Citrate Anticoagulation for CRRT

Ashita Tolwani, MD, MSc
Professor of Medicine
DCI Edwin A Rutsky Endowed Chair
University of Alabama at Birmingham
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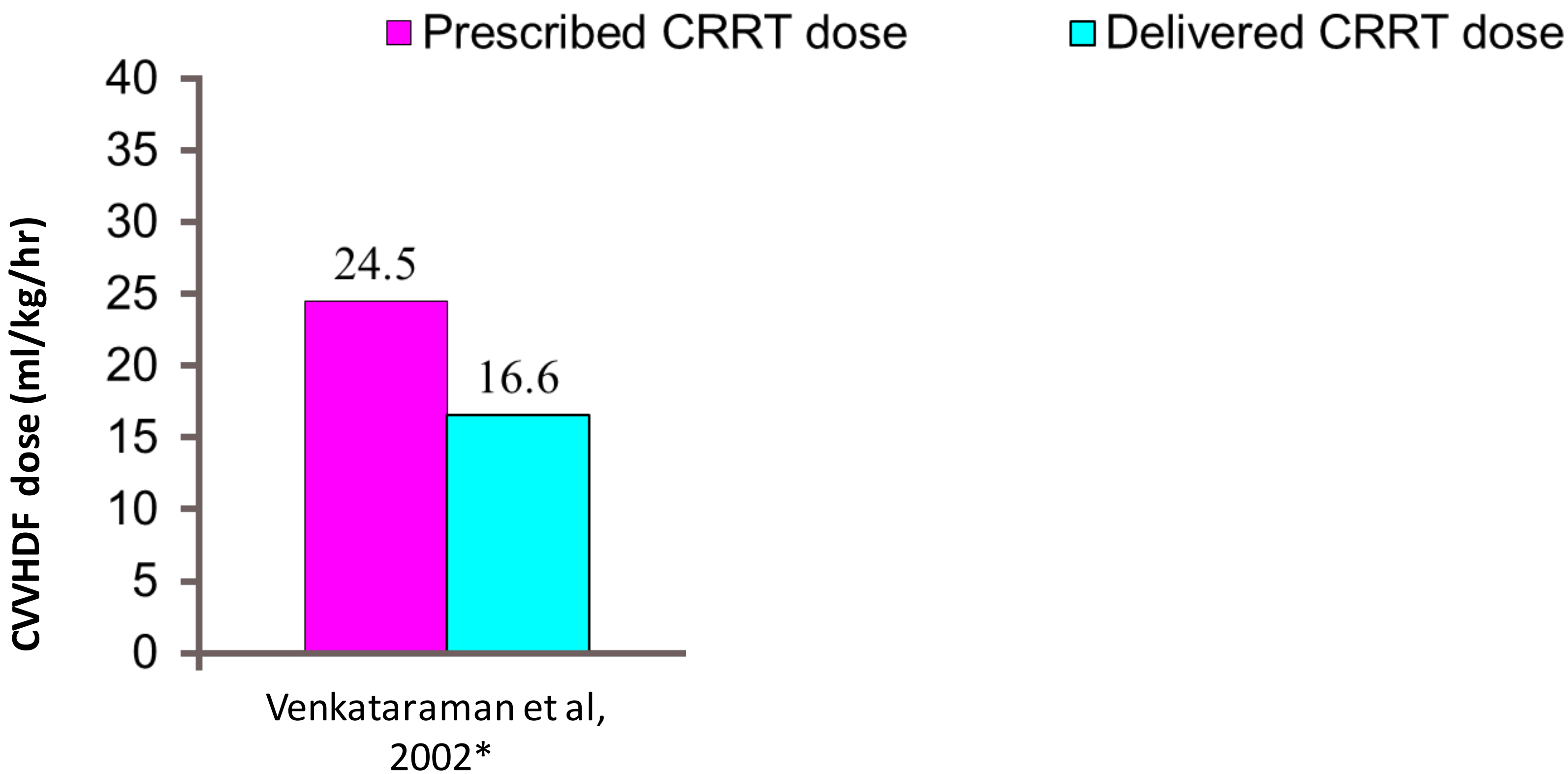
Disclosures

- Consultant for Baxter
- Patent on 0.5% citrate formulation

Prescribed vs. Delivered CRRT Dose



- Delivered CRRT dose ~ 20 - 30% lower than Prescribed dose
- Multifactorial: Rx interruptions + Pre-dilution + Effluent/Delivered dose mismatch

Mean dose; †median dose

Venkataraman R, *et al. J Crit Care* 2002;17:246–50
Vesconi S, *et al. Crit Care* 2009;13:R57
Claure-Del Granado R, *et al. CJASN* 2011;6:467–75

