Fixed Flow Ratio (FFR) Post-Dilution CVVHDF-RCA Prescribing Optimized for Simplicity and Safety

Balazs I. Szamosfalvi and Lenar T. Yessayan

Department of Internal Medicine, University of Michigan

Purpose

RCA is preferred for CRRT anticoagulation, but its use remains limited due to complex adjustments with most protocols, the requirement for (compounded) dilute citrate solutions and the unpredictable complication of severe systemic citrate accumulation with ionized hypocalcemia in many patients with liver disease and/or shock. To address this:

1. We introduce the paradigm of Fixed Flow Ratio (FFR)-CRRT-RCA prescribing that is ultimately simple and can be used by non-expert providers without contraindications.
2. We adapt FFR-CRRT-RCA to use with ACDA citrate and CRRT fluids that are (or could be) commercially available with an easily compounded Ca-infusion.
3. We show optimized FFRs that limit systemic citrate ≤2.5 mM regardless of metabolism and guarantee circuit ionized Ca ≤0.3 mM with targeted systemic Na 140, HCO3 22-25.

Methods

Single-Pool, Fixed Volume Solute Kinetic Equation

$$C_{(t)} = C_F + (C_{(0)} - C_F) \times e^{-\left[(D_f + K_b) \times \frac{t}{V}\right]} + \frac{G}{D_f + K_b} \times \left(1 - e^{-\left[(D_f + K_b) \times \frac{t}{V}\right]}\right)$$

$$C_{(steady\ state)} = C_F + \frac{G}{D_f + K_b} \boxed{\leq C_F + \frac{G}{D_f}}$$

Figure 1: Targeting optimal systemic steady state solute levels with FFR-CRRT-RCA based on kinetic analysis of solute fluxes, by controlling the 3 parameters in the red rectangle: C_F= CRRT fluid solute concentration (mM), **G**= Solute generation non-isomolar to CRRT fluid (mmol/h) and D_f= Filter solute dialysance (L/h). $C_{(t)}$= Plasma solute concentration at time = t (mmol/L; $C_{(0)}$ at CRRT start), K_b= Body solute clearance (L/h); t= time from CRRT start (h), V= Solute volume of distribution (L).

Nipro Elisio-H Filter	Blood Flow QB ml/min	ACDA Flow ml/hour	Dialysate Flow QD mL/hour	Post-Dilution Flow QRF mL/hour	$CaCl_2$ Flow mL/hour	Filter Surface m^2	Effluent Flow ml/hour
Fixed Ratio (R)	1	R_{ACDA}: 3	R_{dia}: 30	R_{rep}: 10	R_{Ca}: 1	R_{FS}: ≥1/50	≈45
Example Rx	60	180	1800	600	60	≥1.2	2700

Table 1: The recommended Fixed Flow Ratios (R) for FFR-CVVHD(F)-RCA. If the systemic Hb ≥11 g/dL then QRF is set to 0 and the QD is increased proportionally to keep QD+QRF unchanged (CVVHD). The above R values and filter type and minimum filter surface ensure single pass citrate removal (E_{cit}) in the 75-95% range. The initial Ca-rate can be adjusted if Hb<7/>11 g/dL OR albumin<1.5/>3.5 g/dL using a precalculated factor (0.7-1.3) provided in a table based on Hct and systemic albumin. The Ca-infusion rate is adjusted ±10-20% of the current Ca-infusion rate based on systemic iCa measurements obtained every 6 hours.

Solute		ACDA Citrate 113 mM	CRRT Fluids (2) 0/4K+25Bic	CRRT Fluids (2) 0/4K+45Bic	81.6 mM $CaCl_2$ in D5/0.9%
Calcium	mM		0 mM	0 mM	81.6 mM
Magnesium	mM		1 mM	1 mM	0 mM
Chloride	mM		115.5 or 119.5 mM	95.5 or 99.5 mM	299 mM
Glucose	mM	124 mM	0 mM	0 mM	244 mM
Sodium	mM	225 mM	140 mM	140 mM	135.5 mM
Citric Acid	mM	38 mM			
$Citrate^{3-}$	mM	75 mM			
Potassium	mM		0 or 4 mM	0 or 4 mM	
Bicarbonate	mM		25 mM	45 mM	
Phosphate	mM		1.1 mM	1.1 mM	

Table 2: Composition of the commercially available ACDA citrate infusion (citrate level C_{ACDA} = 0.113 mmol/ml) and of 4 types of CRRT fluids optimized for FFR-CRRT-RCA. The Ca-infusion is compounded from 120 ml of 10% $CaCl_2$ and 880 ml of D50.9% saline.

