	PT, % Normal	36.7(17)	63.3(12)
	Fibrinogrn (G/L)	2.8(1.4)	5.0(1.3)
	ATIII level, %	37.3(11)	79.3(14)
	Platelets	87.9(37)	99.6(83)
	Bilirubin, umol/L	263(184)	82(118)
Outcomes	ICU stay, days	17.5(17)	29.6(23)
	Dialysis duration, days	8.3(7)	6.9(4)
	Membrane duration, days	1.7(0.7)	2.3(0.7)
	% Mortality	89	39

From Bastien et al: Contrib Nephrol 1995, 116:154-158

Prostacyclin

Vasodilator
Inhibits platelet aggregation and adhesion
Short acting
Vasodilator half life 2 min
Antiplatelet effect 2 hrs

Hemostatic system

Platelet aggregation

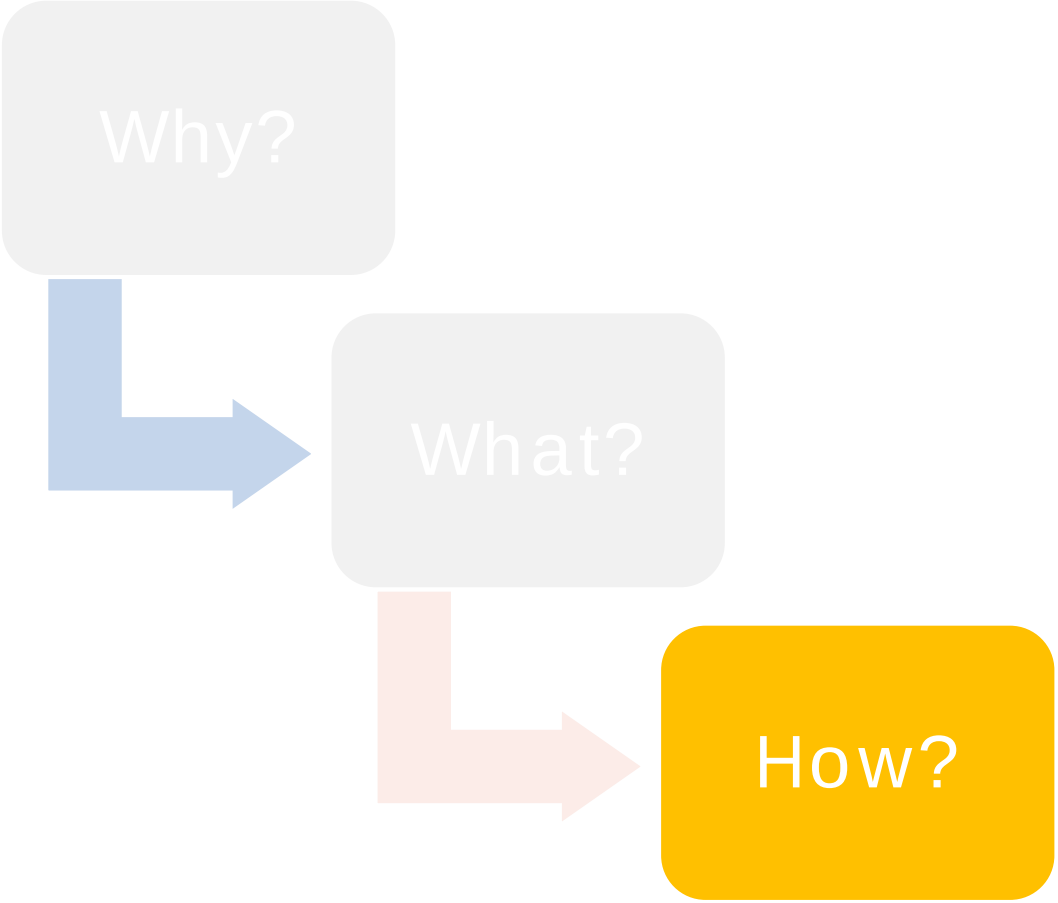
Coagulation cascade

Fibrin clots

Prostacyclin

Heparin
LMW heparin
Citrate
Regional anticoagulation

Anticoagulation for CRRT



No Anticoagulation

Usually used in patients with intrinsic coagulopathies such as hepatic failure or low platelet counts

Methods:

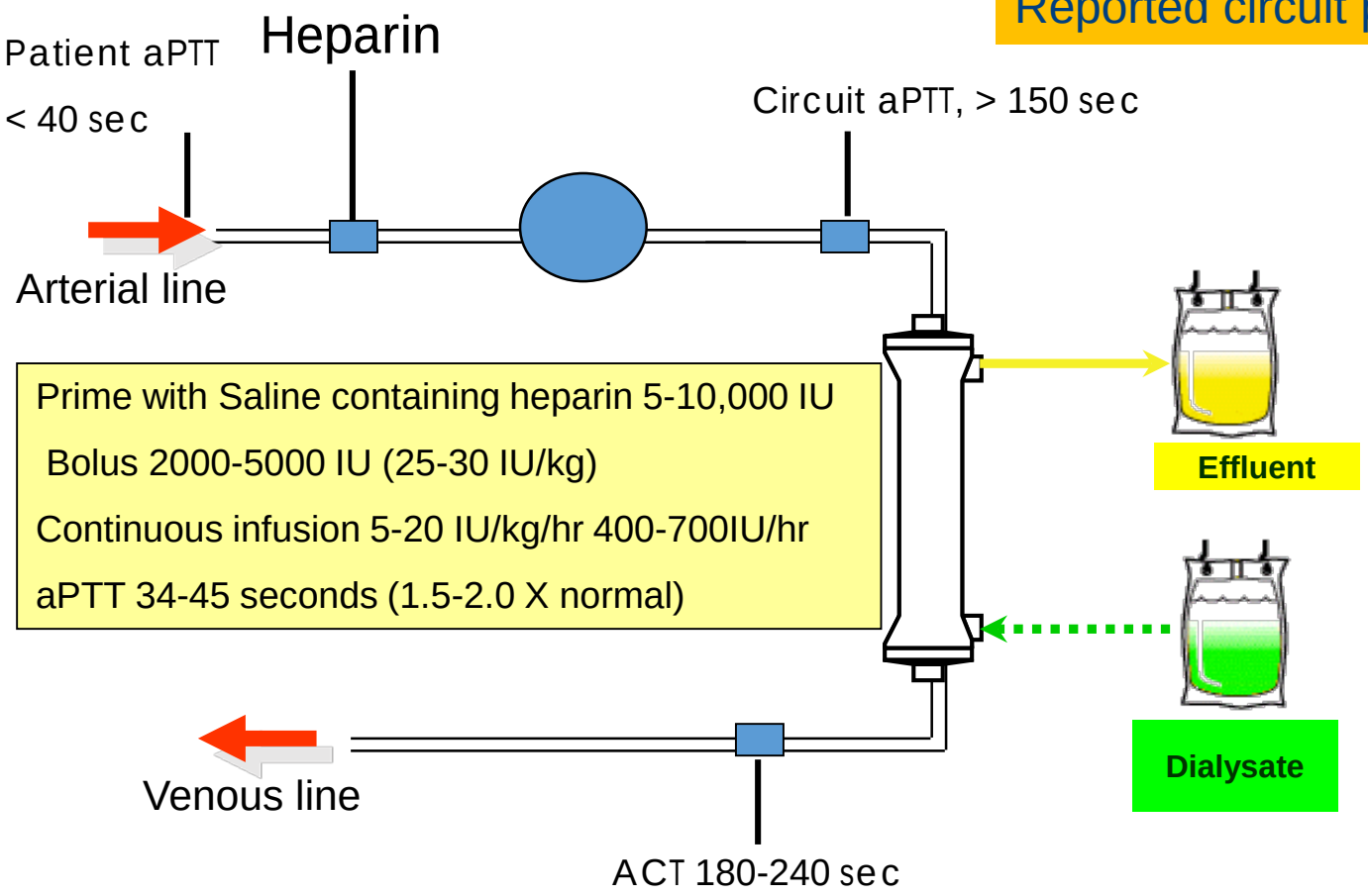
- Prime circuit: Saline or Heparin prime
- Intermittent 0.9% NS flush 50-200 ml q 30-60 mins

Results:

- Rates of filter clotting vary widely
- Mean filter life between 16 - 70 hrs if coagulopathic
- Shorter filter life 6 -18 hrs unless severe coagulopathy

UFH Protocol

Reported circuit patency 20-40 hrs



Prime with Saline containing heparin 5-10,000 IU

Bolus 2000-5000 IU (25-30 IU/kg)

Continuous infusion 5-20 IU/kg/hr 400-700IU/hr

aPTT 34-45 seconds (1.5-2.0 X normal)

Recommended Unfractionated Heparin dose in CRRT

Risk group	Initial loading dose IU/kg	Continuous dose IU/kg/h	Target PTT
Low risk	50	10 - 20	1.5 – 2x normal
Moderate risk	15 - 25	10	10 – 15 sec > normal
High risk	10	5 - 8	< upper limit of normal

Platelets before CRRT	PTT (sec) before CRRT	Heparin requirement (IU/h)	PTT (sec) during CRRT	Filter life time (h)
< 50000	61	none	50	22
50-200000	46	100 - 700	45	25
> 200000	42	> 700	40	23

Unfractionated Heparin

Advantages

- Effective
- Widely available
- Simple monitoring (aPTT)
- Reversed with protamine
- Inexpensive
- Short half life

Disadvantages

- Systemic bleeding
- Unpredictable kinetics
- PTT not reliable predictor for bleeding
- Heparin resistance due to low patient antithrombin levels
- Heparin induced thrombocytopenia (HIT)

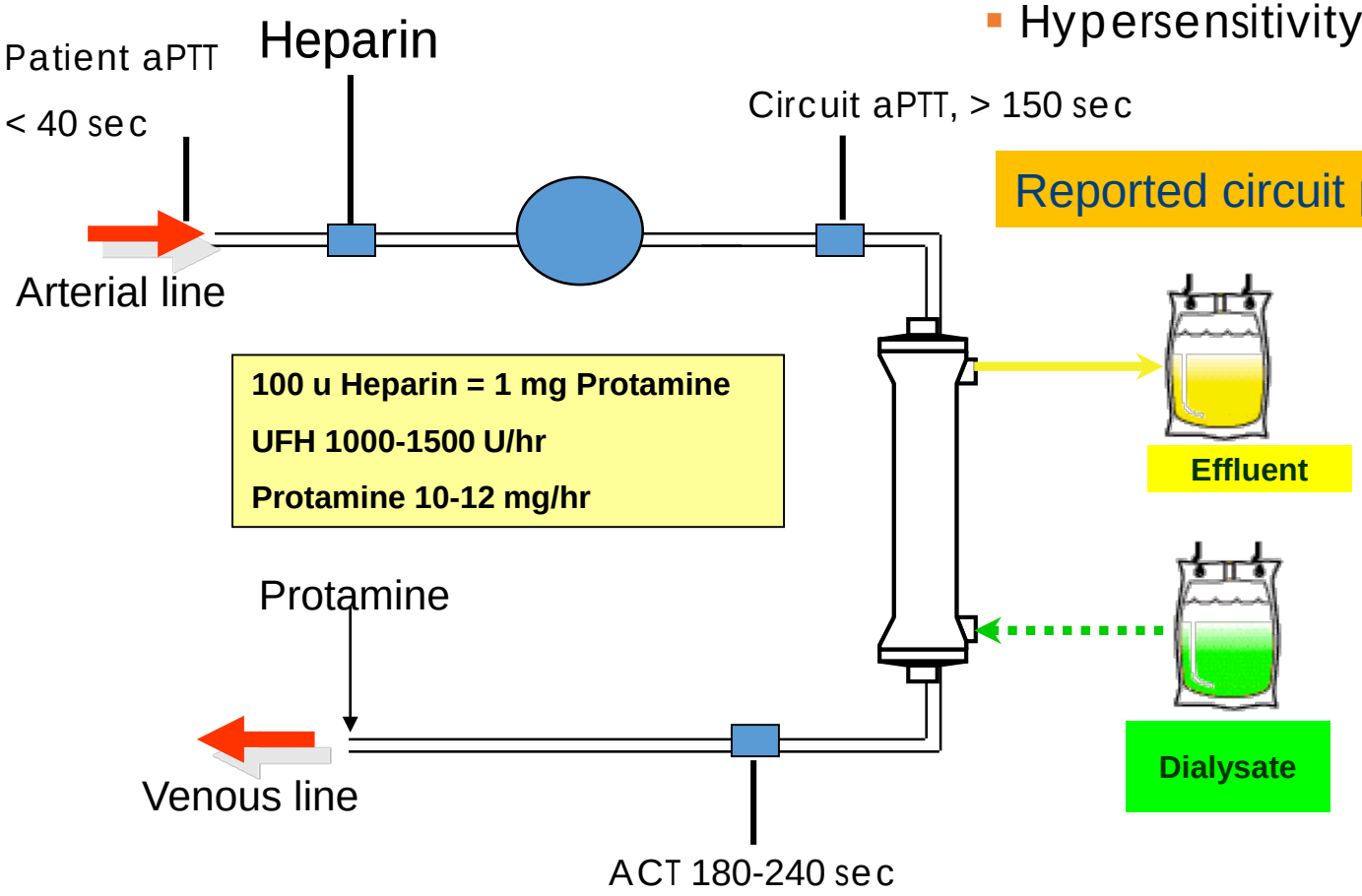
UFH – Protamine Sulfate Regional Anticoagulation