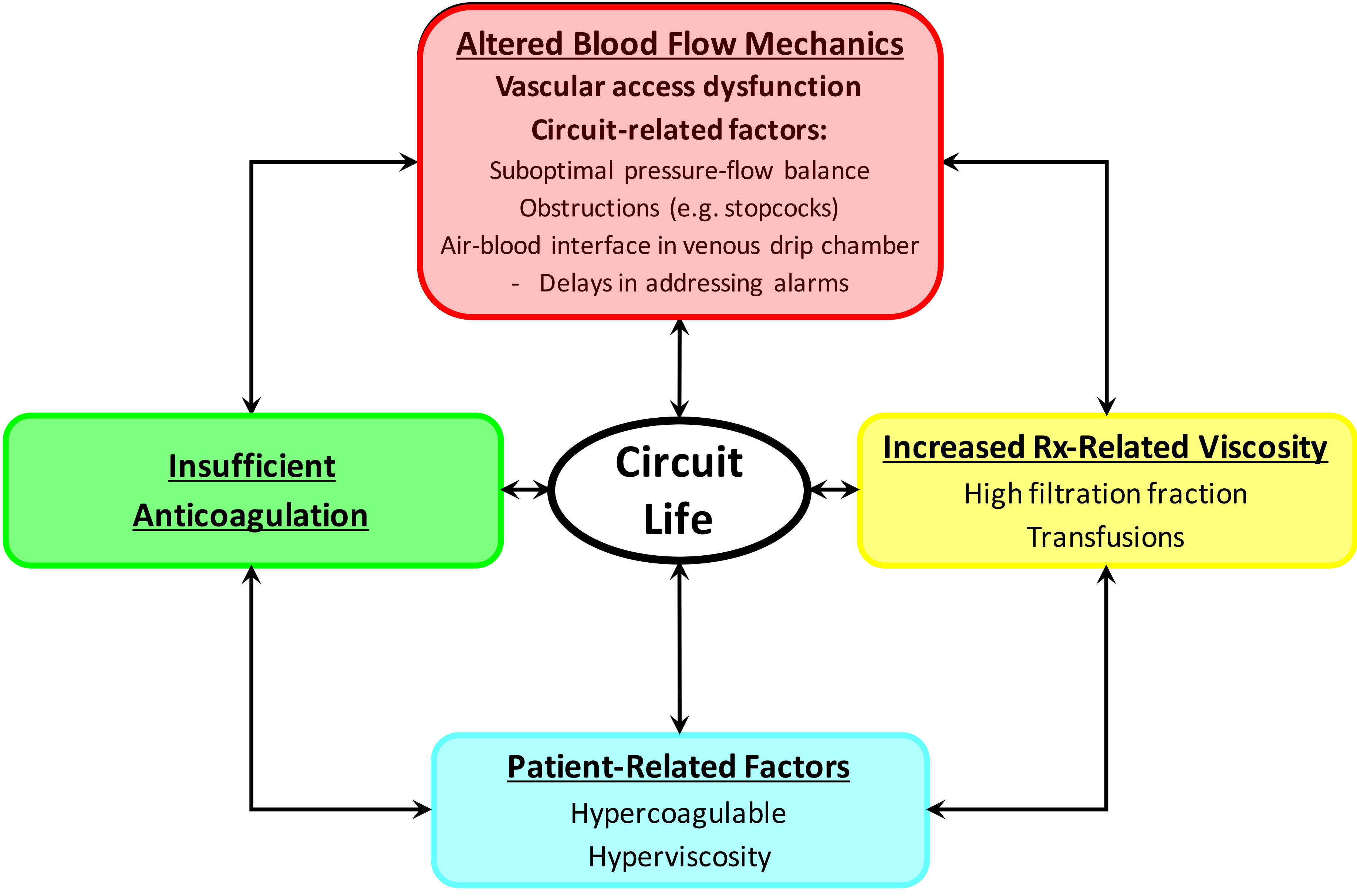
Consequences of Decreased Circuit Life

1. Decreased Dose/Clearance Delivered.
2. Increased loss of blood products
3. Altered medication dosing.
4. Fluid removal is inconsistent.
5. More setup manipulations.
   - Increased infection risk.
   - Increased error risk.

(Items 1–5: Directly Impacts Patients)

6. Increased Burden and Costs.
   - Filter / setups
   - Solution waste
   - Nursing time
   - Pharmacy time

Potential Causes of Short Circuit Life



Anticoagulation Options for CRRT

CRRT Anticoagulation

1. **No anticoagulation**
2. **Saline flushes**

Regional anticoagulation

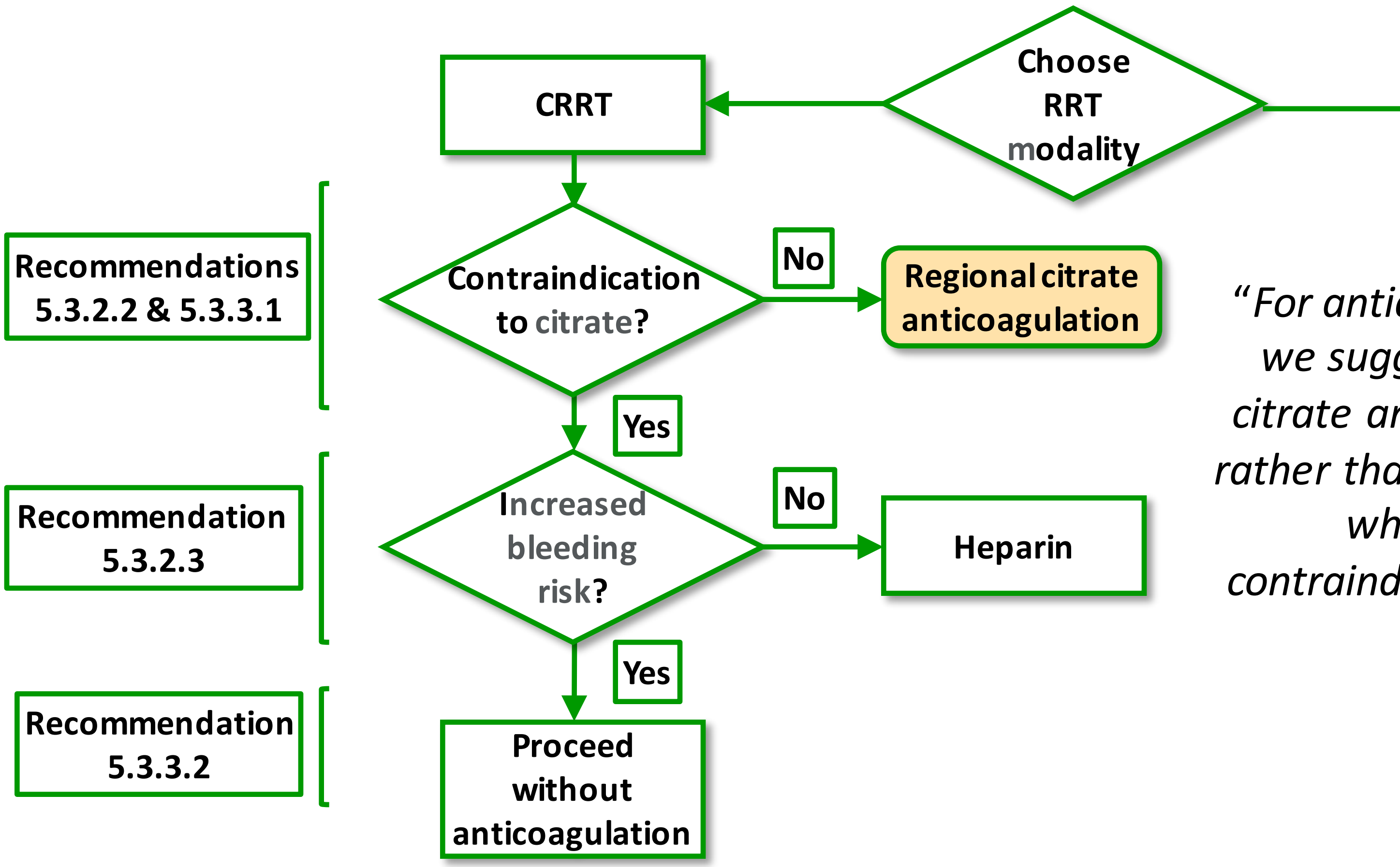
1. Regional citrate anticoagulation
2. Heparin with protamine reversal

