Citrate : How To Avoid Side Effects

1.-Mechanism Of Action-KDIGO – Recent Trials

2.- Targeted Ionized Calcium in the Circuit & in the Patient

3.- What About New Citrate Formulations Available Today ?

4.-What About Our VUB Protocol Re Safety & Monitoring

5.- Metabolic Complications of RCA

6.- How To Fix Metabolic Alkalosis ?

7.- Conclusions-Perspectives

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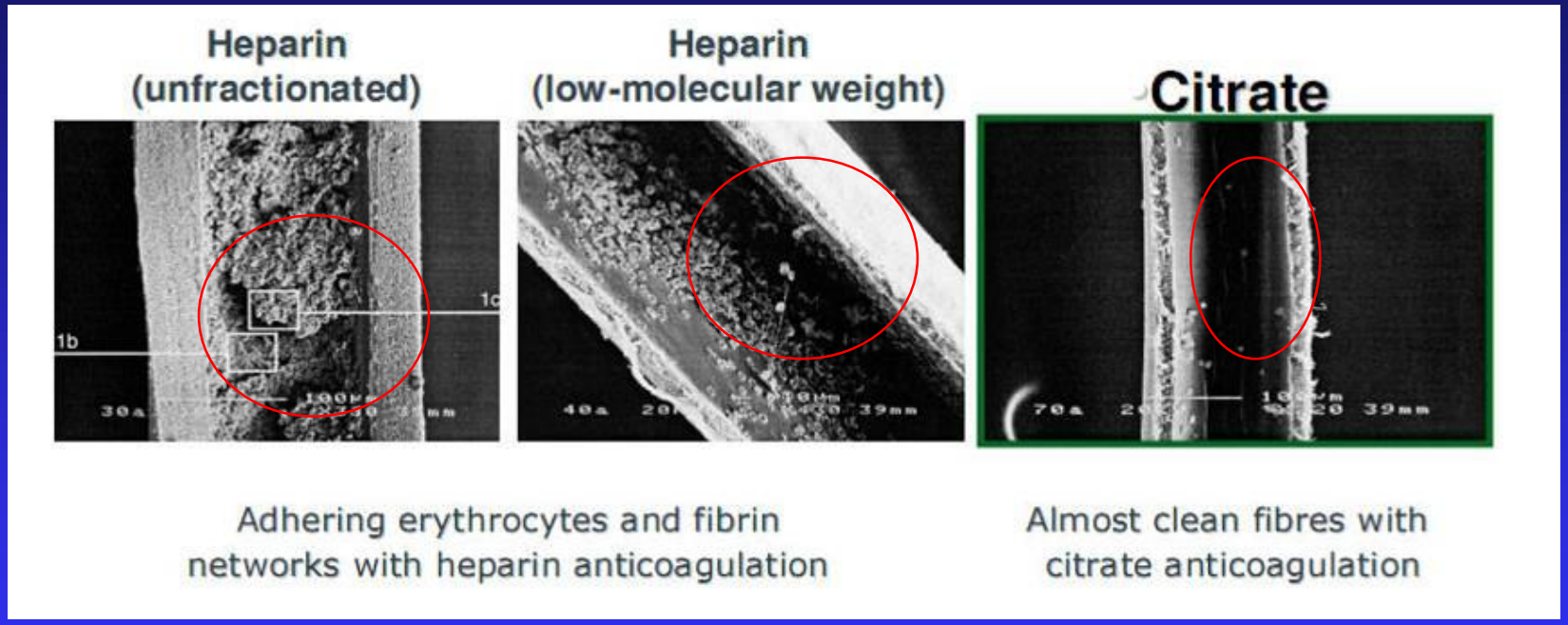
2° International Intercongress Conference of the PTAIT