Advantages

- Anticoagulation effects restricted to extracorporeal circuit

Disadvantages

- Rebound (instable heparin-protamine complex)
- Hypotension
- Hypersensitivity



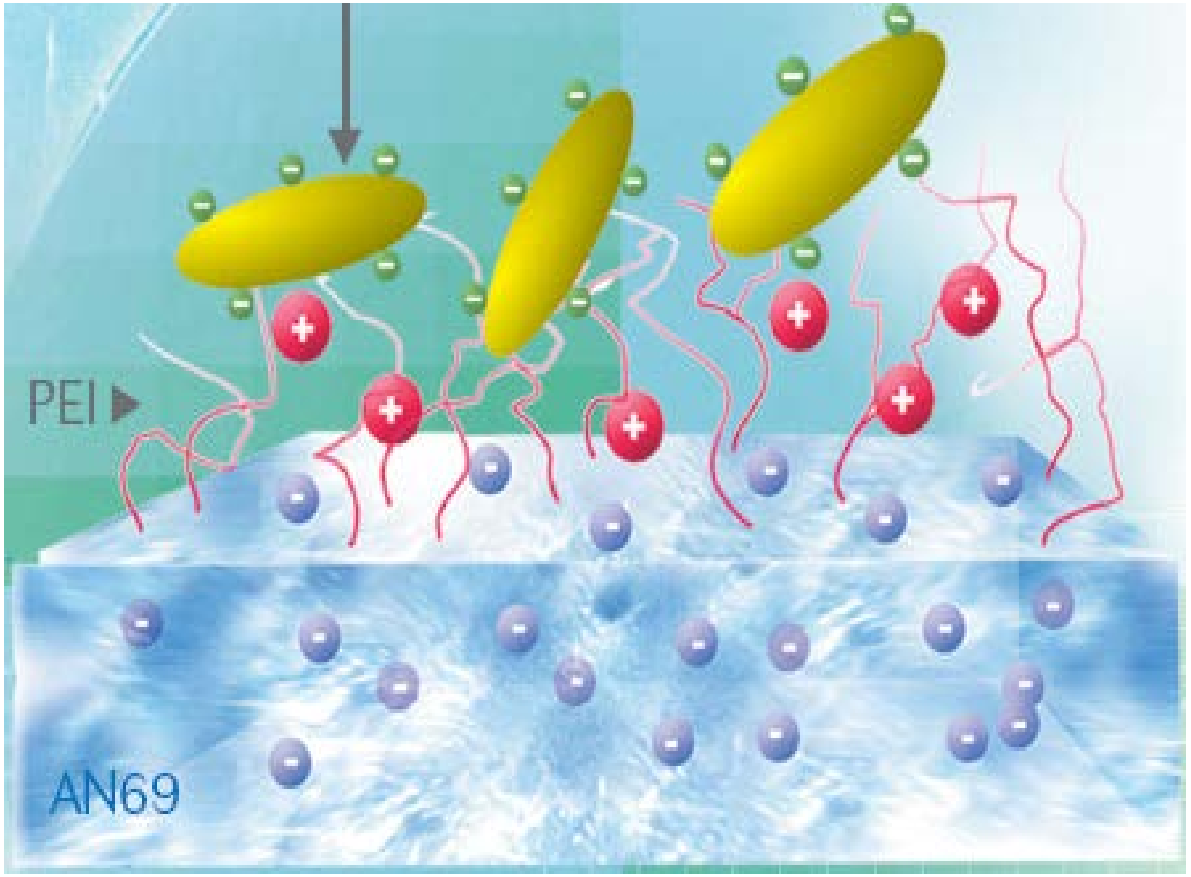
Reported circuit patency 20-40 hrs

Kaplan AA et al. Trans Am Soc Artif Organs 1987

Van der Voort PH et al. Blood Purif 2005

AN 69 –ST Mb-A Bi-Dimensional View

heparin



***PEI=PolyEthylene Imine*

Honore PM et al.ASAIO 2013: 59 :99-106

LMWH Protocols

Fixed dose vs. dose based on anti-Xa

Target anti-Xa level 0.25-0.35 U/ml

Enoxaparin

- Loading dose 0.15 mg/kg
- Maintenance dose 0.05 mg/kg/hr
- Mean filter life 31 hrs

Nadroparin, Dalteparin

- Loading dose 15-25 IU/kg
- Maintenance dose 5-10 IU/kg/hr
- Median filter life 18-50 hrs

Advantages

- Effective
- Predictable pharmacokinetics
- Lower incidence of HIT

Disadvantages

- Systemic bleeding
- Only partially reversed with protamine
- anti Xa activity not everywhere available
- Expensive

Pont AC de et al. Crit Care Med 2000

Reeves JH et al. Crit Care Med 1999

Journois D et al. Ann Fr Anesth Reanim 1990

Joannidis M et al. Intensive Care Med 2007

Lepirudin (r-Hirudin)

6980 Da

Irreversibly inhibits thrombin

Eliminated by the kidneys

Half life of 1-2 hrs prolonged in renal failure

Monitoring: Ecarin clotting time (ECT)

Protocols

- Continuous infusion 0.005-0.01 mg/kg/hr
- Or bolus dose 0.002 g/kg
- ECT target 80-100 seconds

Disadvantages

- No antidote!
- ECT not easily available

Fischer KG et al. Kidney Int 1999
Vargas O et al. Int Care Med 2001

Bivalirudin

Reversibly inhibits thrombin

80% eliminated by nonorgan-dependent proteolysis

20% excreted unchanged by the kidneys

Half life of 25 min

- Clearance reduced approximately 20% in patients with severe renal impairment and by 80% in dialysis-dependent patients
- Bivalirudin is hemodialyzable and approximately 25% is cleared by hemodialysis

Protocols

- Continuous infusion 1 mg/hr (0.009 mg/kg/h)
- aPTT target 1-1.4 times baseline

Disadvantages

- Limited studies
- 1 RCT 2010:
  - 10 pts randomized to bivalirudin (2 mg/hr) vs. heparin (400 u/hr)
  - Hemofilter survival time was significantly increased in patients receiving bivalirudin vs. those receiving heparin (29.6 ± 20.7 vs. 16.5 ± 13.6 hrs, p=0.045)

Kiser et al. Pharmacotherapy. 2010
Mueller et al. Annals of Pharm. 2009
Kisere et al. Annals of Pharm. 2008

Argatroban

Second generation direct thrombin inhibitor

526 Da

54% protein bound

½-life 35-51 min

Metabolized by the liver

Dose

- Loading dose 100-250 µg/kg
- Maintenance dose 0.1-2 µg/kg/min
- Adjusted to achieve aPTT 1.5-3.0 times baseline

No antidote

Mean circuit life 44 hrs

Reddy et al. Ann Pharmacother 2005
Tang IY et al. Ann Pharmacother 2005

Prostacyclin –PGI2

Vasodilator

Inhibits platelet aggregation and adhesion

Short acting

- Vasodilator half life 2 min
- Antiplatelet effect 2 hrs

Protocol

- 2-8 ng/kg/min infused pre-filter

Disadvantages

- Hypotension
- Expensive

Median filter life

- 15-19 hrs
- 20-22 hrs with low dose heparin

Langenecker et al. Crit Care Med 1994
Kozek-Langenecker et al. Crit Care Med 1998
Fiaccadori et al. Int Care Med 2002
Balik et al. Blood Purif 2005

Nafomostat

Synthetic Serine Protease inhibitor prostacyclin analogue

Inhibits platelet aggregation and adhesion

Short acting

- Vasodilator half life 2 min
- Antiplatelet effect 2 hrs

Protocol

- 0.1 mg/kg/hour infused pre-filter

Disadvantages

- studies have demonstrated that levels of thrombin–antithrombin III complex and prothrombin activation fragment 1 + 2 increase, while protein C activity decreases, leading to circuit clotting
- Several side effects (anaphylaxis, agranulocytosis, hyperkalemia)

Median filter life

- 15-19 hrs
- 20-22 hrs with low dose heparin

Citrate

Citrate solutions

Desired Effects

- Anticoagulation
  - Circuit longevity
- Replete Base
  - Acid base balance

Protocols

- Titration of citrate based on iCa^2
- Fixed relationship between BFR & citrate delivery

Advantages

- Regional, avoids bleeding complications
- Doubles as buffer
- Highly effective in studies (> heparin)
- No thrombocytopenia

Disadvantages

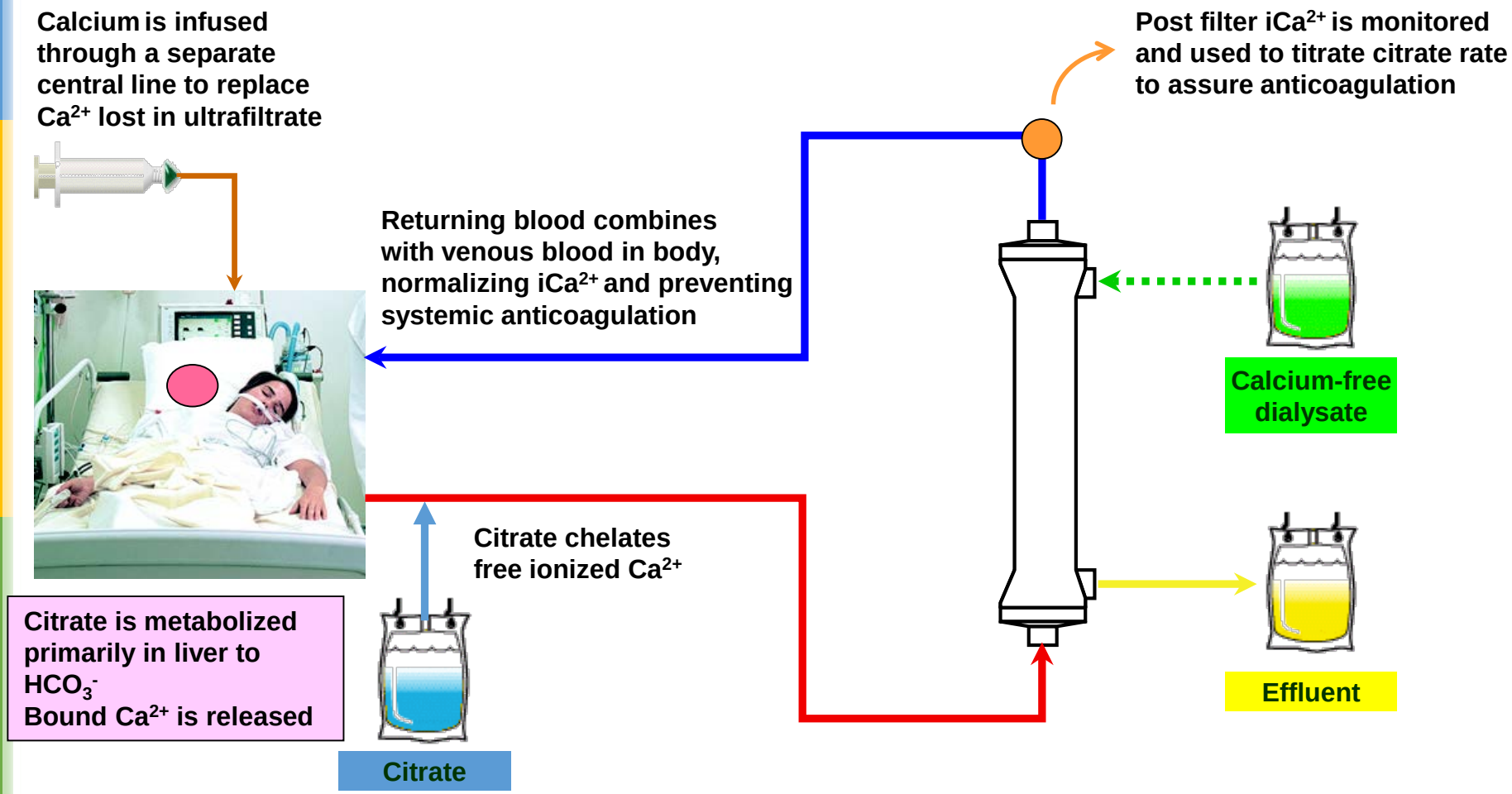
- Metabolic complications
- Complex protocols