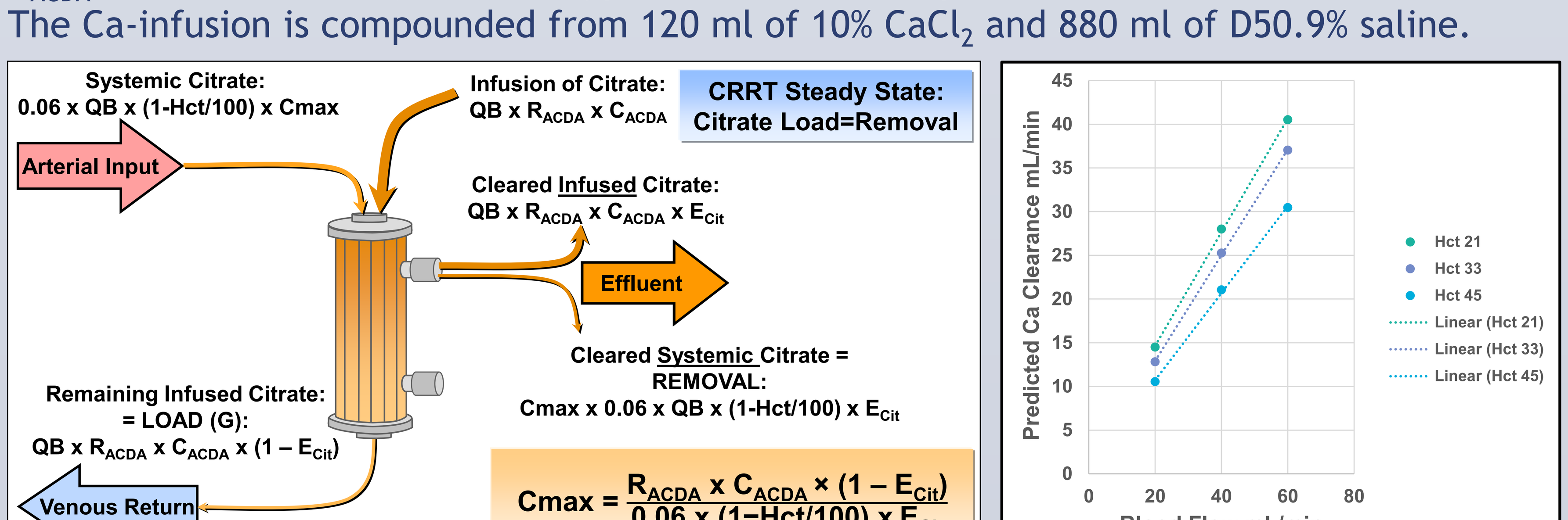

Figure 2 Left panel: FFR-CRRT-RCA limits the maximum systemic citrate level, **Cmax ≤ 2.5 mM** with absent metabolism by ensuring that D_f = Filter citrate clearance is a linear function of QB like QP (circuit plasma flow) and D_f/QP = E_{Cit} is always ≥0.75.
Right panel: predicted linear relationship of Ca- (≈ citrate) clearance with QB during FFR-CVVHDF-RCA using a clearance simulation program (Walther; KI (2006) 69;1056-1063)