Karpacz,24-26 Nov 2016-Poland

Less Clotting and Clogging in Hollow Fibers Membrane

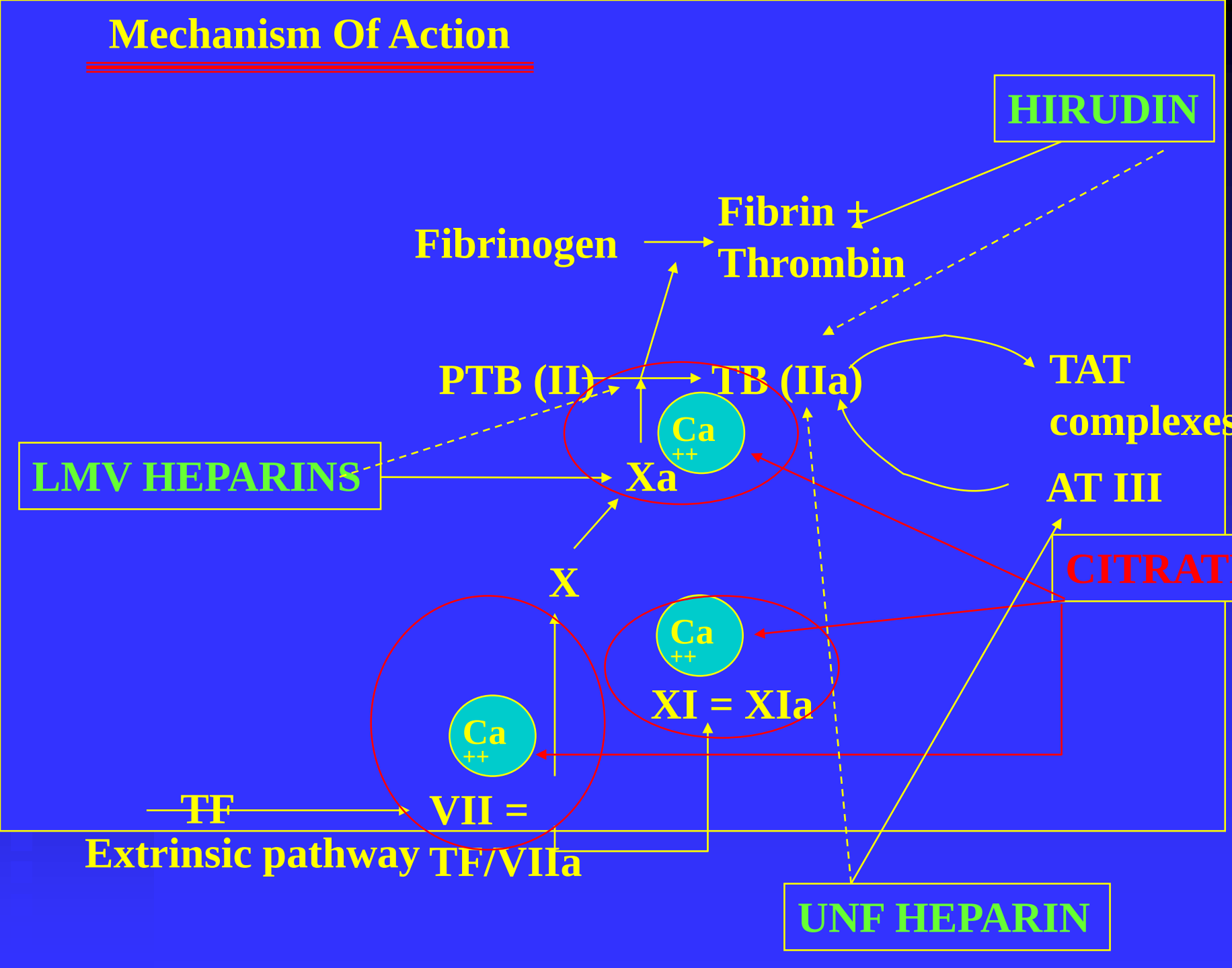


Reducing Clotting and Clogging will modify the filtration fraction but also the filter permeability After 24-48 h as compared to UNH
So, dose using citrate might be different from UFH dose