Components	4% Sodium Citrate	ACD A: 2.2% Sodium Citrate	ACD B: 1.32% Sodium Citrate	Prismocitrate (only available in Europe)
Na (meq/L)	408	224	135	136
Sodium Citrate (mmol/L)	136	113	68	10
Citric Acid (g/L)		7.3	4.4	4.2
Dextrose (g/L)		24.5	14.6	
Bag Size (mL)	**250 & 500**	**500 & 1000**	**500**	**5000**

QB (mL/min)	4% TSC (mL/hr)	ACD-A (mL/hr)
100	175	210
125	218	262
150	262	315
200	350	420

Amount of citrate delivered to achieve blood citrate concentration of 4 mmol/L depends on blood flow

Citrate Anticoagulation in CRRT: Regional Effect in the Circuit



Citrate

Normal blood levels of citrate: 0.05 mmol/L

Bleeding time → ∞ at citrate levels of 4 to 6 mmol/L (iCa^{2+} < 0.35 mmol/L)

Levels of 12 to 15 mmol/L required for stored blood products for transfusion therapy

Extracorporeal clearance

- Clearance same as urea
- Sieving coefficient 0.87- 1.0
- CVVH = CVVHD clearance
- Depends on citrate concentration in the filter and filtration fraction

Citric acid has plasma half life of 5 mins

Rapidly metabolized by liver, kidney and muscle cells

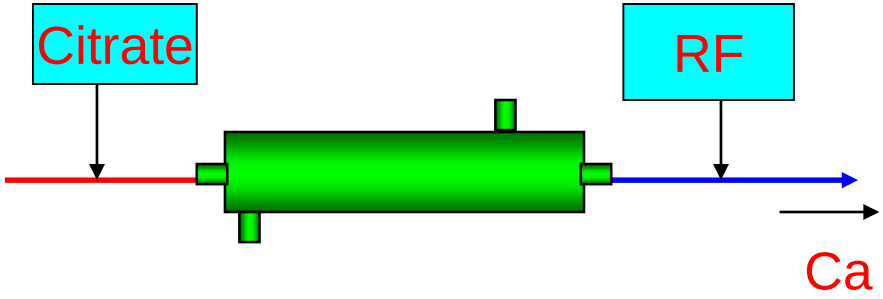
$$Na_3Citrate + 3H_2CO_3 \leftrightarrow Citric\ Acid + 3NaHCO_3$$

$$\downarrow$$

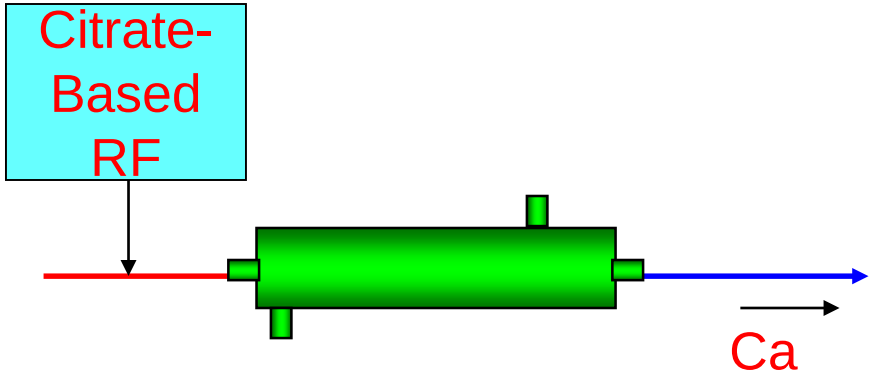
$$3H_2CO_3 + H_2O + 3NaHCO_3 \leftrightarrow 4H_2O + 6CO_2$$

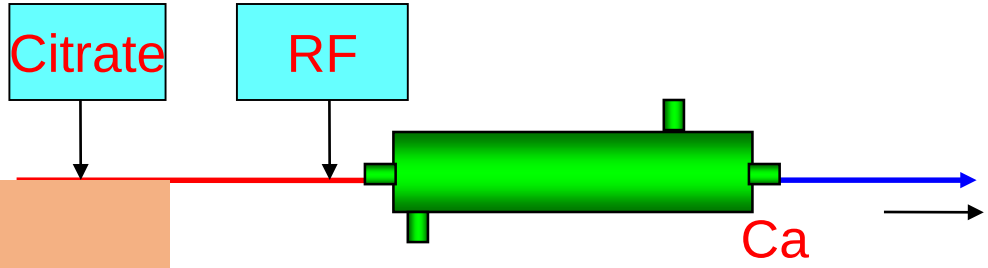
Circuit Options for CVVH

Post-dilution



Pre-dilution





Blood flow 120-200 ml/min

UF 1200-4000 ml/min

Citrate 15-40 mmol/L

Targets Systemic Ca 1.12-1.25mmol/L

Post Filter Ca <0.4 mmol/L

Palsson and Niles, KI, 1999, 55: 1991-1997

Munjal and Ejaz. Nephrology 2006; 11: 405-409

Morabito et al Critical Care 2012.

UAB Citrate Protocol (CVVHD)

Prefilter Fluid: 3L bag

2% Trisodium Citrate

$Citrate^{3-}$	204 mEq/L
Na^+	204 mEq/L
Dextrose	2.5%

Rate: 250 mL/hr

17.5 mmol/h citrate

Dialysate: 3L bag

Na^+	140 mEq/L
Cl^-	143 mEq/L
K^+	3 mEq/L
$MgSO_4$	1 mmol/L

Rate: 1000 mL/hr

Baxter Prisma Pre-Pump Pre-Dilution Set

Q_R

Q_D

PF iCa^{2+} (0.25-0.5 mmol/L)

V

Baxter Prismaflex with M60 AN69 Filter

V

Patient

iCa^{2+} 1.1-1.3 mmol/L

Q_B

100-150 mL/min

(actual $Q_B = Q_{B,\ machine} - Q_R$)

Ca^{2+} Gluconate

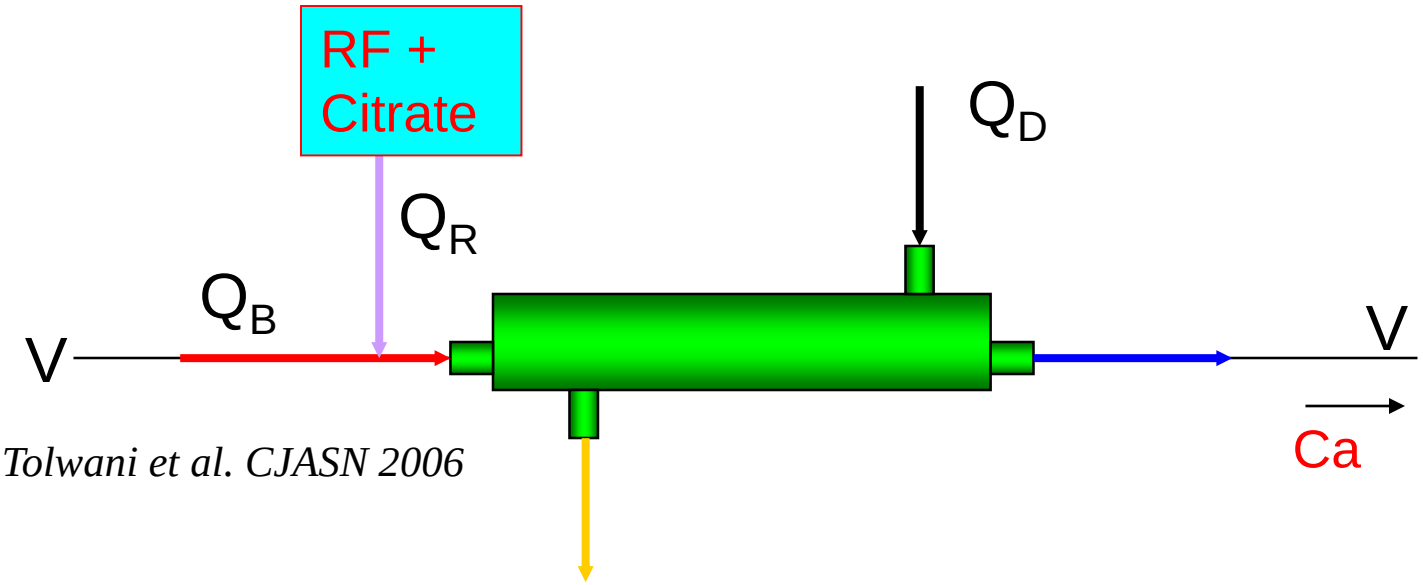
93 mEq/L (20 g/L) in D5W or H_2O

Rate: 60 mL/hr

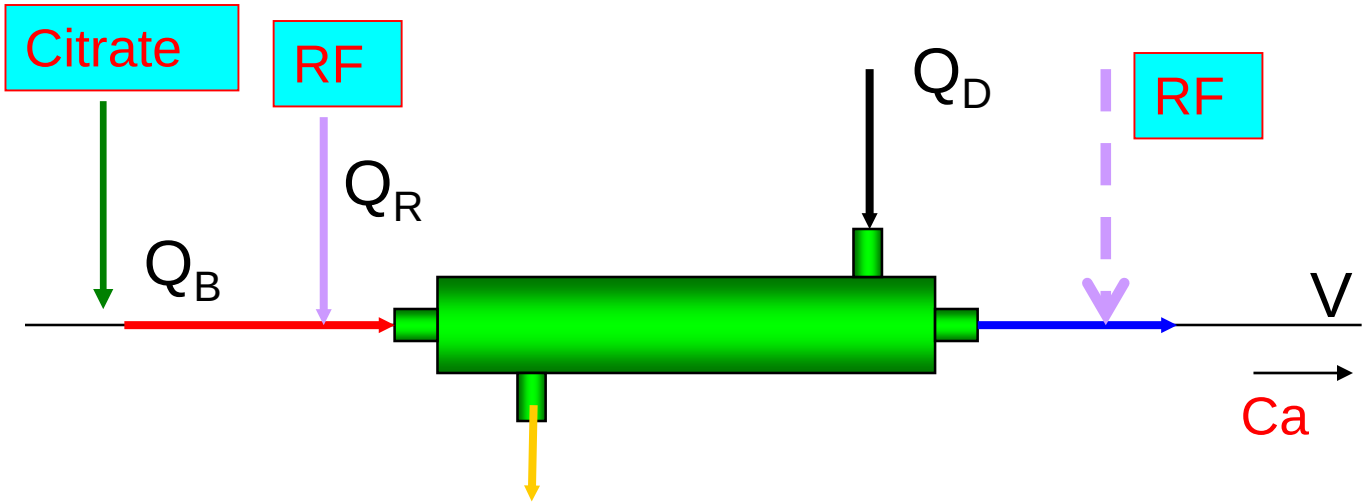
$$Q_E = Q_R + Q_{FR} + Q_D$$

Tolwani AJ et al, KI, 2001, 60: 370-374.

Circuit Options for CVVHDF



Tolwani et al. CJASN 2006



Mehta et al, KI, 1990 38(5): 976-981.