Results

Fixed Flow Ratio (FFR)-CVVHDF-RCA *Ex Vivo* Validation

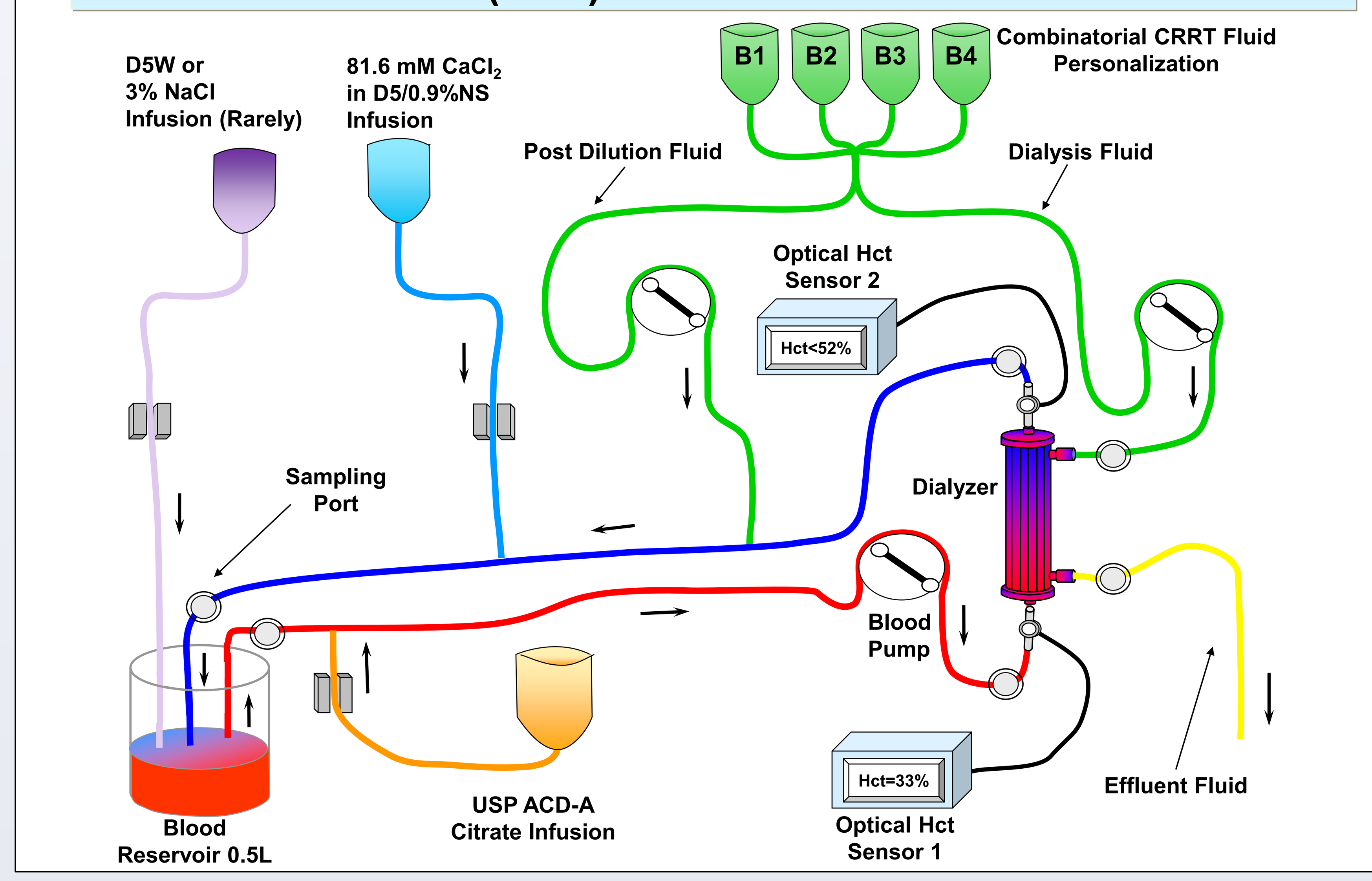

Figure 3: Since FFR-CRRT-RCA does not require any citrate metabolism to approximate physiologic target systemic solute levels, it can be tested in *ex vivo* CRRT simulations.

Reservoir Solute Steady State Level	Exp 1-12 Mean ± SD	Exp 13-18 Mean ± SD
Na^+ (mEq/L)	**138.2 ± 0.8**	**139.8 ± 0.8**
HCO_3^- (mEq/L)	**26.0 ± 0.9**	**20.3 ± 2.3**
K^+ (mEq/L)	3.5 ± 0.2	3.6 ± 0.1
Total Mg (mg/dL)	2.1 ± 0.0	2.3 ± 0.1
Phosphate (mg/dL)	5.0 ± 1.4	4.0 ± 0.1
Total Ca mg/dL	**8.7 ± 0.4**	**11.7 ± 0.2**
Glucose (mg/dL) CRRT Glu-	101.2 ± 6.5	134.0 ± 6.1
Glucose (mg/dL) CRRT Glu+	134.2 ± 13.1	141.3 ± 14.7
$Citrate^{3-}$ (mM)	**1.4 ± 0.5**	**2.0 ± 0.3**
Systemic iCa^{2+} (mM)	**1.2 ± 0.1**	**1.4 ± 0.1**
Circuit iCa^{2+} (mM)	All < 0.3	All < 0.3
Albumin (g/dL)	**1.6 ± 0.3**	**3.9 ± 0.1**

Table 3: Systemic (S) solute levels vs CRRT fluid (F) levels: K(S) ≈ K(F), HCO3(S) ≈ HCO3(F)-10, Na(S) ≈ Na(F), Phos(S) ≈ Phos(F)