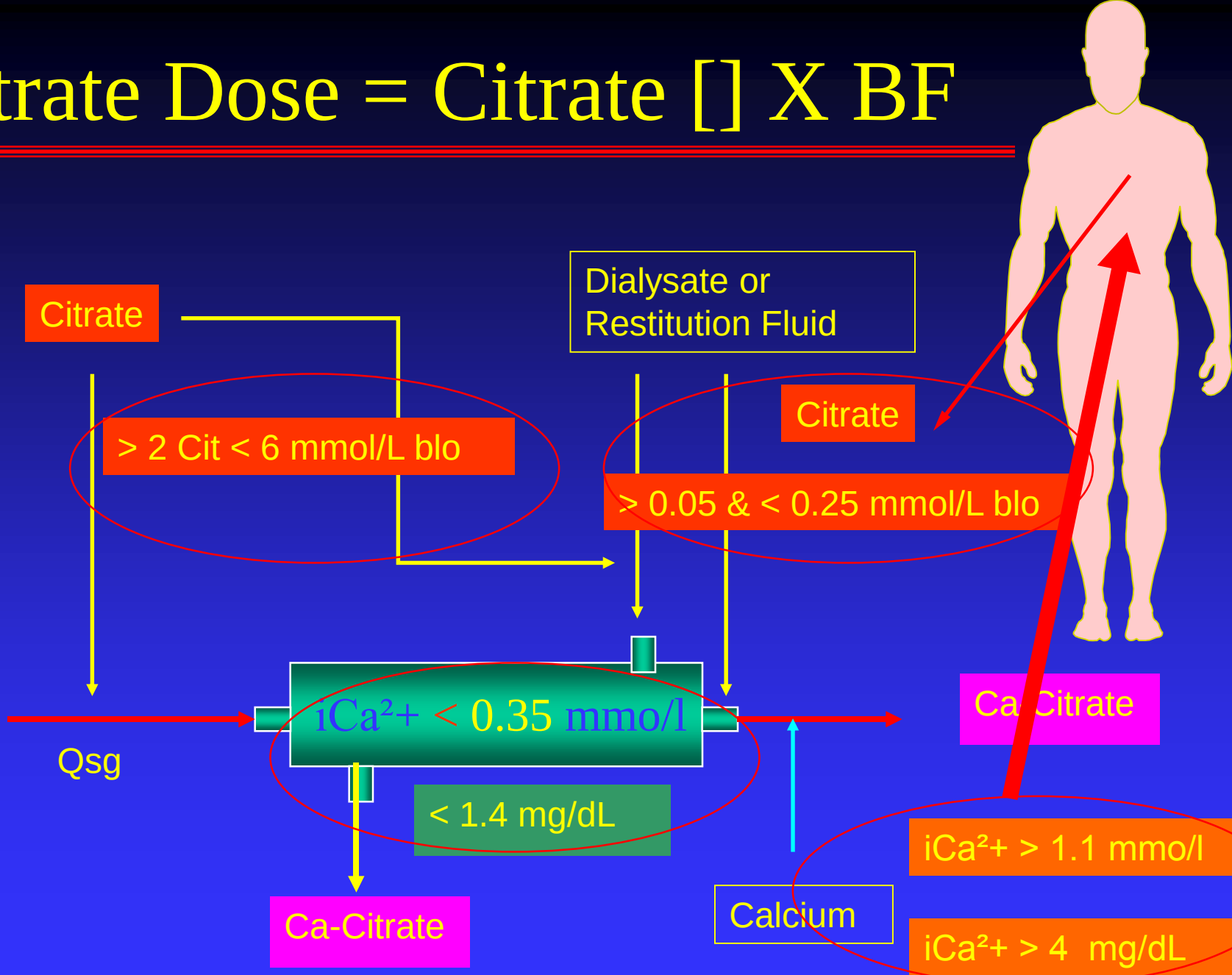
Hofbauer R et al.Kidney Int 1999;56:1578-83