San Diego Protocol (CVVHDF)*

Dialysate: 4L bag

Na^+	117 mEq/L
K^+	4 mEq/L
$MgS0_4$	1 mmol/L
HCO_3^-	0-40 mEq/L
Cl^-	81-121 mEq/L
Dextrose	0.1%

Rate: 1000 mL/hr

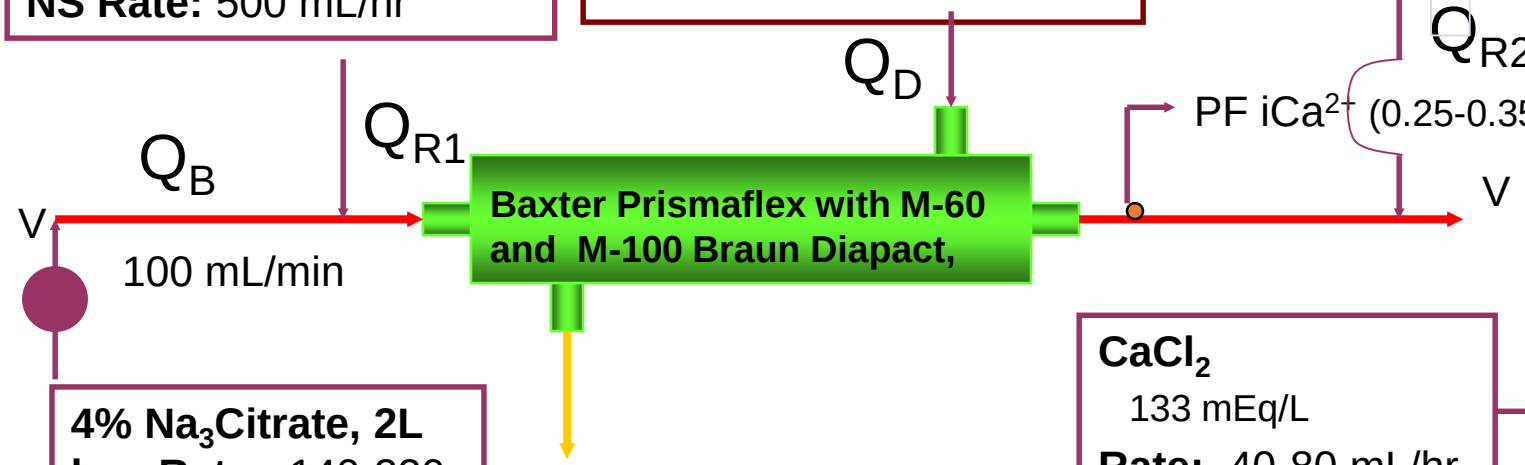
IV Replacement Fluid: 0.9% NS, 0.45% NS + 75 meq HCO3; Sterile water + 150 meq Hco3

Rate: 500-750 mL/hr

Postfilter Fluid: 0.9% NS

Rate: 200 mL/hr

Predilution Fluid: 0.9% NS Rate: 500 mL/hr



Patient

iCa^{2+} 1.12-1.32 mmol/L

$CaCl_2$

133 mEq/L

Rate: 40-80 mL/hr

4% Na_3Citrate, 2L bag Rate: 140-220 mL/hr

19-29 mmol/hr citrate

$$Q_E = Q_{R1} + Q_{FR} + Q_D$$

Av Filter life > 72 hrs

Customized solutions

Mehta et al, KI, 1990 38(5): 976-981.

San Diego Protocol (CVVHDF)**

Dialysate: 5L bag

B25GK4/2.5: 5 L bag

Na^+	140 mmol/L
Cl^-	120.5 mmol/L
HCO_3	22 mmol/L / lactate 3 mmol/L
K^+	4.0 mmol/L
Mg	0.75 mmol/L
Gluc	110 mg/dL
Ca	**2.5 Meq/L**

Rate: 1000 mL/hr

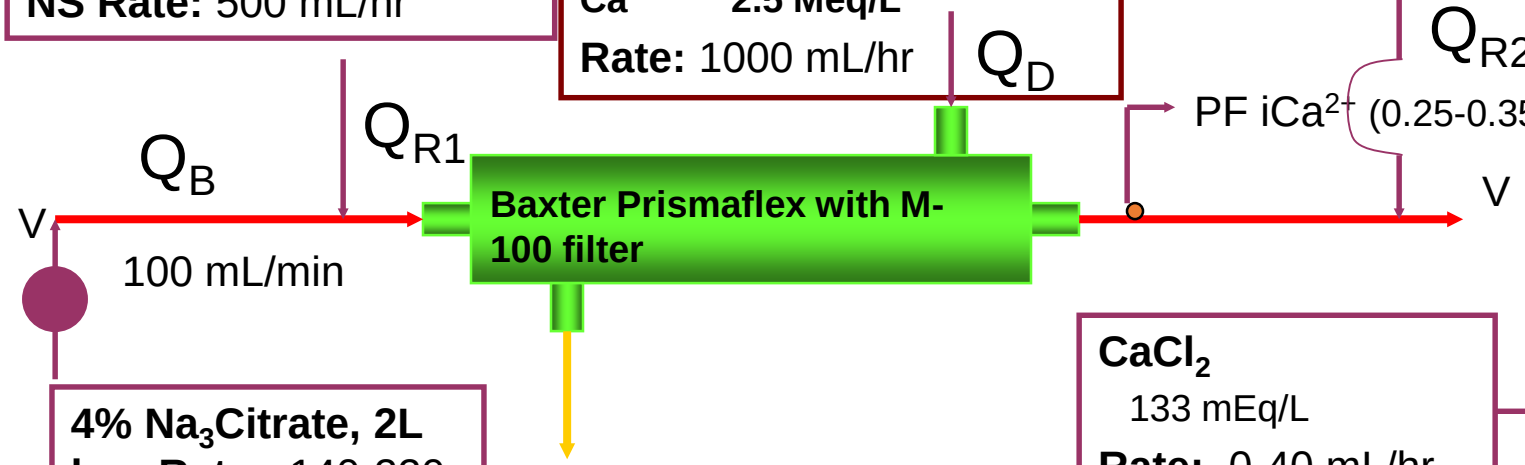
IV Replacement Fluid: Prismasol with calcium BGK4/2.5/ or BGK 0/2.5

Rate: 500-750 mL/hr

Postfilter Fluid: 0.9% NS

Rate: 200 mL/hr

Predilution Fluid: 0.9% NS Rate: 500 mL/hr



Patient

iCa^{2+} 1.12-1.32 mmol/L

$CaCl_2$

133 mEq/L

Rate: 0-40 mL/hr

4% Na_3Citrate, 2L bag Rate: 140-220 mL/hr

19-29 mmol/hr citrate

$$Q_E = Q_{R1} + Q_{FR} + Q_D$$

Av Filter life > 72 hrs

Commercial solutions

Mehta et al, KI, 1990 38(5): 976-981.

UAB Protocol (CVVHDF)

Prefilter Fluid: 4 L bag

0.5% Trisodium Citrate

Citrate^{3-} 18 mmol/L

Na^+ 140 mmol/L

Rate: 1000-2000 mL/hr

Gambro Prisma Pre-Pump Pre-Dilution Set

Dialysate PrismaSate

B25GK4/0: 5 L bag

Na^+ 140 mmol/L

Cl^- 120.5 mmol/L

HCO_3 22 mmol/L / lactate 3 mmol/L

K^+ 4.0 mmol/L

Mg 0.75 mmol/L

Gluc 110 mg/dL

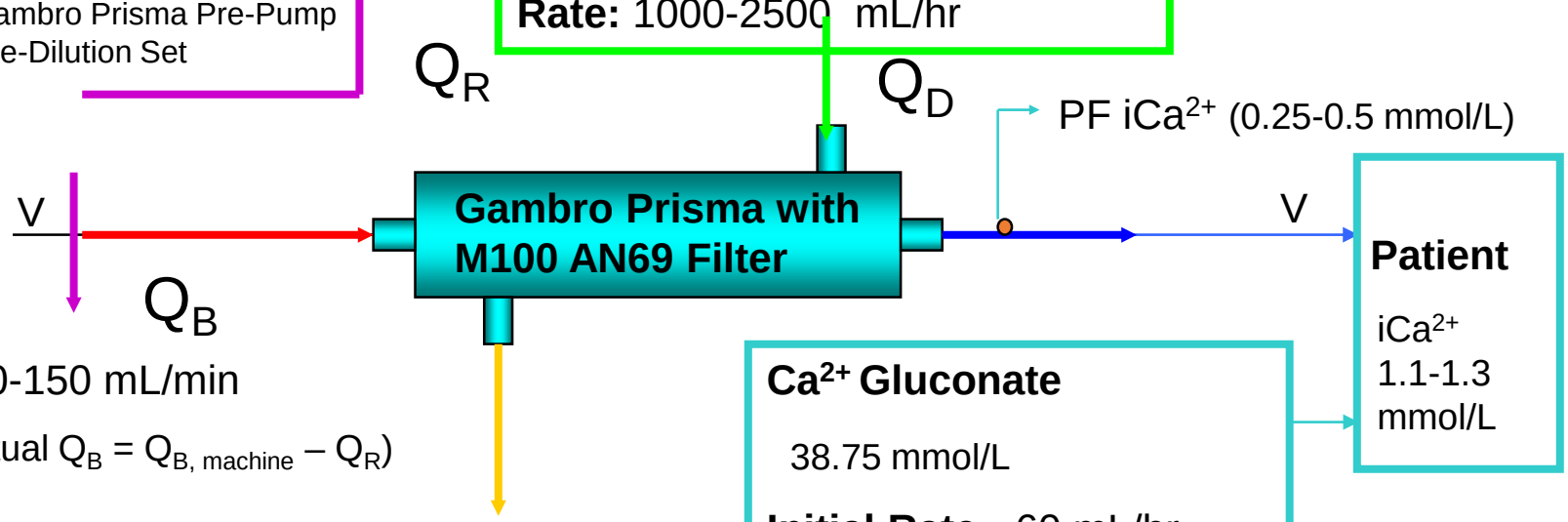
Rate: 1000-2500 mL/hr

Filter patency:

24 hrs-89%

48 hrs-82%

72 hrs-80%



100-150 mL/min

(actual $Q_B = Q_{B,\ machine} - Q_R$)

$$Q_E = Q_R + Q_{FR} + Q_D$$

Tolwani et al. CJASN 2006

Citrate dose for fixed BFR to Citrate

- Amount of citrate required to anticoagulate one liter of blood.
- Citrate dose is determined by:
  - → Blood flow rate (in mL/min)
  - → Citrate solution flow rate (in mL/h)
  - → Concentration of citrate in the solution (in mmol/L)

$$\text{Citrate Dose} = \frac{Q_{citrate} \times C_{citrate}}{BFR \times 60}$$

$$3 \text{ mmol/L} = \frac{2250 \times 12}{150 \times 60}$$

$Q_{citrate}$ in mL/h 2250 mL/h

$C_{citrate}$ in mmol/L 12 mmol/L

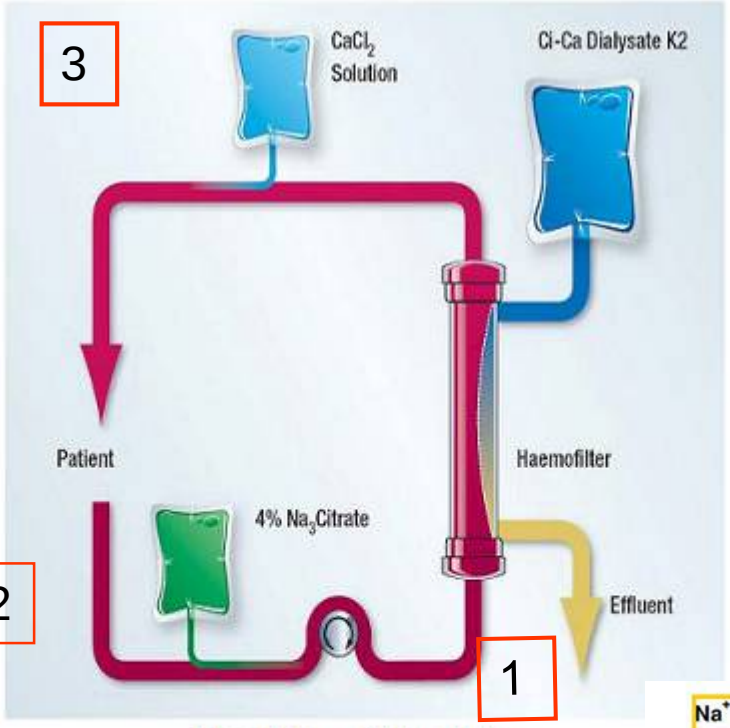
BFR in mL/min (150 ml/min)