Regional citrate
+
Systemic heparin
(in patients with COVID-19)

Pre-filter or Systemic anticoagulation

1. Unfractionated heparin
2. Low molecular weight heparin
3. Platelet inhibiting agents
   a. Prostacyclin (epoprostenol)
   b. Nafamostat mesilate
4. Thrombin inhibitors
   a. Argatroban
   b. Bivalirudin
5. Heparinoids

KDIGO Recommendations for Anticoagulation During CRRT



"For anticoagulation in CRRT, we suggest using regional citrate anticoagulation (RCA) rather than heparin in patients who do not have contraindications for citrate."

Figure adapted from: Kidney Disease Improving Global Outcomes (KDIGO). *Kidney Int. Suppl.* 2012; 2:1–138;

Citrate vs. Heparin Anticoagulation: Updated Meta-analysis of RCTs

13 RCTs with 1612 patients:

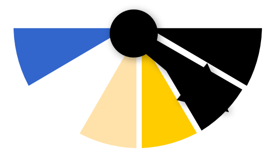
Less circuit loss

Compared with regional heparin (MD = 16.98, p < 0.0001)

Less bleeding

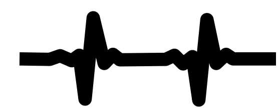
Compared with systemic heparin (RR = 0.32, p < 0.00001)

No difference in metabolic alkalosis



Compared with regional and systemic heparin combined (RR = 1.73, p = 0.40)

No difference in mortality



Compared with regional and systemic heparin combined (RR = 0.95, p = 0.40

Li R et al. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: A meta-analysis of randomized controlled trials. Ther Apher Dial. 2022

Effect of RCA vs Systemic Heparin AC during CRRT RCT

JAMA Network™

QUESTION In critically ill patients with acute kidney injury, what is the effect of using regional citrate anticoagulation vs systemic heparin anticoagulation during continuous kidney replacement therapy on dialysis filter life span and mortality?

CONCLUSION This randomized trial showed that in patients with acute kidney injury, anticoagulation with regional citrate, vs systemic heparin anticoagulation, increased filter life span, but the trial was underpowered to reach conclusions regarding mortality.

POPULATION

413 Men
183 Women

Adults with acute kidney injury or indication for kidney replacement therapy, an additional condition, and planned intensive care

Mean age: **67.5** years

LOCATIONS

26
Centers in Germany

INTERVENTION

596 Patients analyzed

300
Regional citrate anticoagulation
Citrate added continuously to the blood before the filter of extracorporeal circuit; adjusted to ionized calcium levels

296
Systemic heparin anticoagulation
Heparin administered through IV lines at 30 mL/kg/h; adjusted to partial thromboplastin time of 45-60 seconds

COPRIMARY OUTCOMES

Filter life span and 90-day all-cause mortality

FINDINGS

Median filter life span

Regional citrate anticoagulation	Systemic heparin anticoagulation
47 hours	**26 hours**

The median filter life span difference was significant:
15 hours (95% CI, 11 to 20); *P* < .001