Jacobs R, Honore PM et al. Blood Purif 2015 ;40:194-202

Mechanism Of Action



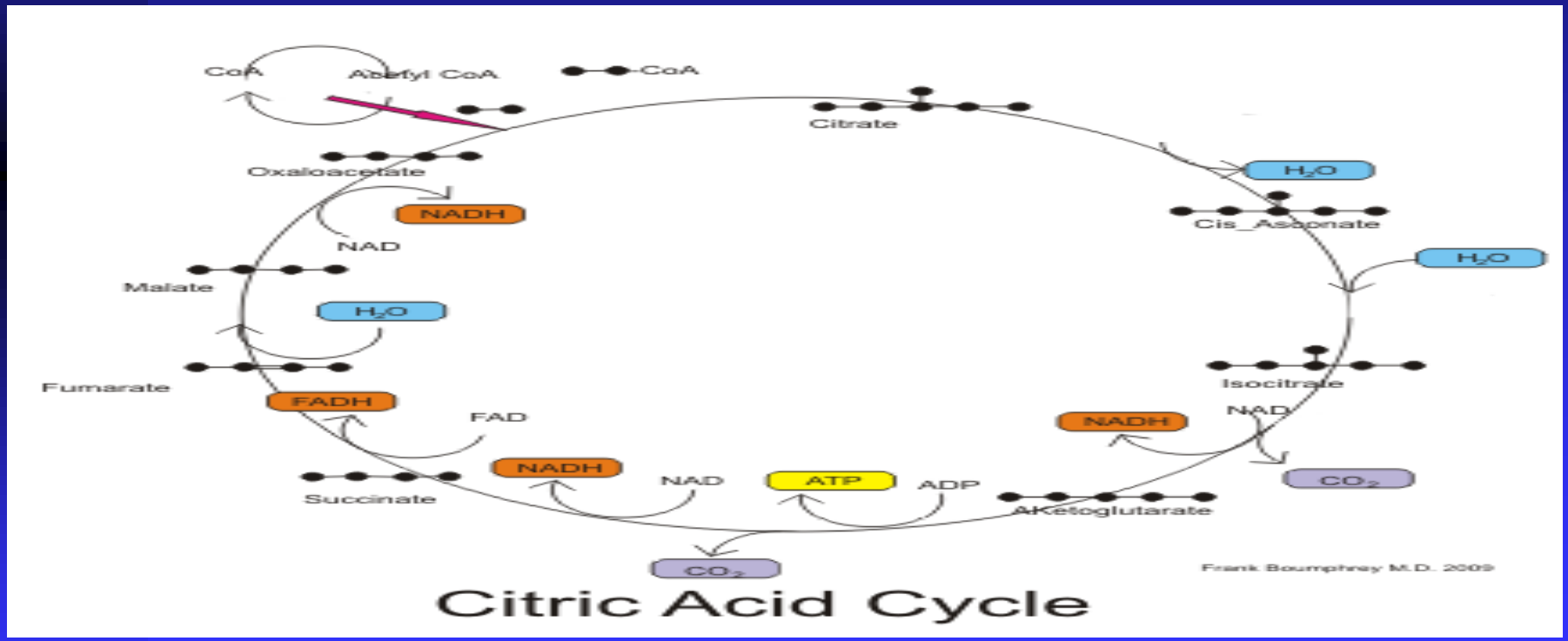
Citrate Dose = Citrate [] X BF



Mariano F et al.ICM 2010;36:1735-43

Citrate Metabolism

- Citrate is Metabolized into the Mitochondria
- Citrate goes into the Citric Acid Cycle
- This is a Fully Oxygen Dependent Pathway



Kishen R, Honore PM,Jacobs R et al.Int J Nephrol Ren Dis 2014;40: 194-202

Oudemans van-Straaten HM et al.Crit Care 2012 ;16:-24

Metabolism of Citrate :O^2 Dependent

Liver 65 %

Kidney 5 %

Muscle 30 %

glucose

pyruvate

H^+

lactate

2 ATP

citrate

anaerobic

cytosol

O_2

aerobic

mitochondria

pyuvate

acetyl-CoA

Citric acid cycle

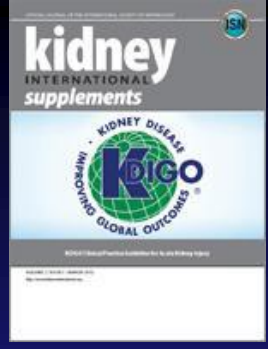
Respiratory chain

30 ATP

Oudemans van Straten HM et al.Crit Care 2012 ;16:-24

Kishen R, Honore PM, Jacobs R et al.Int J Nephrol Ren Dis 2014;40: 194-202

AKI Guideline 5.3



- 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)

Kidney Int. Suppl. Volume 2, No 1 (March 2012)

Recent Randomised Studies of RCA vs UFH

	Schilder L et al	Gattas DJ et al	Stucker F et al
Year	2014	2015	2015
Center	Multi	Multi	Single
No. of patients	C: 66 H: 73	C: 105 H: 107	C: 54 H: 49
Treatment	Citrate vs. UFH	Citrate vs. heparin/protamine	Citrate vs. UFH
Circuit lifespan (hrs)	C: 46 (p = 0.02) H: 32	C: 39.2 (p = 0.004) H: 22.8	C: 49 (p = 0.004) H: 28
Bleeding / Adverse events	C: 0% (p < 0.001) H:33%	C: 2 (p = 0.011) H: 11	C: 0 H: 8%
Metabolic alkalosis (%)	C: 2 H: 0	NR	C: 6 H: 0
Hypocalcemia	C: 12% (iCa <0.9 mmol/L) H: NR	NR	C: 11% (severe) H: 2%
Mortality	No difference	No difference	No difference