Citrate Dose in mmol/L of blood

Fresenius Ci-Ca system

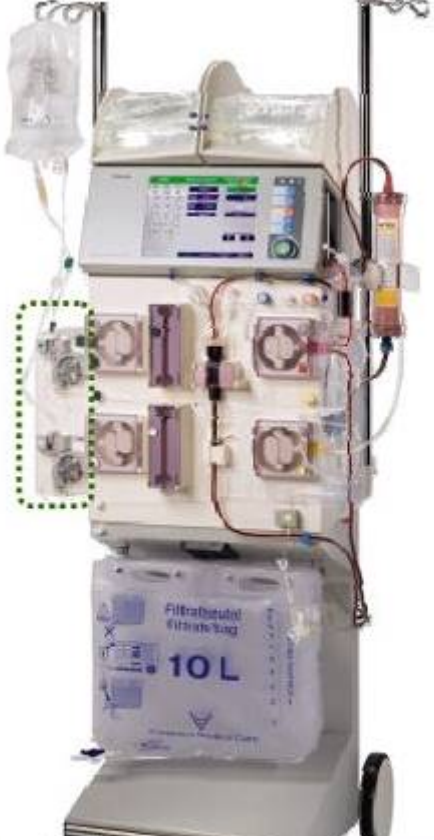
Calcium flow:
35 ml/h
(91 mmol/l Ca)

3



4

Dialysate flow:
2000 ml/h



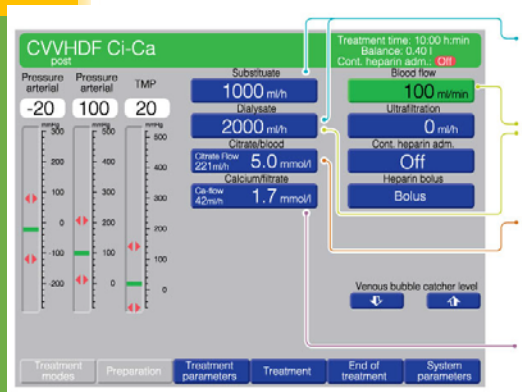
5

Effluent flow:
ca. 2300 ml/h
depending on the net-UF

2

Citrate flow:
180 ml/h

Blood flow: 100 ml/min



Display of the multiFiltrate Ci-Ca® postCVVHDF during the treatment, illustrated with the standard settings

Substituate and dialysate flow
→ adjustment of convective and diffusive CRRT efficacy

Blood and dialysate flow
→ adjustment of the acid-base status

Citrate dose
→ adjustment of the regional anticoagulation, selected as mmol citrate per litre of treated blood

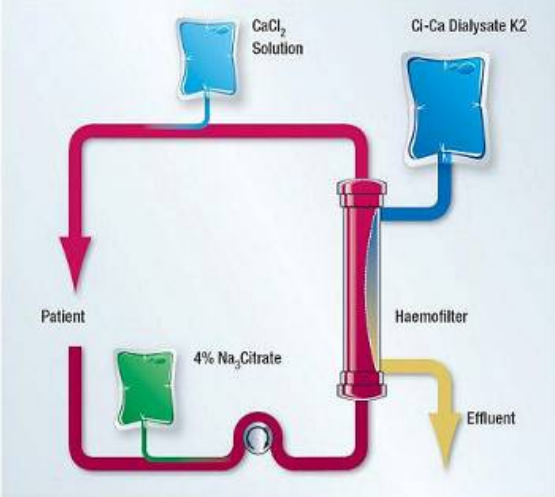
Calcium dose
→ adjustment of the calcium balance, selected in mmol calcium per litre of generated filtrate

Na^+	133	mmol/l
K^+	2	mmol/l
Mg^{++}	0.75	mmol/l
Ca^{++}	0	mmol/l
HCO_3^-	20	mmol/l
Cl^-	116.5	mmol/l
Glucose	1	g/l

- Sodium and bicarbonate reduced, in order to compensate the systemic infusion of Na_3Citrate
- Calcium-free, to avoid an unnecessary increase of the citrate requirement => Ca-substitution mandatory
- Packaging in a double-chamber bag

Morgera et al A Safe Citrate Anticoagulation Protocol *CCM 2009;37:2018-24*

	Group 1 (Below 60 kg Body Weight)	Group 2 (Between 60 and 90 kg Body Weight)	Group 3 (Above 90 kg Body Weight)
Number of patients included	19	97	45
Predefined starting values	80	100	120
Blood flow (mL/min)			
Dialysate flow (mL/hr)	1500	2000	2500
Citrate solution flow (mL/hr; 4% sodium citrate, containing 136 mmol/L citrate ions)	140	170	205
Calcium solution flow (mL/hr; 91 mmol/L calcium ions)	38	50	65



Na^+	133	mmol/l
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Ca^{++}	0	mmol/l
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Morgera et al A Safe Citrate Anticoagulation Protocol *CCM 2009;37:2018-24*

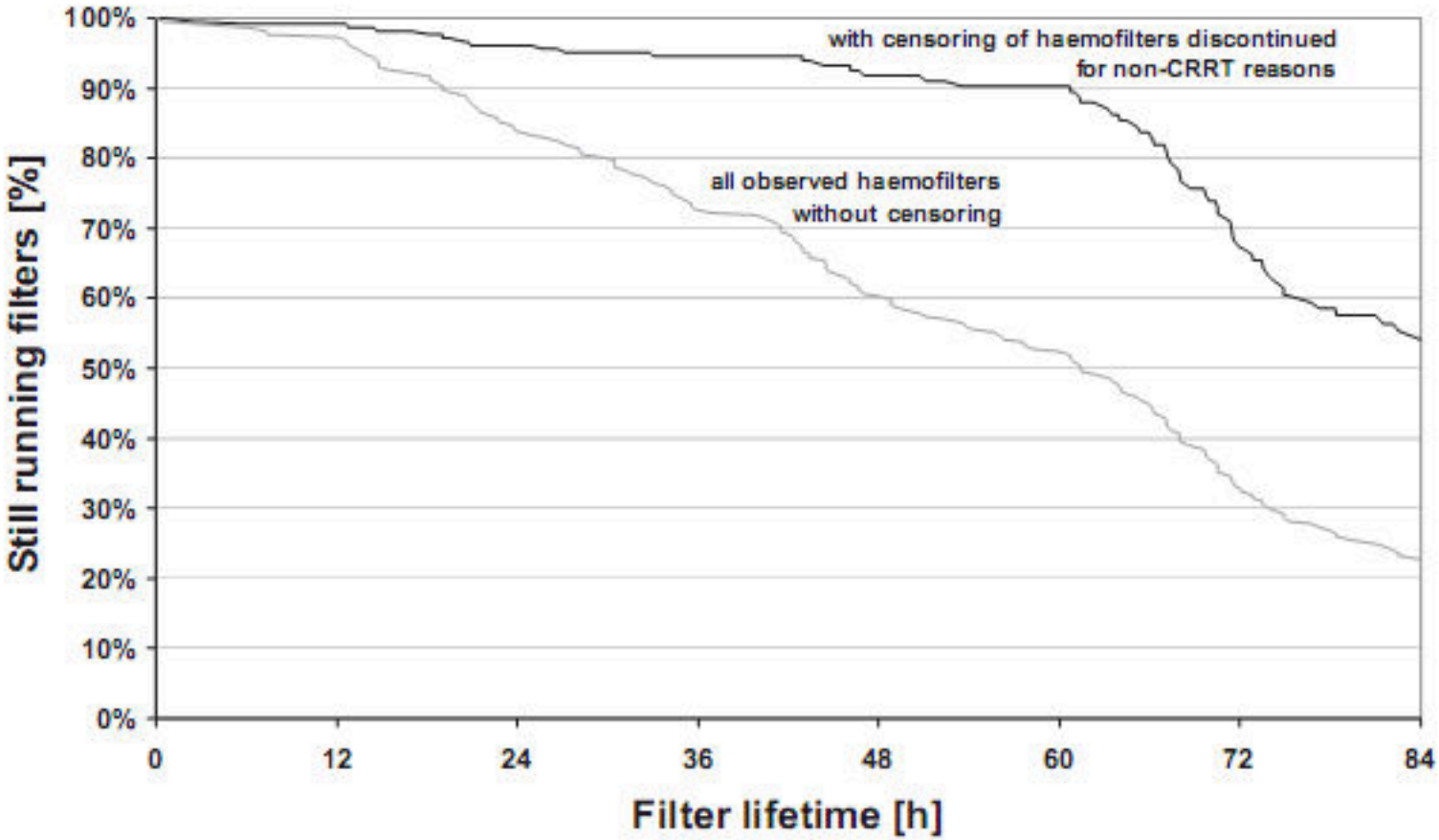


Figure 4. Filter patency during the study for all filters as observed during the study (*gray line*) and with censoring of filters discontinued for noncontinuous renal replacement therapy (*CRRT*) reasons (*black line*).

Median filter life is 61.5 hrs and 43.7 hrs in those clotted filter.
Only 5% of filters needed to be changed because of clotting

Slowinski et al. Critical Care (2015) 19:349
DOI 10.1186/s13054-015-1066-7

CRITICAL CARE

RESEARCH Open Access

Safety and efficacy of regional citrate anticoagulation in continuous venovenous hemodialysis in the presence of liver failure: the Liver Citrate Anticoagulation Threshold (L-CAT) observational study

Table 3 RCA-CVVHD flows and citrate dose at start of treatment and end of observation

	Normal liver function (bilirubin ≤2 mg/dl)		Mild liver failure (bilirubin 2–7 mg/dl)		Severe liver failure (bilirubin ≥7 mg/dl)	
	Start	End	Start	End	Start	End
Blood flow (ml/min)	109 ± 24	114 ± 25	109 ± 25	117 ± 28	110 ± 24	107 ± 20
Dialysate flow (ml/h)	2144 ± 502	2292 ± 500	2128 ± 405	2328 ± 567	2098 ± 403	2319 ± 501
Net ultrafiltration (ml/h)	77 ± 108	74 ± 114	68 ± 100	84 ± 105	84 ± 103	85 ± 102
Citrate dose (mmol/L blood)	4.0 ± 0.1	3.8 ± 0.2	4.0 ± 0.1	3.9 ± 0.3	4.0 ± 0.1	4.1 ± 0.4

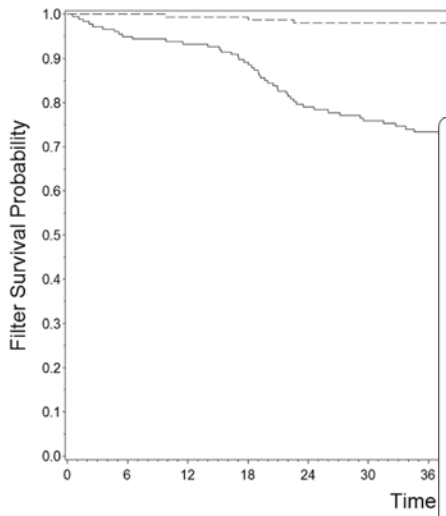


Fig. 1 Survival probability of filters of regional citrate anticoagulation and con
line: all filter discontinuations. *Dashed line*: Clotting only (i.e., censored for non-