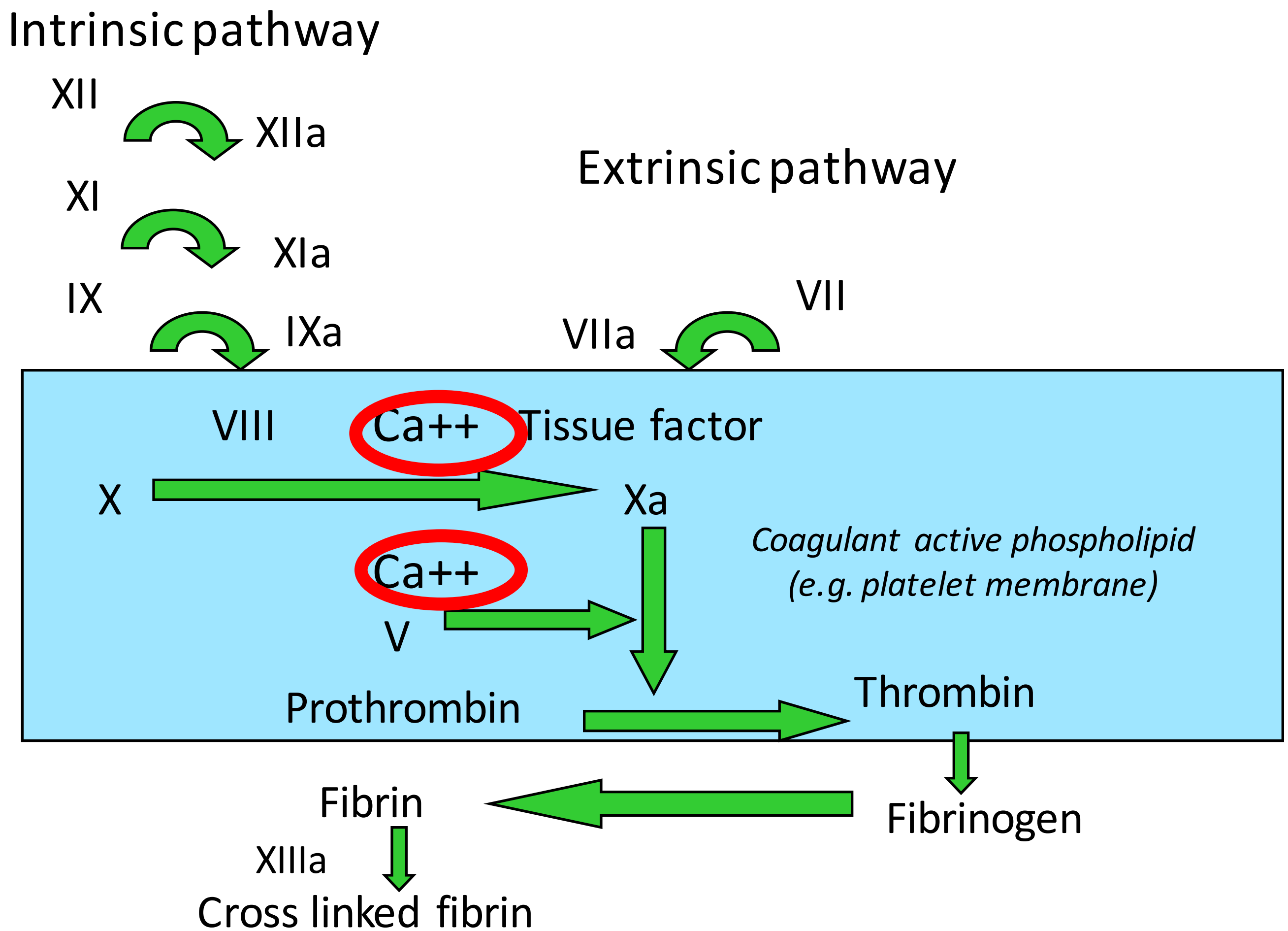
90-day mortality

Regional citrate anticoagulation	Systemic heparin anticoagulation
51%	**54%**

Adjusted 90-day mortality was not significant:
HR, **0.79** (95% CI, 0.63-1.004),
but the trial was underpowered for this outcome

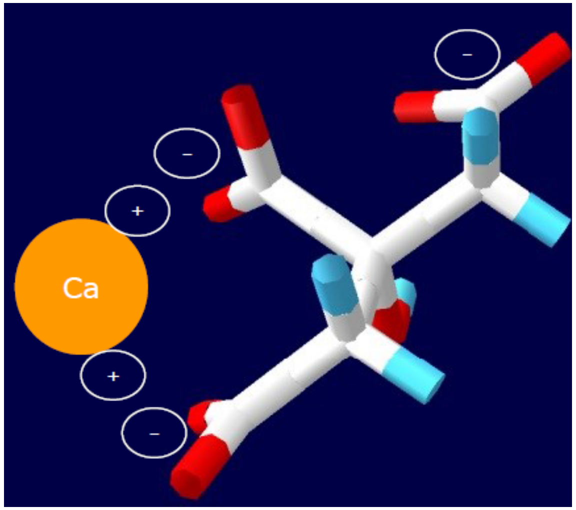
Zarbock A, Küllmar M, Kindgen-Milles D, et al. Effect of regional citrate anticoagulation vs systemic heparin anticoagulation during continuous kidney replacement therapy on dialysis filter life span and mortality among critically ill patients with acute kidney injury. *JAMA*. doi:10.1001/jama.2020.18618

Citrate Anticoagulation



Citrate Anticoagulation

- ❑ 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



Citrate + iCa → Calcium citrate

Biologically inactive
measurable as total Ca

- Normal blood levels of citrate: 0.05 mmol/L
- Bleeding time → ∞ at citrate levels of 3–5 mmol/L (Ca^{2+}< 0.35 mmol/L)

Fealy N. Regional citrate anticoagulation. *Continuous renal replacement therapy*. Vol. 1, 2010; pp. 142; Davenport A & Tolwani A. *NDT Plus.* 2009; 2:439–447; 3. Beeck H, *et al. Transfusion.* 1999; 39:1266–1270.

Citrate Metabolism

- Citric acid has a plasma half-life of 5 minutes
- Rapidly metabolized by liver, kidney, and muscle cells