Schilder L et al.Crit Care 2014 ;18-472

Strucker F et al .Crit Care 2015 ;19:91

Gattas DJ et al Crit Care Med 2015-April 6

New Citrate Formulations

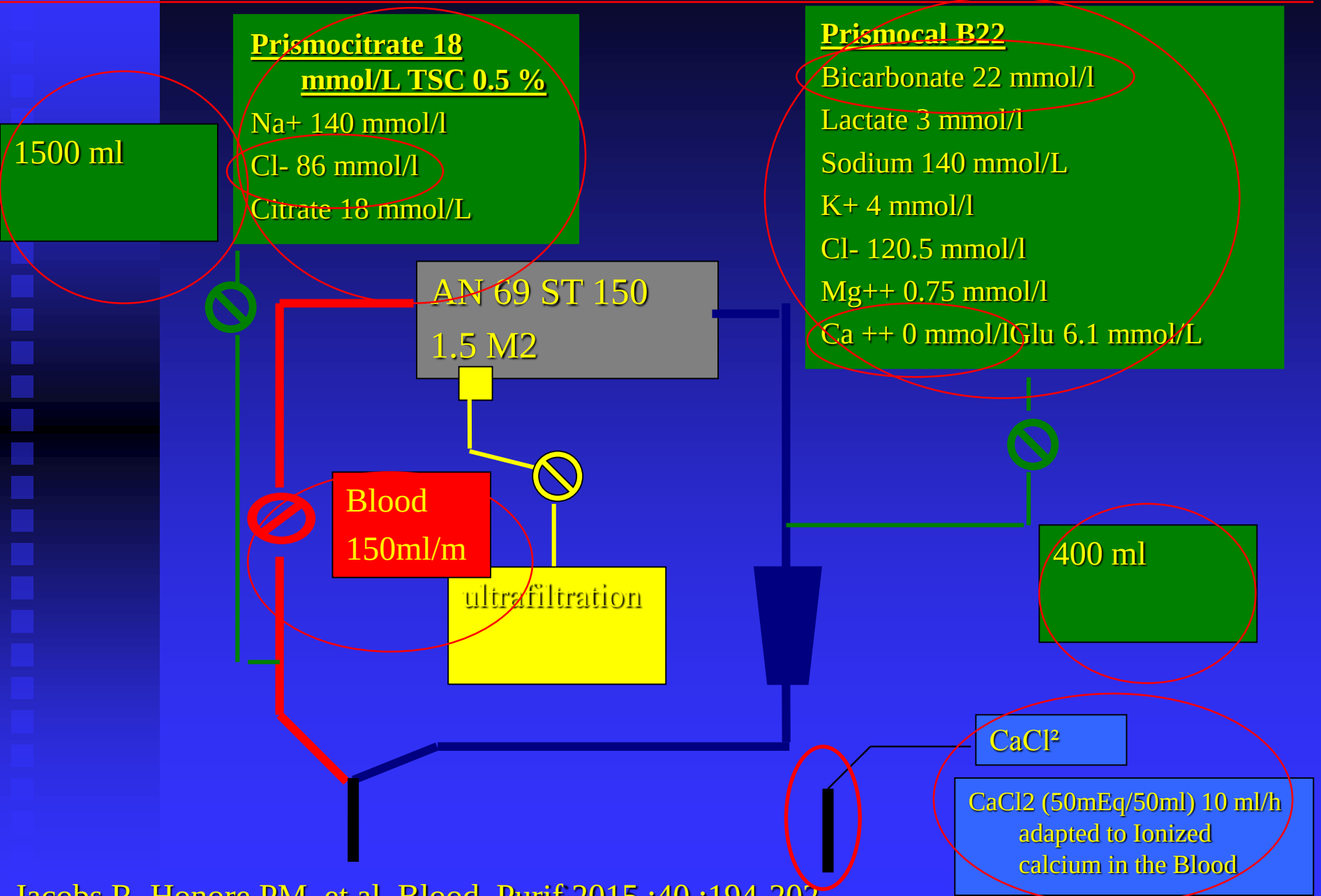
Table 2. Comparison of CVVHDF protocols using regional citrate anticoagulation[a]