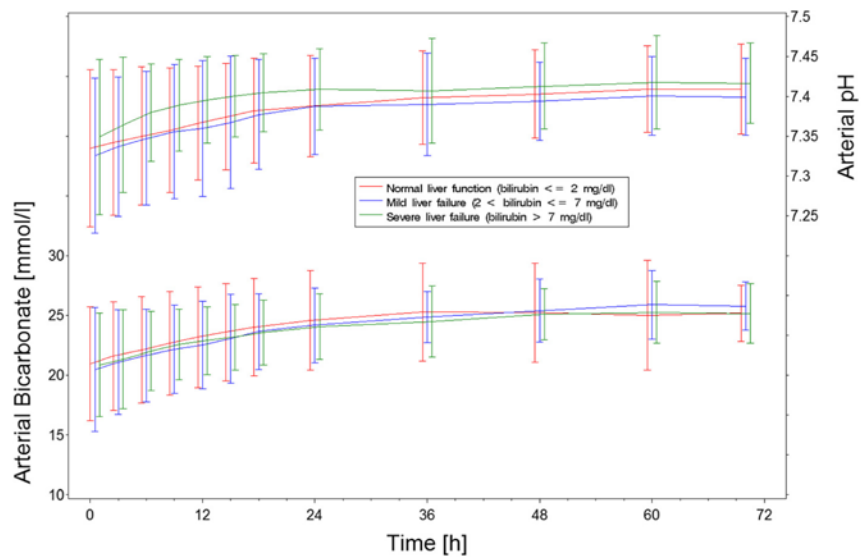
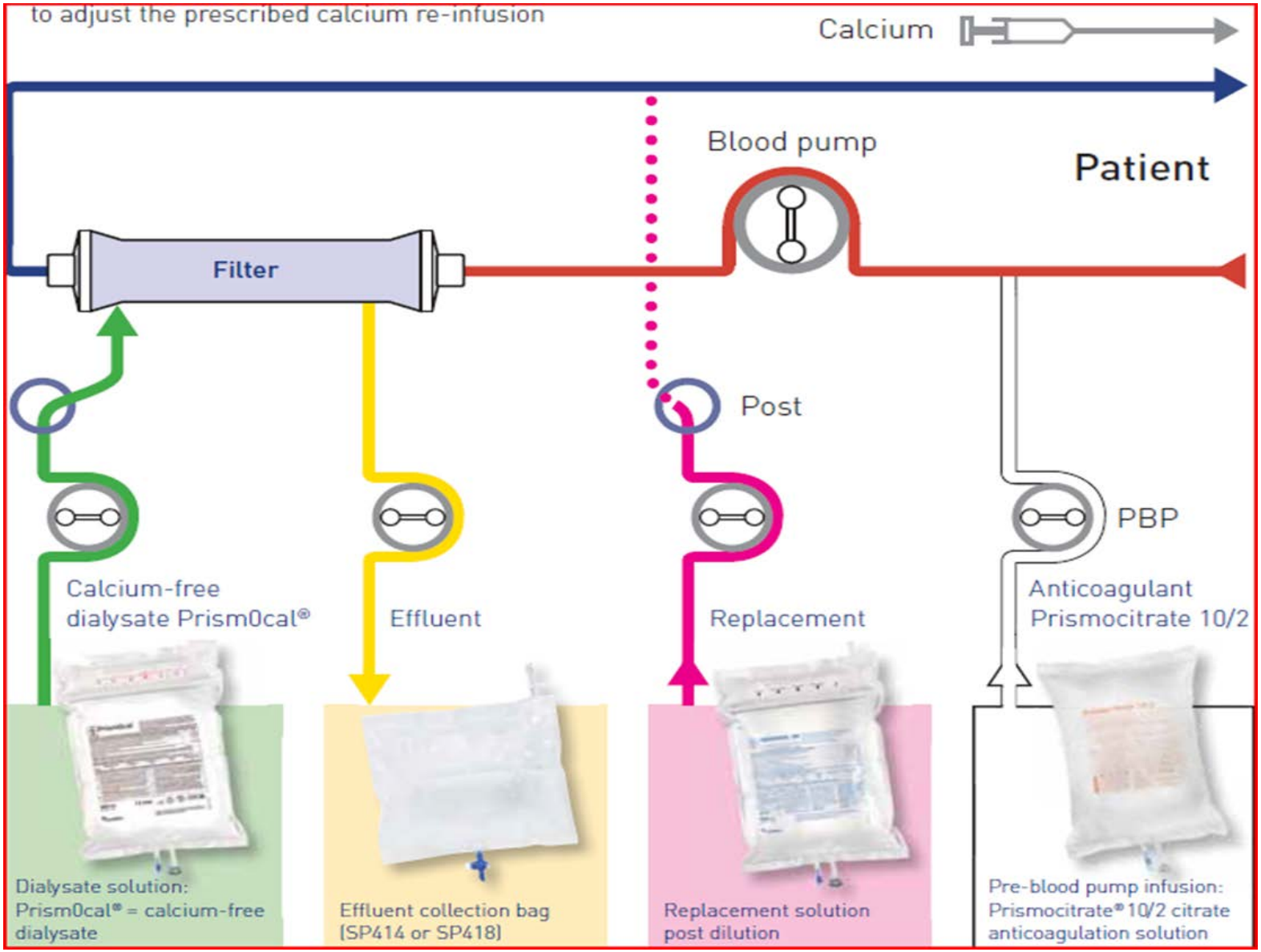


Fig. 2 Estimated mean ± standard deviation of arterial pH and serum bicarbonate concentrations during regional citrate anticoagulation and continuous venovenous hemodialysis according to liver groups

Baxter The Prismaflex eXeed™ System



Baxter The Prismaflex eXeed™ System

Therapy mode:

CVVHDF or CVVH

Prismocitrate® 10/2
Citrate anticoagulant

Composition:

Citrate 10 mmol/l
Citric acid 2 mmol/l
Sodium 136 mmol/l
Chloride 106 mmol/l

PrismOcal®
Calcium-free dialysate

Composition:

Bicarbonate 32 mmol/l
Lactate 3 mmol/l
Sodium 140 mmol/l
Magnesium 0.5 mmol/l
Chloride 106 mmol/l

Optional post-dilution replacement solution (upon physician prescription)

Calcium-free solutions are recommended. However, one may consider using a calcium-containing solution in post-dilution provided the amount of calcium delivered into the circuit does not increase the circulating ionized calcium to a greater value than the targeted post-filter ionized calcium level.

Baxter vs Fresenius

	Fresenius		Baxter	
	4% TSC	Ci-Ca Dialysate K2	Prismocitrate 10/2	Prism0Cal
Na	408	133	136	140
K	-	2	-	-
Ca	-	-	-	-
Mg	-	0.75	-	0.5
Bicarbonate	-	20	-	32
Lactate	-	-	-	3
Citrate	136	-	12	-
Chloride	-	116.5	106	106
	CE-Mark	CE-Mark	CE-Mark	CE-Mark

	Fresenius	Baxter
Citrate concentration in the citrate solution [mmol/l]	136	12
Recommended citrate dose (typical) [mmol/l]	4.0	3.5
Citrate flow / Blood flow	2.9%	29.2%

Anticoagulation in CRRT Monitoring

Anticoagulant effect	• Post filter values for ACT, PTT, ionized calcium
Filter and circuit Patency	• Visual checks • Access pressures • Filtration fraction
Filter efficacy	• FUN/BUN ratios
Complications	• Systemic anticoagulation • Metabolic problems

Anticoagulation in CRRT
Monitoring Methods

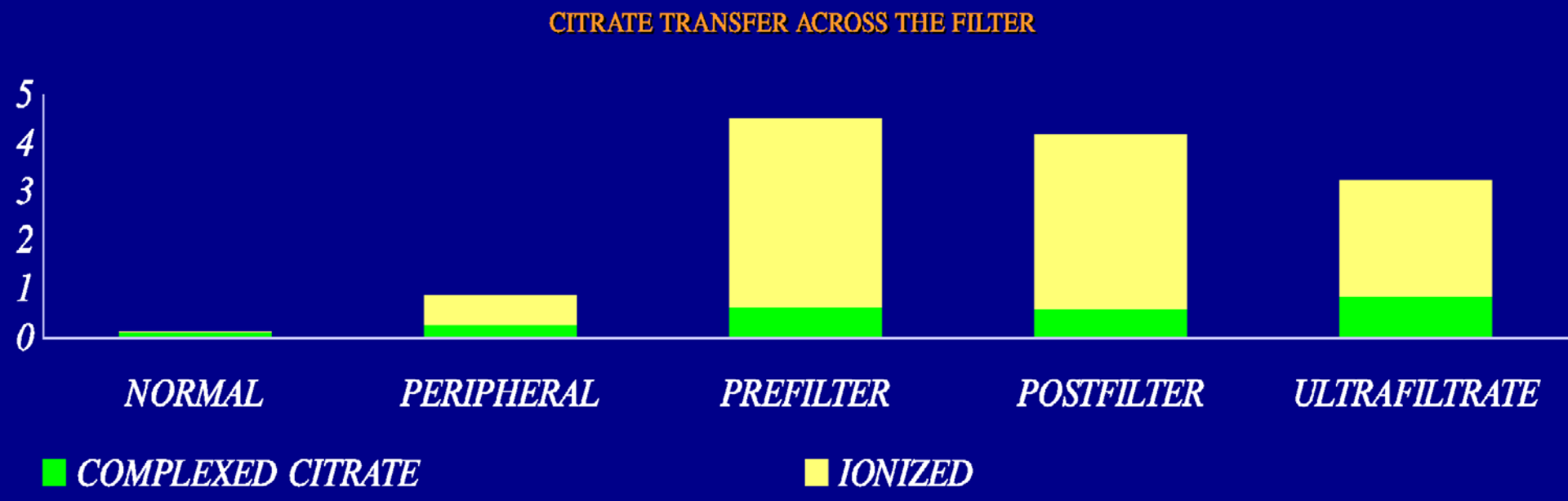
Modality	Technique
Mechanical	Visual Check; Access pressures; FUN/BUN ratios
Unfractionated Heparin (UFH)	ACT, aPTT systemic and post filter, Bleeding, HIT
LMWH	Anti-Factor Xa, ATIII, PMN Elastase
Citrate	Ionized calcium systemic and post filter
Prostacyclin	Thromboelastography
Lepuridin	aPTT, Ecarin Clotting time
Bivalirudin	aPTT
Nafomostat	6KetoPGF1 aplha

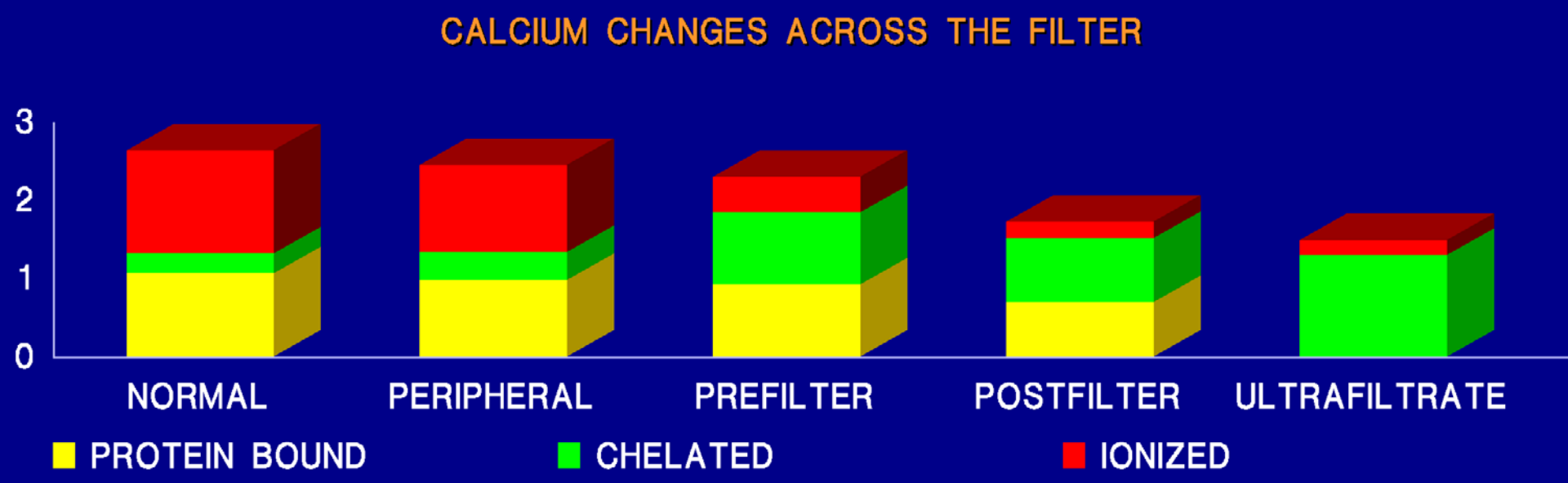
Heparin Induced Thrombocytopenia (HIT)

	Type1	Type 2
Frequency	10 to 20 percent	1 to 3 percent
Timing of onset	1 to 4 days	5 to 10 days
Nadir platelet count	100,000/μL	30,000 to 55,000/μL
Antibody mediated	No	Yes
Thromboembolic sequelae	None	30 to 80 percent
Hemorrhagic sequelae	None	Rarely
Management	Observe	Cessation of heparin, alternative anticoagulation, additional therapy

Adapted from Brieger, DB, Mak, KH, Kohke-Marchant, K, et al. J Am Coll Cardiol 1998; 31:1449.