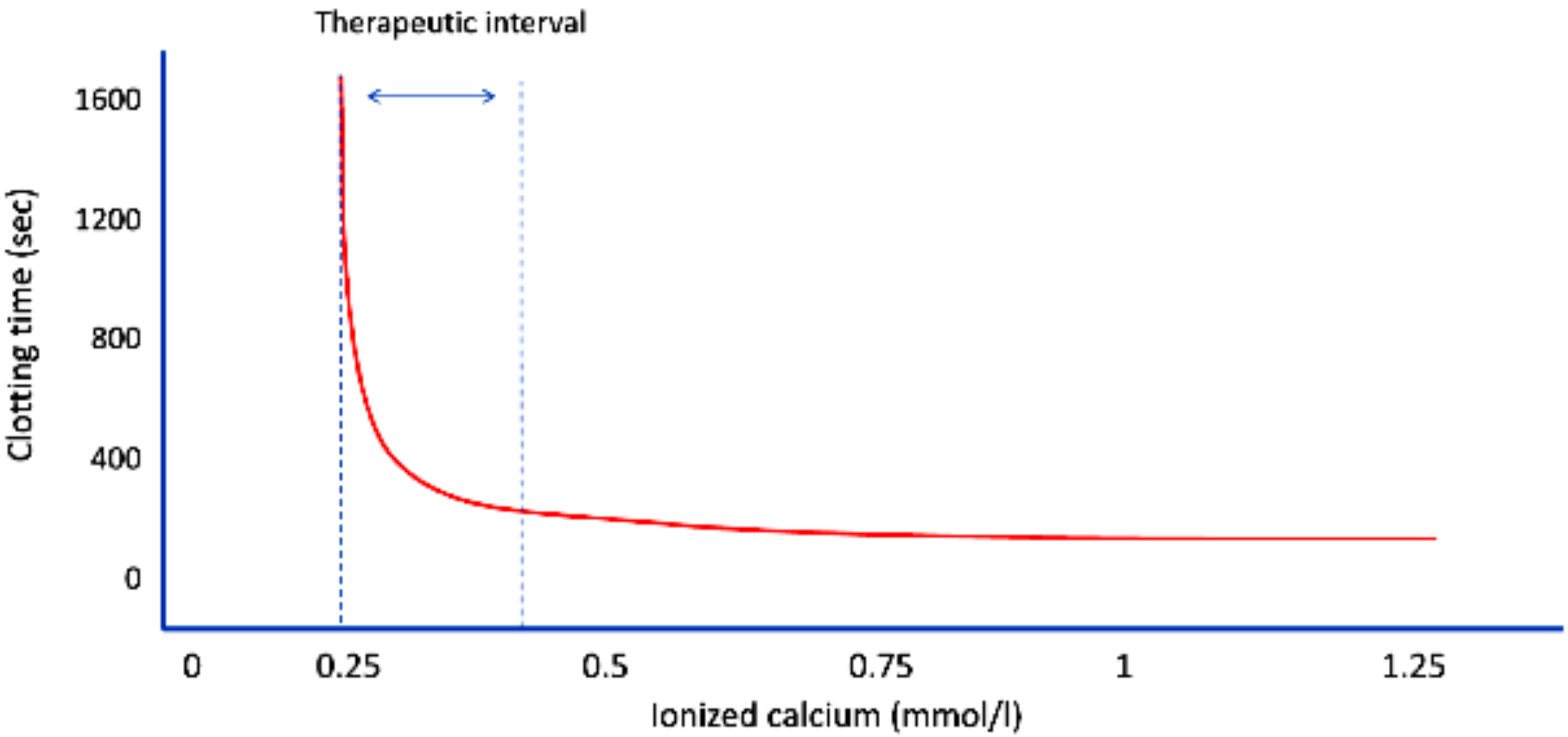
$$Na_3Citrate + 3H_2CO_3 \leftrightarrow Citric\ acid + 3NaHCO_3$$

$$Citric\ acid + 3NaHCO_3 \rightarrow 3H_2CO_3 + H_2O + 3NaHCO_3$$

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

Flanigan MJ, *et al. Am J Kidney Dis.* 1996; 27:519–524
Davenport A & Tolwani A. *NDT Plus.* 2009; 2:439–447.

Dose-Response Relationship: Ca^{2+} and Clot Formation



Calatzis A, *et al. Nephron.* 2001; 89:233–236.

Clearance of Citrate

- 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
  - 40 to 60% of citrate cleared

Chadha V et al. Pediatr Nephrol 2002, 17:819-824

Citrate

- Advantages
  - Regional, avoids bleeding complications
  - Doubles as buffer
  - Highly effective in studies (> heparin)
  - No thrombocytopenia
- Disadvantages
  - Metabolic complications
  - Complex protocols

Commercial Citrate Solutions

Components	4% Sodium citrate	ACD A: 2.2% Sodium citrate	Prismocitrate™ (10/2)	Prismocitrate™ (18/0) Regiocit	Citra-HF Pre® (Dirinco)
Sodium (mmol/L)	408	225	136	140	139.9
Trisodium Citrate (mmol/L)	136	75	10	18	13.3
Citric Acid (mmol/L)	-	38	2	-	
Dextrose (mmol/L)	-	124	-	-	5
Bag Size (mL)	1000	500 & 1000	5000	5000	5000