Author, Year	Patient	BFR (ml/min)	Citrate Solution (mM/L)	Citrate Rate	Replacement Solution (mM/L)	Replacement Solution Flow Rate	Dialysate Composition (mM/L)	D Rate	Ca Solution (mM of Elemental Ca/L)	Ca Rate	Circuit Survival Time 48 h	No. of CRRT Solutions
Mehta *et al.*, 1990 (10)	18	100	TSC$^+$ 4% Citrate 140 Na 408	140 to 220 ml/h (19.6 to 30.8 mM/h)	Prefilter: NS 0.9% Postfilter: NS 0.9% and Variable	Prefilter: 500 ml/h Postfilter: 0.2 to 1.5 L/h	Na 117 Cl 81 to 121 K 0 to 4 Mg 1 Dextrose 0.1% HCO_3 0 to 40	1 L/h	CaCl 0.8%	40 to 60 ml/h	68%	5
Kutsogiannis *et al.*, 2000 (9)	9	100 to 125	TSC 4% Citrate 140 Na 408	140 to 190 ml/h (19.6 to 26.6 mM/h)	Prefilter: Na 150.3 Cl 121 HCO_3 33.3 K 3 to 4 Mg 0.7	Prefilter 1 to 1.5 L/h	Na 117 Cl 121.5 K 3 to 4 Mg 0.7	1 to 1.5 L/h	CaCl 0.75%	40 to 60 ml/h	68%	4
Gabutti *et al.*, 2002 (6)	12	150	Citrate 13.3 Na 139.9 Mg 0.75 (K as needed)	1.5 L/h (23 mM/h)	See citrate solution	See citrate solution	Citrate 13.3 Na 139.9 Mg 0.75 (K as needed)	500 ml/h	5% CaCl or 350 mM/L	Mean rate: 10 ml/h or 3.31 mM/h	15%	3
Dorval *et al.*, 2003 (7)	14	125	Hemocitrasol-20 Na 145 Citrate 20 Glucose 10 (K and PO4 as needed)	1.25 L/h (25 mM/h)	See citrate solution	See citrate solution	(Dialysate added in only 27% patients) NS 0.9% Na 154	1 L/h as needed	Mg 16 mM/L and 7% CaCl 70 mM/L	50 ml/h or 3.5 mM/h	50%	3
Tobe *et al.*, 2003 (8)	15	100	ACD-A Citrate 113 Na 224	150 ml/h (17 mM/h)	Prefilter: NS 0.9% or 0.5 NS	0 to 1 L (started for $HCO_3 > 25$	Normocarb® Na 140 HCO_3 35 Cl 106.5 Mg 0.75 (K as needed)	1 to 1.5 L/h	CaCl 4 g in 1 L of D_5W	50 ml/h	approx. 50%	4
Cointault *et al.*, 2004 (5)	17	125	ACD-A Citrate 113 Na 224	250 ml/h (30 mM/h)	Prefilter: Hemosol and Hemosol with Bicarbonate Na 144 HCO_3 35 Lactate 3 Mg 0.5 Calcium 1.75 (mixture of two solutions)	1.2 L/h	Hemosol and Hemosol with Bicarbonate Na 144 HCO_3 35 Lactate 3 Mg 0.5 Ca 1.75 (mixture of solutions are varied to adjust bicarbonate)	1.2 L/h	CaCl 45.6 mM/L	30 ml/h or 1.37 mM/h	41%	4
Tolwani *et al.*, 2005 (15)	32	100 to 150	TSC 0.5% Citrate 18 Na 140	1 to 1.5 L/h (18 to 27 mM/h)	See citrate solution	See citrate solution	Na 140 K 4 HCO_3 25 Mg 0.58 (similar solution commercially available)	1 to 2 L/h	Ca gluconate 38.75 mM/L	60 ml/h or 2.3 mM/h	82%	3

[a]BFR, blood flow rate; D, dialysate; TSC$^+$, trisodium citrate; ACD-A, anticoagulant citrate dextrose solution, Formula A.

Tolwani A et al.CJASN 2006 ;1 : 79-87

Citrate 0.5 %: The VUB CVVH Protocol:Only 2 Solu



Jacobs R, Honore PM et al. Blood Purif 2015 ;40 :194-202

Advantages of Citrate in Predilution

- We used Standardized Commercially Available Solutions(less risk of errors as compared to Home Made)
- Electrolytes are at Physiological [], accidental interchanges (of solutions)will have negligible consequences
- Only Two Solutions are needed and thus reducing the risk of errors (VUB Protocol)
- The use of Diluted Citrate (0.5 %) do reduce dramatically the risk of Error (eg: TSC 4 % increase from 200 to 1000 ml !!!!)
- Still the same efficacy as the TSC 4 % and ACDA 3 %

Jacobs R, Honore PM.Citrate in CRRT.Lambert Academic Publishing-Released in Feb 2016

Monitoring during RCA CRRT

- Blood: Every 4 hourly and latter 6 or 8 hourly
  - Na, K, iCa++ (> 1.1 mmol/L or > 4 mg/dl), ABG
  - pH > 7.25 & < 7.45 –Lactate-
- Every 12 hours
  - Total calcium, phosphate & magnesium
  - Total Calcium (< 2.5 iCa) /corrected < 3 mmol/L)/Citrate Gap
- Post-Filter: Every 4 hourly and latter 6 or 8 hourly
  - Post-filter ionized Ca++ (0.25 to 0.35 mmol/L or below 1.3 mg/dL)
- Why Monitoring of iCa in the Filter ?
  - Need of Citrate differs from Patient to Patient
  - Can increase Filter lifespan as shown in some studies
  - Can Detect Early on Citrate Accumulation
  - Adopted by ADQI XVII-Asiago June 2016

Jacobs R, Honore PM et al. Blood Purif 2015 ;40 :194-202

Citrate Intoxication with New Formulations(0.5 %)

- Dramatic Fall in Ionized Calcium with Cardiac Arrest is not anymore the rule..
- The use of Diluted Citrate (0.5 %) do reduce dramatically the risk of Error (eg: TSC 4 % increase from 200 to 1000 ml !!!!)
- Decrease Ionized calcium will induce (when above 12 mg/dL /3mmol/L (corrected)) encephaopathy, epilepsy, HTA, AKI and PRES syndrome….