CITRATE ANTICOAGULATED CAVHDF





UCSD protocol for RCA titration

Circuit post filter ionized calcium q 6-8^{H}

keep 0.25-0.45 mmol/l

Systemic serum ionized calcium q 6-8^{H}

keep 1.10-1.20 mmol/l

Serum Total Ca, PO_4 and Mg q 12-24^{H}

Anticoagulant:

18. Regional CITRATE anticoagulation 0.14 molar citrate to run into 3-WAY STOPCOCK at vascular access exit at ___ ___ ___ mL/hour (usually 2 to 3% of BFR; eg: 140-180 mL/hr for a BFR = 100 mL/min) to maintain POST-FILTER IONIZED CALCIUM at 0.25-0.3 mmol/L.
    NOTE: Start at lower rate (120 - 140 mL/hr) for patients with hepatic failure.
19. Check POST-FILTER IONIZED CALCIUM at initiation of CRRT and every 4 hours x 24 hours, then every 8 hours x 24 hours, then every 12 hours. Adjust CITRATE flow rate according to sliding scale below. If changes made to citrate drip, recheck postfilter ionized calcium in 2 hours, then every 4 hours for 24 hours if stable.

Citrate Replacement Sliding Scale

Postfilter Ionized Ca	Citrate Flow Rate
<0.25	Decrease by 10 mL/hour (call Renal MD)
0.25 - 0.3	NO CHANGE
0.31 - 0.4	increase by 5 mL/hour
0.41 - 0.45	increase by 10 mL/hour
>0.45	increase by 15 mL/hour (call Renal MD)

Do not decrease citrate rate below ❒ 120 mL/hour ❒ Other _____
Do not increase citrate rate above ❒ 200 mL/hour ❒ Other _____

20. Calcium chloride solution: 8 g $CaCl_2$ in 1000 mL 0.9% sodium chloride (1080 mL total). To run into CENTRAL LINE at ❒ 40 mL/hour ❒ Other _____ to maintain PERIPHERAL IONIZED CALCIUM 1.12-1.2 mmol/L.
21. Check PERIPHERAL IONIZED CALCIUM at initiation of CRRT and every 4 hours x 24 hours, then every 8 hours x 24 hours, then every 12 hours. Adjust calcium chloride according to sliding scale below. If changes made to calcium chloride drip, recheck peripheral ionized calcium in 2 hours, then every 4 hours for 24 hours if stable.

Calcium Chloride Sliding Scale

Peripheral Ionized Ca	Calcium Chloride
0.85 - 0.94	increase by 10 mL/hour + 2 g Ca gluconate (call Renal MD)
0.95 - 1.04	increase by 5 mL/hour + 1 g Ca gluconate
1.05 - 1.09	increase by 5 mL/hour
1.10 - 1.2	NO CHANGE
1.21 - 1.3	decrease by 5 mL/hour
1.31 - 1.45	decrease by 10 mL/hour
>1.45	decrease by 15 mL/hour (call Renal MD)

Do not decrease calcium chloride rate below ❒ 30 mL/hour ❒ Other _____ mL/hour.
Do not increase calcium chloride rate above ❒ 80 mL/hour ❒ Other _____ mL/hour.

Citrate Metabolic Consequences

Metabolic alkalosis

- Citrate overdose/toxicity

Metabolic acidosis

- Citrate toxicity in setting of severe liver disease or hypoperfusion

Hypernatremia

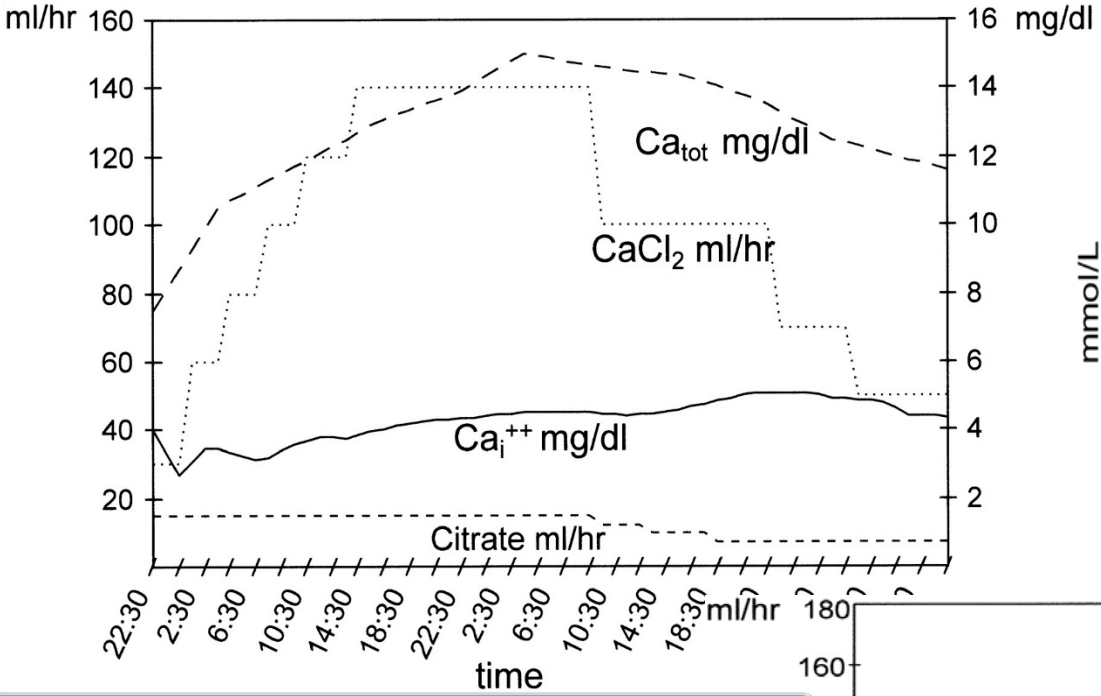
- Hyperosmolar citrate solutions

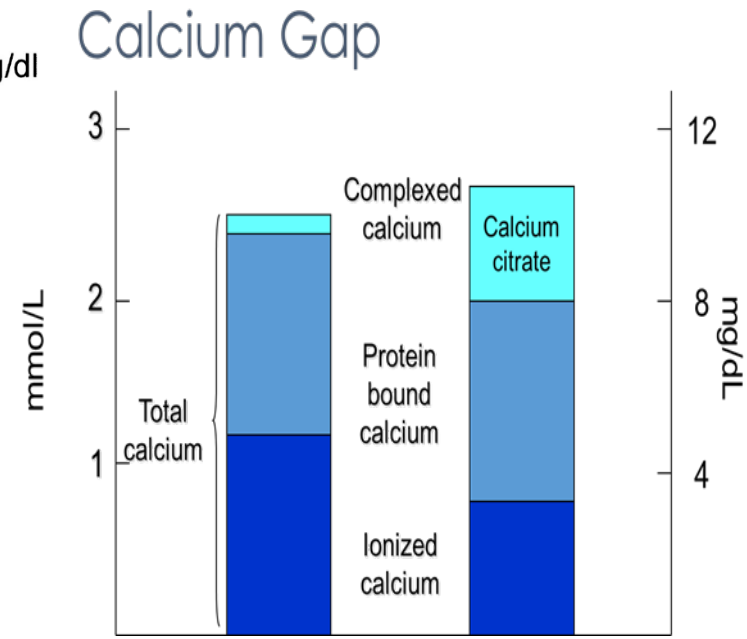
Hypocalcemia and hypercalcemia

- Inappropriate calcium supplementation

Hypomagnesemia

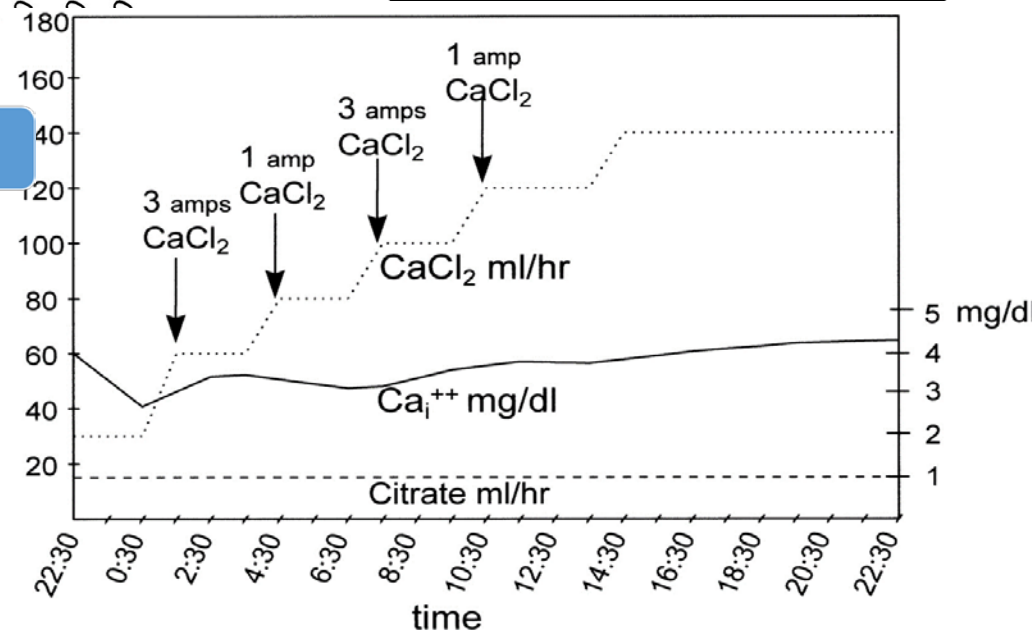
Citrate Gap





Features

- Increased total calcium
- Decreased ionized calcium
- Increased total to ionized calcium ratio
- Increased anion gap
- Alkalemia may occur
- Citrate levels are high
- Bicarbonate levels increase as anion gap resolves



Meier-Kriescheet al American Journal of Kidney Diseases, 1999 Apr, 33(4):e8.

Citrate Toxicity

Risk Factors

- Shock liver; severe hypoperfusion states
- Impaired hepatic function
- H
- L
- L
- P
- N

Cit

- R
  a
- F
- E
- T
  C

Management

- Reduce citrate delivery
  - Blood products
  - Citrate flow rate
- Change thresholds for citrate and calcium replacement
- Stop citrate anticoagulation

Anticoagulation for CRRT

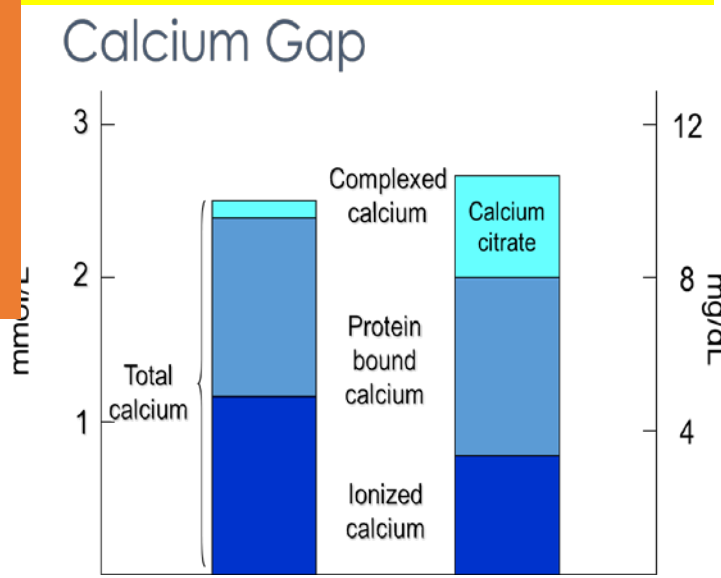
Citrate Content of Blood Products

Product	Standard Volume (ml)	Citrate content (meq/bag)
FFP	200	14
PRBC	250	0
Platelets	40-60	3
Cryoprecipitate	10	1
Whole Blood	250	17
4% trisodium citrate	1000	10.2

$$um\ Ratio = \frac{Total\ Ca^{2+}(mg/dL)\cdot 0.25}{Systemic\ ion\ Ca^{2+}(mmol/L)}$$

Table

	Citrate *v* Total Calcium-Ionized Calcium Ratio		Citrate *v* Total Calcium		Citrate *v* Anion Gap		Citrate *v* pH	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*
Day 3 samples	0.85	<0.001	0.48	0.06	0.36	0.17	−0.15	0.58
All samples	0.79	<0.001	0.58	<0.001	0.41	<0.01	−0.31	<0.01



Citrate Anticoagulation for CRRT Specific Situations

Patients with Hepatic Failure

- Often candidates who benefit most
- Requires lower starting flow rates of citrate
- Major load of citrate is from blood products
- Citrate gap may occur
- Citrate can be used safely and minimizes risk for bleeding
- At UCSD citrate anticoagulation has been used to manage over 500 patients with hepatic failure and has been used for > 50 patients intraoperatively.