Citrate Delivery: Fixed

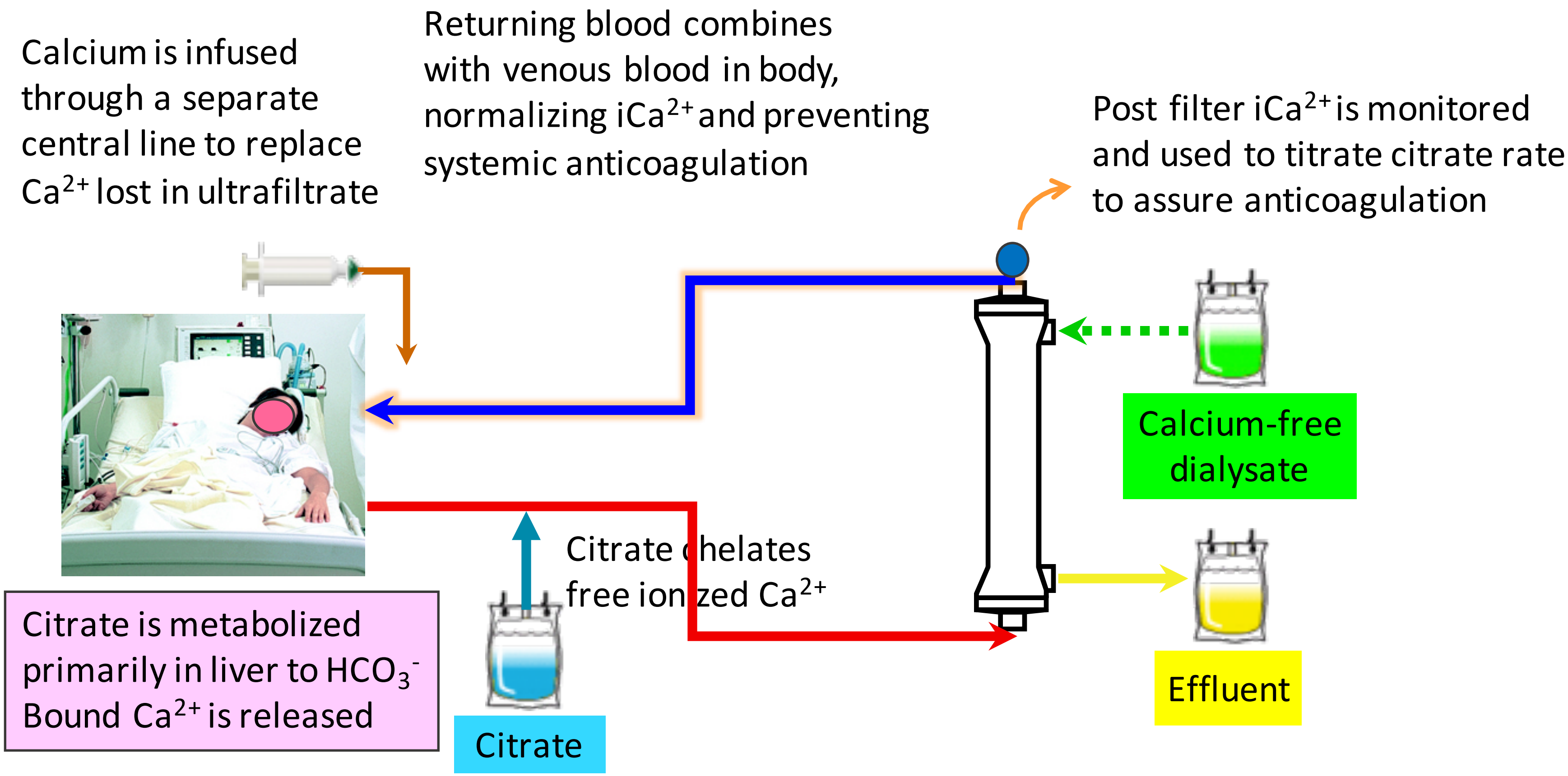
QB (mL/min)	**4% TSC (mL/h) (2-3% BF) (1.33 X BF)**	**ACD-A (mL/h) (1.5 X BF)**	**Regiocit (0.5% Citrate) (mL/h)**
100	132	159	1000
125	165	200	1250
150	199	239	1500
200	265	319	2000

Amount of citrate delivered to achieve blood citrate concentration of 3 mmol/L

For any given citrate fluid, **citrate dose** is a determined by the **ratio** of citrate flow rate to blood flow rate

Flanagan MJ et al. AJKD 27: 519-24, 1996
Tolwani AJ et al. CJASN. 2006

Citrate Delivery: Titrated



Post-filter ionized calcium is essentially a function of citrate dose and not of citrate flow rate

Citrate and Calcium Delivery

- Citrate Delivery
  - If blood flow rate is 200 mL/min, hourly conversion is 12,000 mL/h = 12 L/h
  - Target blood concentration of citrate = 3 mmol/L
  - Required amount of citrate for blood flow = 3 mmol/L X 12 L/h = 36 mmol/h
  - Citrate solutions:
    - ACD-A (113 mmol/L citrate) rate = 36 / 113 = 0.319 L/h or 319 mL/h
    - 4% TSC rate (136 mmol/L citrate) rate = 36 / 136 = 0.265 L/h or 265 mL/h

- Calcium Delivery
  - 5% calcium chloride initial infusion rate: Effluent flow rate (mL/h)/200
  - 10% calcium gluconate infusion rate: Effluent flow rate (mL/h)/125

Achieving Anticoagulation with RCA

Anticoagulant target	Pro	Con
Calculated [citrate] in filter 3-5 mmol/l	Fixed ratio of citrate flow and blood flow No extra monitoring Fixed buffer supply to patient	Anticoagulation may not be optimal
[iCa^{++}] postfilter 0.25-0.35 mmol/l	Optimal anticoagulation	Monitoring of postfilter iCa^{++} Adjustment of citrate flow gives varying buffer supply to patient

Joannidis M, Crit Care 2007; 11:218

Metabolic Consequences

- Metabolic alkalosis
  - Citrate overload with normal metabolism
- Metabolic acidosis
  - Citrate accumulation in setting of severe liver disease or hypoperfusion
  - Normal citrate metabolism but inadequate buffer from citrate
- Hypernatremia
  - Hyperosmolar citrate solutions
- Hypocalcemia and hypercalcemia
  - Inappropriate calcium supplementation
- Hypomagnesemia