Au S et al.IJAO 2012;35:538-541

Citrate Accumulation during RCA CVVH

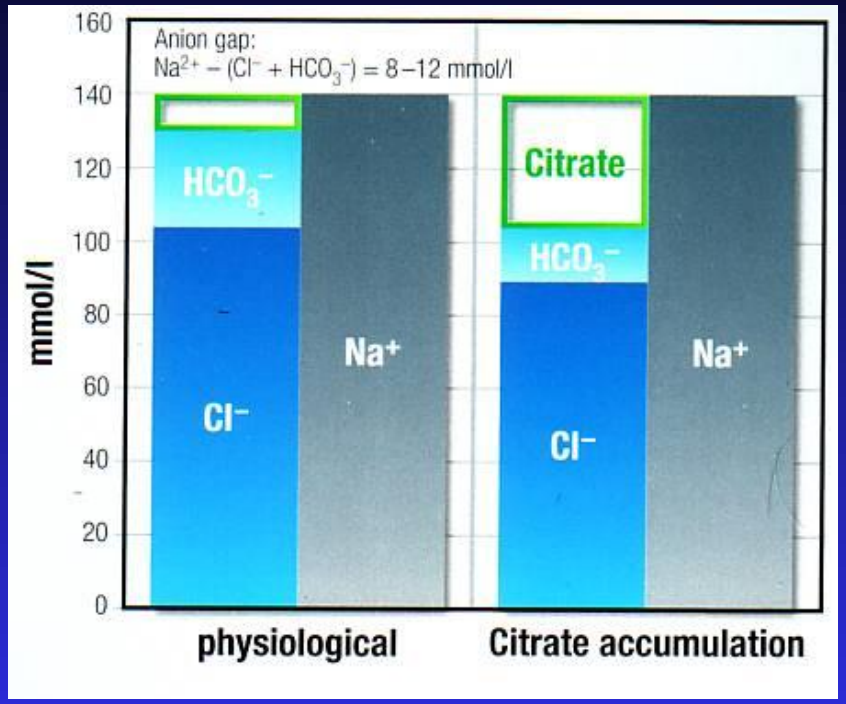
- Metabolic Acidosis Slow to Correct
- Hypernatremia:No anymore
- Hypocalcemia/Hypercalcemia
- Hypomagnesemia/hypok
- Citrate Accumulation:

-Hypercalcemia(Blood)

- Catot/iCa²+ > 2.5 (Citrate G)