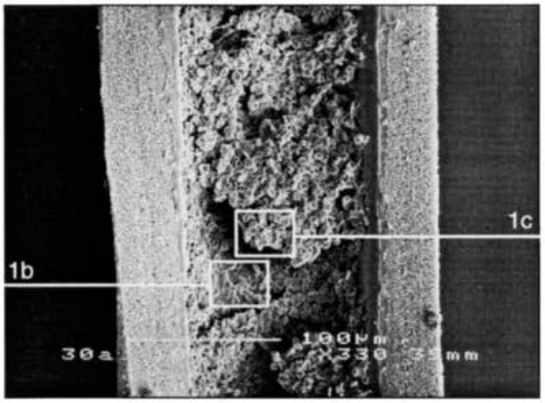
Patients with ARDS and Permissive Hypercapnia

- Citrate anticoagulation combined with addition of bicarbonate to dialysate allows compensation for respiratory acidosis
- Bicarbonate concentrations require adjustment depending on acid-base parameters.

Pediatric Patients

- Successfully used by Pediatric Nephrology in over 100 patients including neonates
- Is the standard mode of anticoagulation for pediatric patients at UCSD

Anticoagulation for Extracorporeal Therapies



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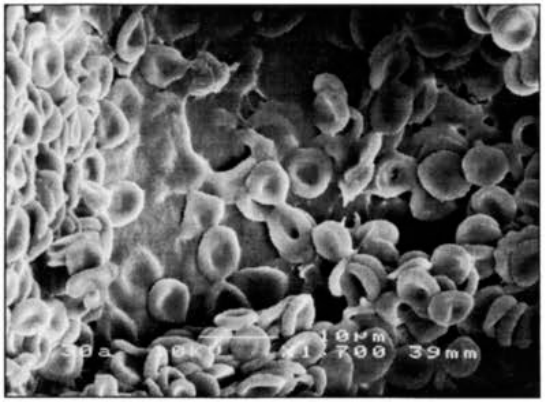
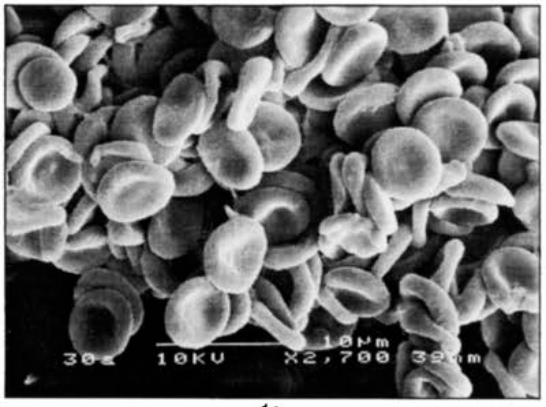


1b



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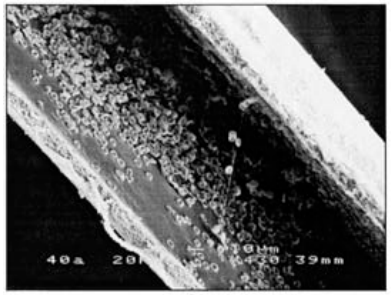
Heparin



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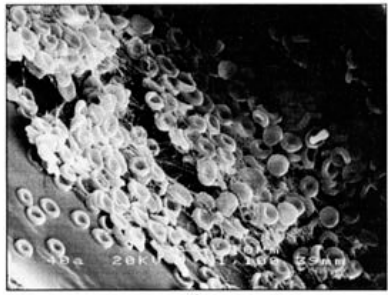

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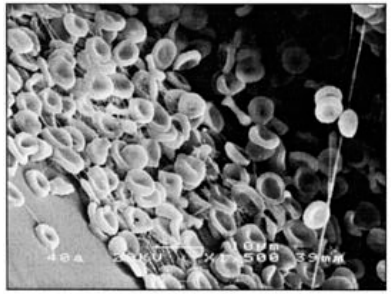

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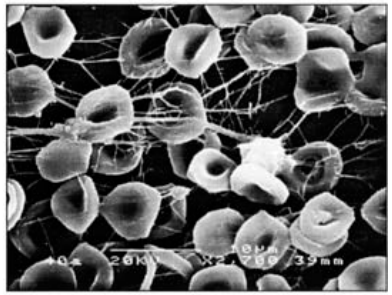
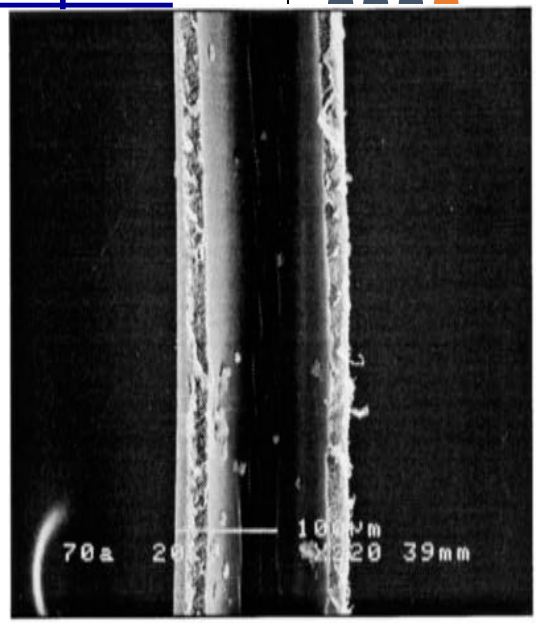


2d

LMW Heparin

Scanning electron micrographs of the inner surface of a polysulfone hollow fiber dialyzer membrane during hemodialysis therapy.



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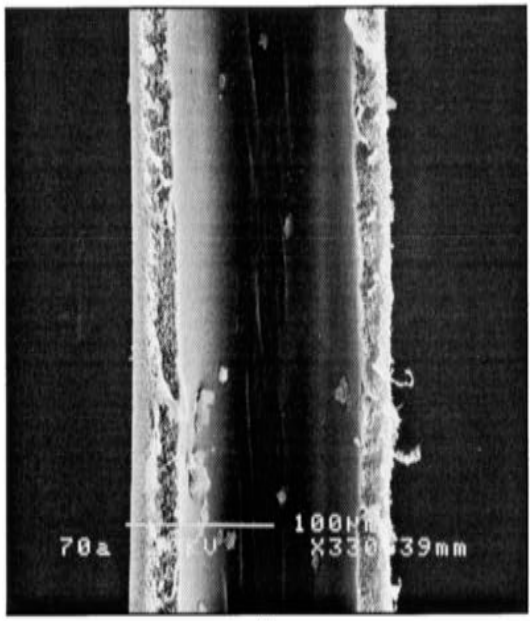

3b

Citrate

Anticoagulation Considerations
KDIGO AKI Guidelines 2012

5.3.2: For patients without an increased bleeding risk or impaired coagulation and not already receiving effective systemic anticoagulation, we suggest the following:

- 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)

5.3.3: For patients with increased bleeding risk who are not receiving anticoagulation, we suggest the following for anticoagulation during RRT:

- 5.3.3.1: We suggest using regional citrate anticoagulation, rather than no anticoagulation, during CRRT in a patient without contraindications for citrate. (2C)

Brain et al. BMC Nephrology (2017) 18:69
DOI 10.1186/s12882-017-0445-5

BMC Nephrology

RESEARCH ARTICLE Open Access

Non anti-coagulant factors associated with filter life in continuous renal replacement therapy (CRRT): a systematic review and meta-analysis

Matthew Brain[1,2,3*], Elizabeth Winson[3], Owen Roodenburg[1,2] and John McNeil[1]

Vascular Access interventions to prolong filter life in CRRT

Temporary Vascular Access Site	Optimal vascular access site ranked by association with longer filter life is: tunneled semi-permanent, femoral or internal jugular, subclavian site.[a]	(9 observational studies)	VERY LOW [a,b,c]
Tunneled Semi-permanent Catheters vs Temporary Catheters	Tunneled semi-permanent vascular access devices were consistently associated with longer filter life. A significant confounder is that these devices were often larger internal diameter than temporary devices however on the basis of current literature they should be considered in any cases expected to have prolonged CRRT requirement	(4 observational studies)	LOW [b,c]
Side of Vascular Access Catheter	Overall there is insufficient data and possibility of significant confounding by order of catheter choice such that optimal side of vascular access cannot be determined	(3 observational studies)	LOW [a]
Catheter length at thoracic vein sites	Favours longer catheter length with atrial placement when thoracic veins utilised. Single study only however unlike most filter life studies this was randomized. No increased in arrhythmias with longer catheter length however underpowered to detect complications.	(1 RCT)	MODERATE [d]
Catheter lumen size	Only one small study directly measured filter life with catheter size however indirect measures (increased renal dose) in RENAL study supports catheter size as important. Possible benefit from tunneled access may be due to catheter size	(3 observational studies)	VERY LOW [a,c,e]
Number of vascular access related alarms	Number of vascular access alarms is likely a significant contributor to poor filter life however data is limited	(1 observational study)	VERY LOW [g]
Access Catheter Type	No significant difference between brands of catheters though trend existed. Tunneled catheters were superior to temporary catheters	(4 observational studies)	LOW [b,e,g]

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Circuit Management Interventions to Prolong Filter Life in CRRT

Haemofilter Membrane Characteristics	Hollow fibre membranes appear superior to flat plate membranes. It is unclear if an advantage exists for polyacrylonitrile membranes compared to polysulfone or cellulose membranes in regards to filter life. Membrane area was not associated with increased filter life in a single study.	(8 observational studies)	VERY LOW [h]
CRRT Modality	CVVH is associated with worse filter life in published studies	(7 observational studies)	LOW [i]
Pre vs Post Dilution in CVVH	One small RCT favoured pre-dilution. Overall affect from all studies trended toward pre-dilution but did not reach significance.	(4 observational studies)	VERY LOW [i]
Blood Flow Rate	Majority of trials suggest a higher blood flow rate increases filter life however it is unclear over what range this applies. Studies directly comparing low and high blood flow are required.	(9 observational studies)	VERY LOW [i]
Saline Flushes to Blood Path	There is no evidence to support intermittent saline flushing of the circuit to prolong filter life	(4 observational studies)	VERY LOW [i]
Education and Alarm Management	Limited evidence suggests focused training to recognise and respond to filter warnings prolongs filter life	(4 observational studies)	VERY LOW [i]

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Non anti-coagulant factors associated with filter life in continuous renal replacement

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Patient Factors associated with prolong filter life in CRRT

Factors with a positive association with filter life	Increasing age (NS), Presence of vaso-active drugs (NS) [f], lower pH (sig), Higher APTT (sig), Higher ATIII level (NS), Correction of ATIII deficiency (sig), Mobilization (sig) [f], Number of position changes (sig) [f]	VERY LOW [b,j,c]
Factors with a negative association with filter life	Being male (NS), Mechanical Ventilation (sig) [f], Increased temperature (NS) [f], Liver failure with bilirubin > 3 mg/dL (NS) [f], Presence of Sepsis (NS) [f], Higher SOFA score (sig) [f], Higher LOD score (sig) [f], Unit increase in ionized calcium (sig), Higher platelet count (sig), RBC transfusion (sig) [f], Platelet transfusion (NS) [f], FFP transfusion (NS) [f], PF4 antibodies [f], Elevated fibrinogen (sig) [f], Prothrombin fragment (F1 + 2) elevation [f]	VERY LOW [b,j,c]

Anticoagulation for CRRT Summary

- Anticoagulation continues to be Achille's heel for CRRT
- Several methods are available and can be individualized for each patient
- Anticoagulation is an important factor affecting dialysis dose delivered
- Continued monitoring is essential
- Further research is required to develop protocols for optimal use of anticoagulants