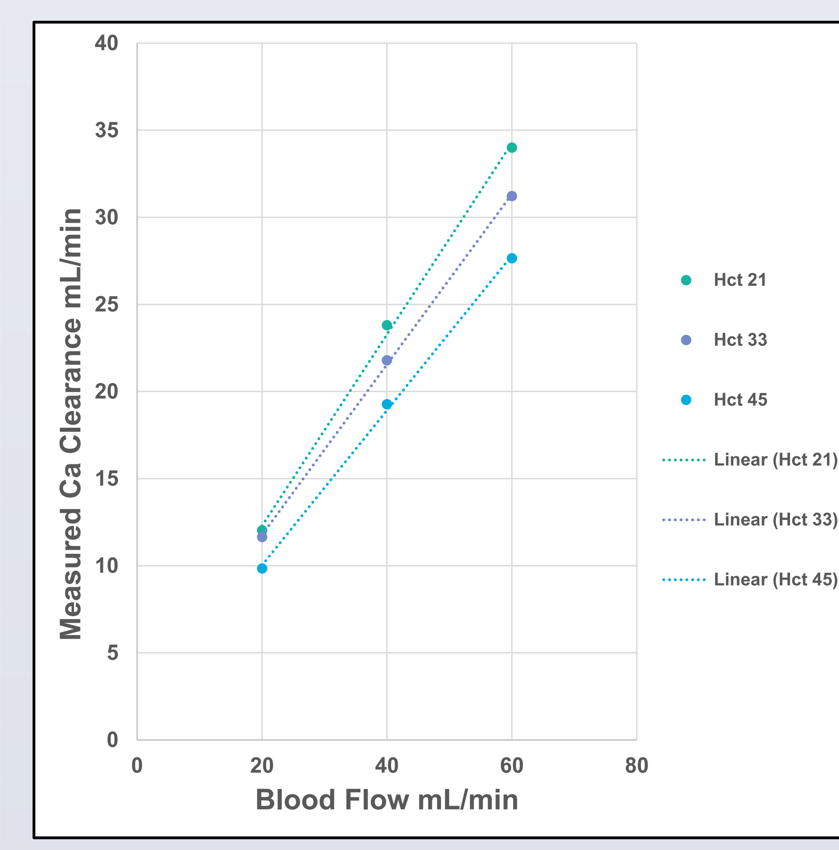

Figure 4: Figure 2: Measured calcium clearance is a linear function of QB

We validated FFR-CRRT-RCA in *ex vivo* simulations (Figure 3) using CRRT Fluids (Na 140, HCO3 35, K4, Mg 0.75 mM, Phos 1.5 mM with/without glucose 5.5 mM (Glu+/-) paired with Ca/Mg (136/13.6 mM) mixed in 0.9% or D5.0.9% saline, respectively. We tested QB 20, 40, 60 x Hct 21, 33, 45 with each fluid pair for a total of 18 experiments (Table 3, Figure 4).

Discussion

The pre-defined FFR-CRRT-RCA flows and fluid compositions achieved near perfect solute outcomes and controlled citrate- and iCa levels in the reservoir with minimal SD confirming that steady state solute levels can be pre-calculated so that providers do not have to do this at the bedside. The SAMI CRRT machine we used has disposable, volumetric diaphragm pumps that may have contributed to the precise results with highly accurate low flow rates. Nipro Elisio-H filters are optimal for FFR-CRRT-RCA (see below). When prescribing, QB (ml/min) is = total desired effluent flow (ml/h)/45. All other flows follow mechanistically from QB. The CRRT fluid K/HCO3 is adjustable without spiking. 3%NaCl or D5W IVF may be used at a fixed ratio to QB to target systemic Na 140±5, 10, 15 mEq/L.

CRRT Technology Suggested for FFR-CRRT-RCA

- **CRRT pumps:** precise delivery of low flows; change steps: QB 1 ml/min, QD/QRF 10 ml/h, QNetUF 1 ml/h. The blood pump should immediately stop if the citrate pump stops.
- **Filter:** Optimized to avoid QB/QD mismatch (shunting) even at low flows and high flux, high efficiency, optionally anti-clotting surface-modified with a broad range of surface area options.
- **CRRT fluids** – see Table 2, optimized for FFR-CRRT-RCA and "Combinatorial CRRT Fluid K/HCO3 Personalization" (Poster/Oral Presentation, Szamosfalvi & Yessayan 2020 CRRT Conference)
- **CRRT fluid source (adult):** should allow 4 x 5-L bags =20L to drain simultaneously by gravity and mix into final "Personalized" CRRT fluid stream split to supply both the QD and QRF pumps

Conclusions

1. FFR-CVVHDF-RCA prescribing avoids dangerous systemic citrate accumulation and is designed for use without contraindications or adjustments even in liver failure.
2. Predictive dosing of the initial Ca/Glu+ infusion rate based on QB, albumin and Hct avoids low systemic iCa levels and maintains a neutral CRRT glucose mass balance.
3. Effluent dose(ml/h) is QB x45; change by setting new QB then all fixed Ratio new flows.
4. Predictable systemic Na, K, HCO3 steady state levels allow custom targeting of these based on CRRT fluid K, HCO3 (±D5W or 3%NaCl IVF for custom goal Na 125-155 mM).