Citrate Accumulation

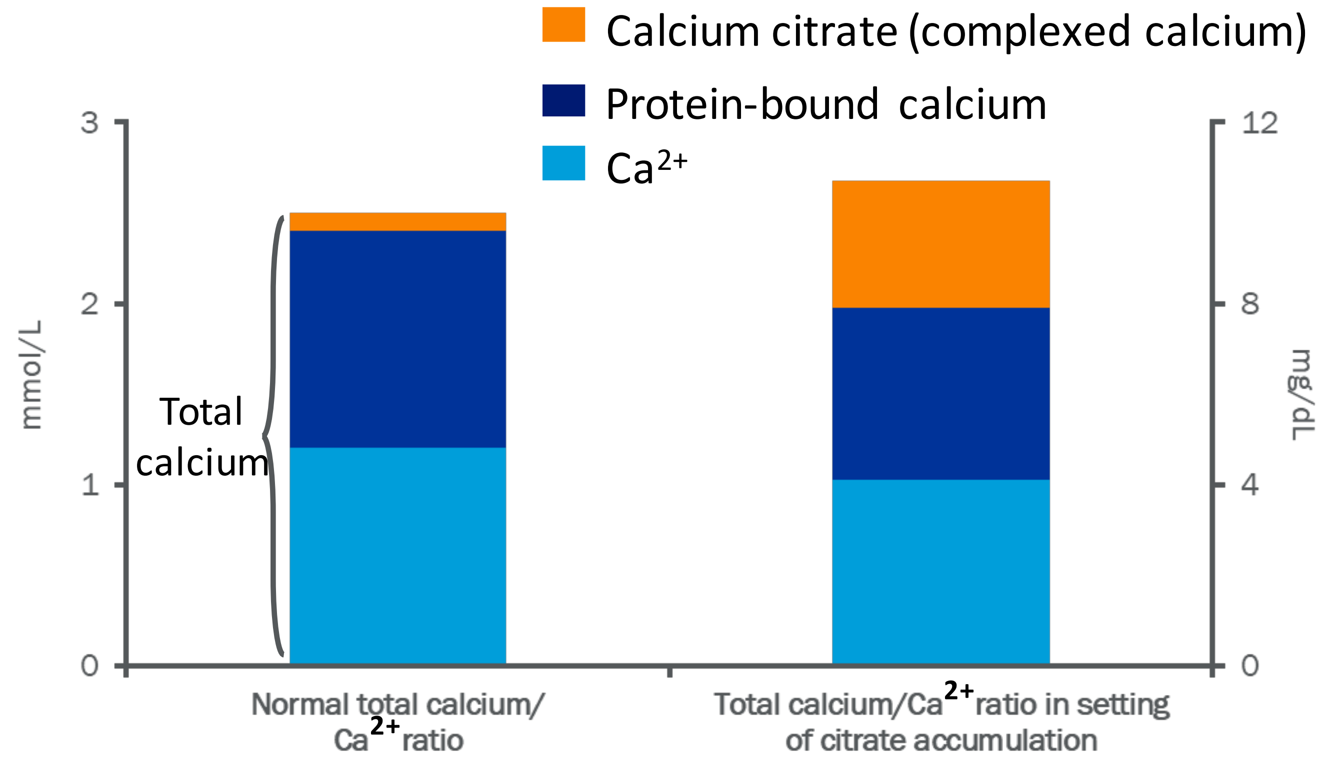
- Risk Factors
  - Persistent shock (cardiogenic/ septic)
  - Poor microcirculation
  - Elevated serum lactate >4 mmol/L at initiation or impaired "lactate clearance" in patients with serum lactate >4 mmol/L
  - Severe liver failure (e.g. ischemic hepatitis/ "shock" liver)
  - Mitochondrial disorders or mitochondrial function impairment

- Detection
  - Worsening metabolic acidosis
  - Elevated total calcium
  - Decreased Ionized calcium → increasing Ca^{++} infusion
  - Total Calcium: Ionized Calcium ratio >2.5 (if both mmol/L)

Tan JN, J Int Care Med 2017; ePub April 4 2017

Meier-Kriesche HU et al. Crit Care Med. 2001, 29:748-752

Calcium Gap



Davenport A & Tolwani A. Citrate anticoagulation for continuous renal replacement therapy (CRRT) in patients with acute kidney injury admitted to the intensive care unit. *NDT Plus.* 2009; 2(6):439–447 by permission of Oxford University Press.

Monitoring

- Circuit serum ionized calcium q 6-8^{H}
  - keep 0.25-0.35 mmol/l
- Systemic serum ionized calcium q 6-8^{H}
  - keep 0.90-1.0 mmol/l
- Serum Total Ca, PO_4 and Mg q 12 -24^{H}

RCA for CRRT Cases

Case 1

A 35-year-old man is admitted with septic shock and ARDS from multifocal MRSA pneumonia. He is started on CRRT for anuric AKI. Regional citrate anticoagulation is added due to frequent circuit clotting. CaCl is infused in the return line of the CRRT access. 48h later, you are called by the ICU RN due to the following labs.

Laboratory	12/20/2019 09:15 MST	12/20/2019 09:11 MST	12/20/2019 08:10 MST	1: (
Electrolytes Plus				
Sodium			142	
Potassium			5.1	
Chloride			107	
Carbon Dioxide (lab)			(H) 32	
Blood Urea Nitrogen			(H) 32	
Creatinine			(H) 2.75	
Glucose (lab)			* (H) 121	
POC - Glucose				(H)
Calcium			(H) 11.1	
Ionized Calcium		(H) 1.48		
Anion Gap			(L) <6	
Other Routine Chemistry				
Est Glomerular Filtration Rate			NOT CALCULA	
Blood Gases - POC				
Pump Calcium	0.42			
Arterial Blood Gases				

Case 1

What is the next best step?

A. Decrease the rate of citrate

B. Increase the rate of citrate

C. Increase the rate of CaCl infusion

D. Decrease the rate of CaCl infusion

Laboratory	12/20/2019 09:15 MST	12/20/2019 09:11 MST	12/20/2019 08:10 MST	1 (
Electrolytes Plus				
Sodium			142	
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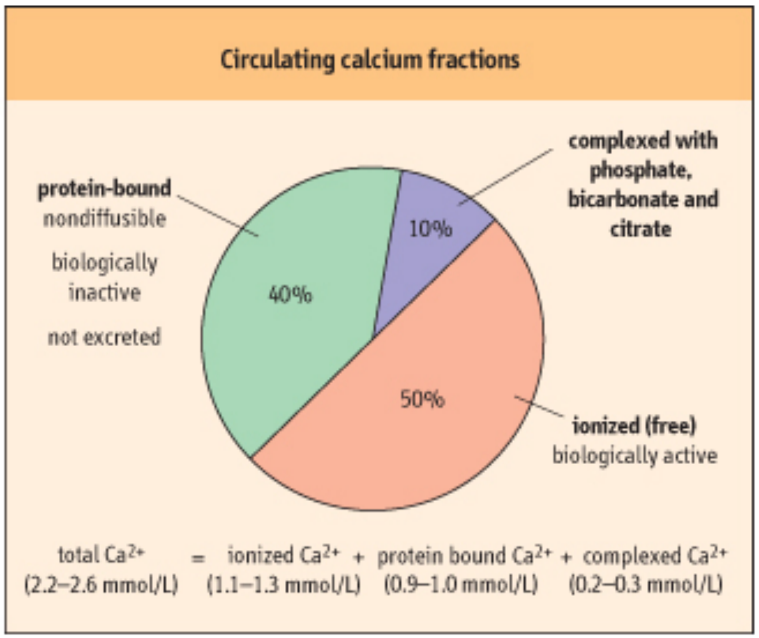
Calcium			(H) 11.1	
Ionized Calcium		(H) 1.48		
Anion Gap			(L) <6	
Other Routine Chemistry				
Est Glomerular Filtration Rate			NOT CALCULA	
Blood Gases - POC				
Pump Calcium	0.42			
Arterial Blood Gases				

Citrate Toxicity is likely when ratio of Total Calcium to Ionized Calcium rises to 2.5-to-1 (or, in the most commonly used units, 10 mg/dL to 1 mmol/L)



Normal Ca Levels in Different Units				
	%	mmol/L	mEq/L	mg/dL
Ionized Ca^{++}	50%	1.25	2.5	5
Total Ca^{++}	100%	2.5	5	10

Citrate Toxicity?? No

Laboratory	12/20/2019 09:15 MST	12/20/2019 09:11 MST	12/20/2019 08:10 MST	1
Electrolytes Plus				
Sodium			142	
Potassium			5.1	
Chloride			107	
Carbon Dioxide (lab)			(H) 32	
Blood Urea Nitrogen			(H) 32	
Creatinine			(H) 2.75	
Glucose (lab)			* (H) 121	
POC - Glucose				(H
Calcium			(H) 11.1	
Ionized Calcium		(H) 1.48		
Anion Gap			(L) <6	
Other Routine Chemistry				
Est Glomerular Filtration Rate			NOT CALCULA	
Blood Gases - POC				
Pump Calcium	0.42			
Arterial Blood Gases				

- The ratio of total to ionized calcium is:
  - 11.1/1.48 = 7.5
  - Or, if using same units (by converting ionized Ca^{++} from mmol/L to mg/dL), 11.1/5.9 = 1.9
- The ratio of total-to-ionized calcium is normal → *no evidence of citrate accumulation*
- As both the ionized and total calcium levels are high, the cause of hypercalcemia is *too much calcium*

Case 1: Answer D

A 35-year-old man is admitted with septic shock and ARDS from multifocal MRSA pneumonia. He is started on CRRT for anuric AKI, to which regional citrate anticoagulation is added due to frequent circuit clotting. CaCl is infused in the return line of the CRRT access. About 48h later, you are called by the ICU RN due to the following labs.

Laboratory	12/20/2019 09:15 MST	12/20/2019 09:11 MST	12/20/2019 08:10 MST	1
Electrolytes Plus				
Sodium			142	
Potassium			5.1	
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Carbon Dioxide (lab)			(H) 32	
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Anion Gap			(L) <6	
Other Routine Chemistry				
Est Glomerular Filtration Rate			NOT CALCULA	
Blood Gases - POC				
Pump Calcium	0.42			
Arterial Blood Gases				

What is the next best step?

A. Decrease the rate of citrate

B. Increase the rate of citrate

C. Increase the rate of CaCl infusion

D. Decrease the rate of CaCl infusion

Why not increase the rate of citrate?

Case 2

- You are reviewing early AM labs for 18 CRRT patients when on call. One patient has an ionized calcium 0.9 mmol/L that fell from 1.2 mmol/L 8 hours ago. According to your sign out there were no prescription changes made 8 hours ago. The patient has been on CRRT for 24 hours.
- The prescription is CVVH at 1.5 L/hour (weight is 60 kg) with ACD-A citrate at 230 mL/h and blood flow at 150 mL/min, IV calcium chloride replacement at 24 grams per day. You spoke to the bedside RN and the calcium replacement is running as prescribed.
- Current Labs:

• Potassium	4.1 mg/dL
• Calcium, total	11.4 mg/dL
• Patient ionized Calcium	0.9 mmol/L
• CRRT ionized Calcium	0.25 mmol/L
• CO2	17 mg/dL
• Sodium	139 mg/dL
• Anion Gap	21

Case 2

Based on your diagnosis, which one of the following is the next best management plan?

A. Reduce the citrate by 10%, increase the replacement fluid delivery rate, and increase the calcium infusion rate
B. Stop the citrate, increase the calcium infusion rate, and change to CVVHD
C. Increase the blood flow rate and the citrate infusion rate to treat acidosis and decrease the calcium infusion rate
D. Stop the citrate, increase the blood flow rate, and decrease the calcium infusion rate

Case 2: Answer A

Rationale

- Citrate lock occurs when the rate of citrate infusion is higher than the patient's ability to convert/metabolize the citrate.
- Calcium citrate accumulates contributing to the rise in total calcium and worsening acidosis.
- There is lab evidence of rising anion gap, worsening acidosis, rising total calcium and often falling ionized/free calcium.
- The ratio of total to ionized calcium will rise > 2.5; in this case the calcium ratio is 3.2.
- Citrate has a short half life and is easily removed by CRRT.
- Options for clearing citrate include reducing or removing the citrate infusion and increasing CRRT clearance. The most critical action is always to replace Ionized calcium to a normal level.

Case 2: Incorrect Answers

- Option B is incorrect. Although stopping CRRT altogether is an option for preventing further citrate accumulation, there is no need to change modality to CVVHD for removal of citrate. CVVH would be as effective in removing the citrate once citrate has been stopped.

- Option C is incorrect. Although increasing blood flow and citrate rate will maintain the citrate concentration in the filter at 3 mmol/L, it will increase the citrate load to the patient and cause further citrate accumulation. The acidosis is not due to insufficient buffer from citrate; it is due to citrate accumulation from lack of metabolism. Increasing citrate load to the patient will worsen citrate accumulation, metabolic acidosis, and ionized hypocalcemia. Decreasing the calcium rate would also worsen the ionized hypocalcemia.

- Option D is incorrect. Although stopping the citrate is reasonable given citrate accumulation, increasing blood flow will not substantially increase citrate removal. Citrate is a small molecule and will be effective removed by increasing the effluent rate if needed. Furthermore the calcium infusion should not be decreased or stopped until the ionized calcium has normalized.