-Metabolic Acidosis with High Anion Gap –Incr Lactate

-Citrate Level > 28.8 mg/dL

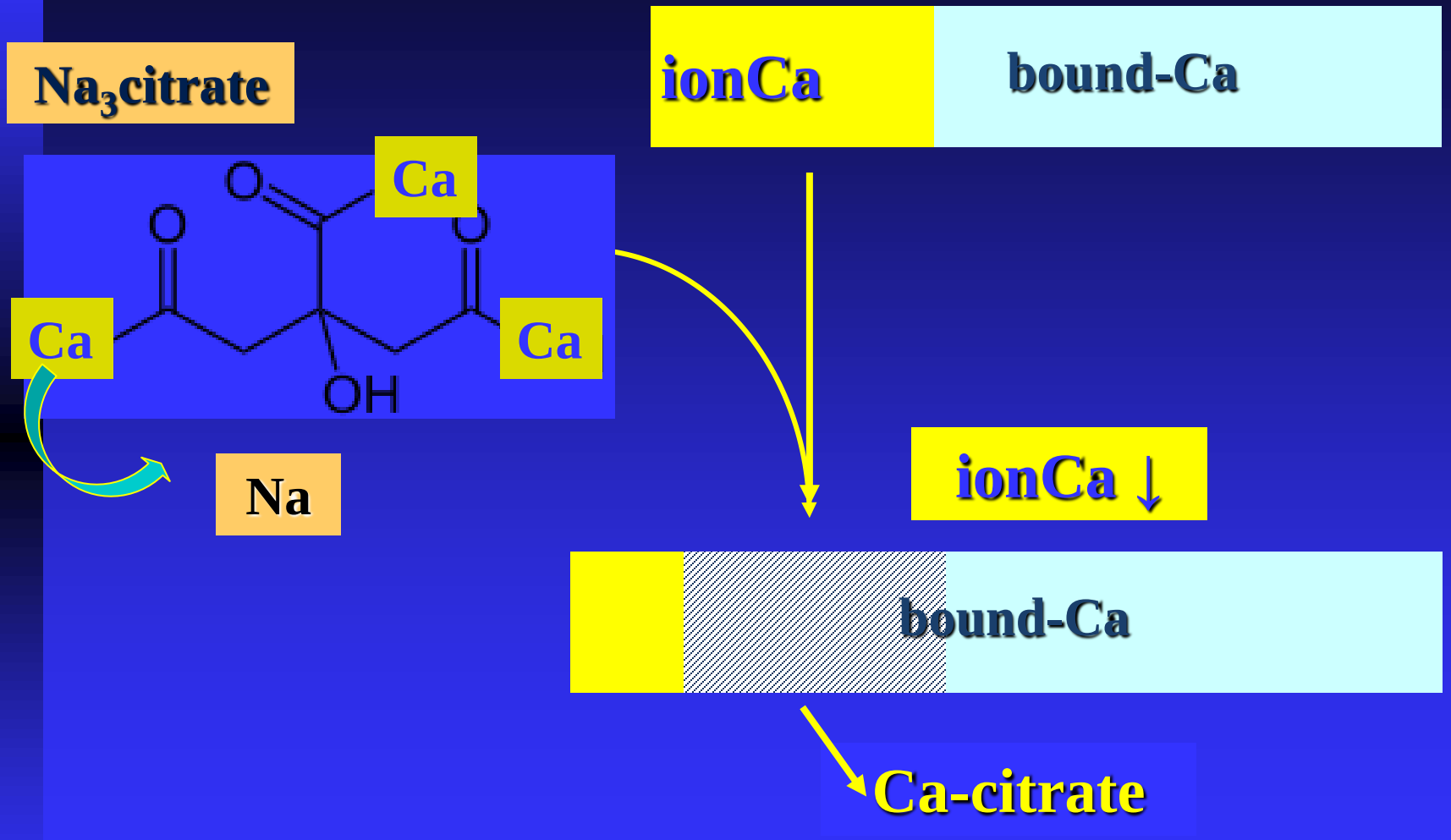


Catot/iCa²+ > 2.5

Jacobs R, Honore PM et al. Blood Purif 2015 ;40 :194-202

Mariano F et al.ICM 2010;36:1735-43

Metabolism of Citrate :Accumulation



Kishen R, Honore PM, Jacobs R et al.Int J Nephrol Ren Dis 2014;40: 194-202

Citrate: Alkalosis or Acidosis?

Look at SID!

Citrate is metabolized

$$SID = (Na^+ + K^+) - (Cl^- + \cancel{citrate^{3-}} + lactate^- + ..)$$

SID ↑ → alkalosis

Citrate is not metabolized

$$SID = (Na^+ + K^+) - (Cl^- + citrate^{3-} + lactate^- + ..)$$

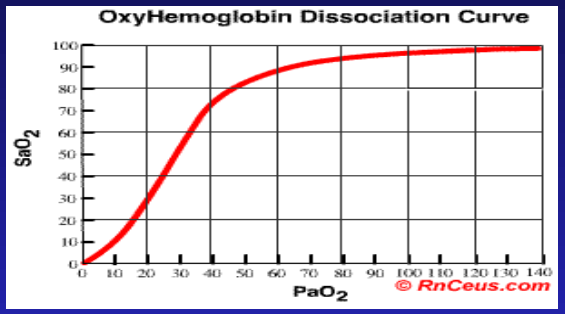
SID ↓ → acidosis

Fencl V et al.AJRCCM 2000;162:2246-2251

Oudemans van Straaten HM et al.Crit Care 2012 ;16:-24

Late Metabolic Alkalosis

- More Citrate is Metabolized into Bicarbonate (1 mol of Citrate is giving rise to three mol of Citrate)
- Start generally after 24-36 Hours…
- Mild : pH > 7.45/BE > + 3
- Severe: pH > 7.55/BE > + 10
- Extreme : pH > 7.65/Bicar > 40 mmol (Mortality can reach 50 to 80 %-Left shift –Tissue Hypoxia)
- If Not Corrected & Remains Severe, Therapy has to be Stopped..
- If Steward is used, SIDa > 45 can detect > 95 % of Metabolic Alkalosis instead of only 10 % when using pH > 7,5 after 24 H…

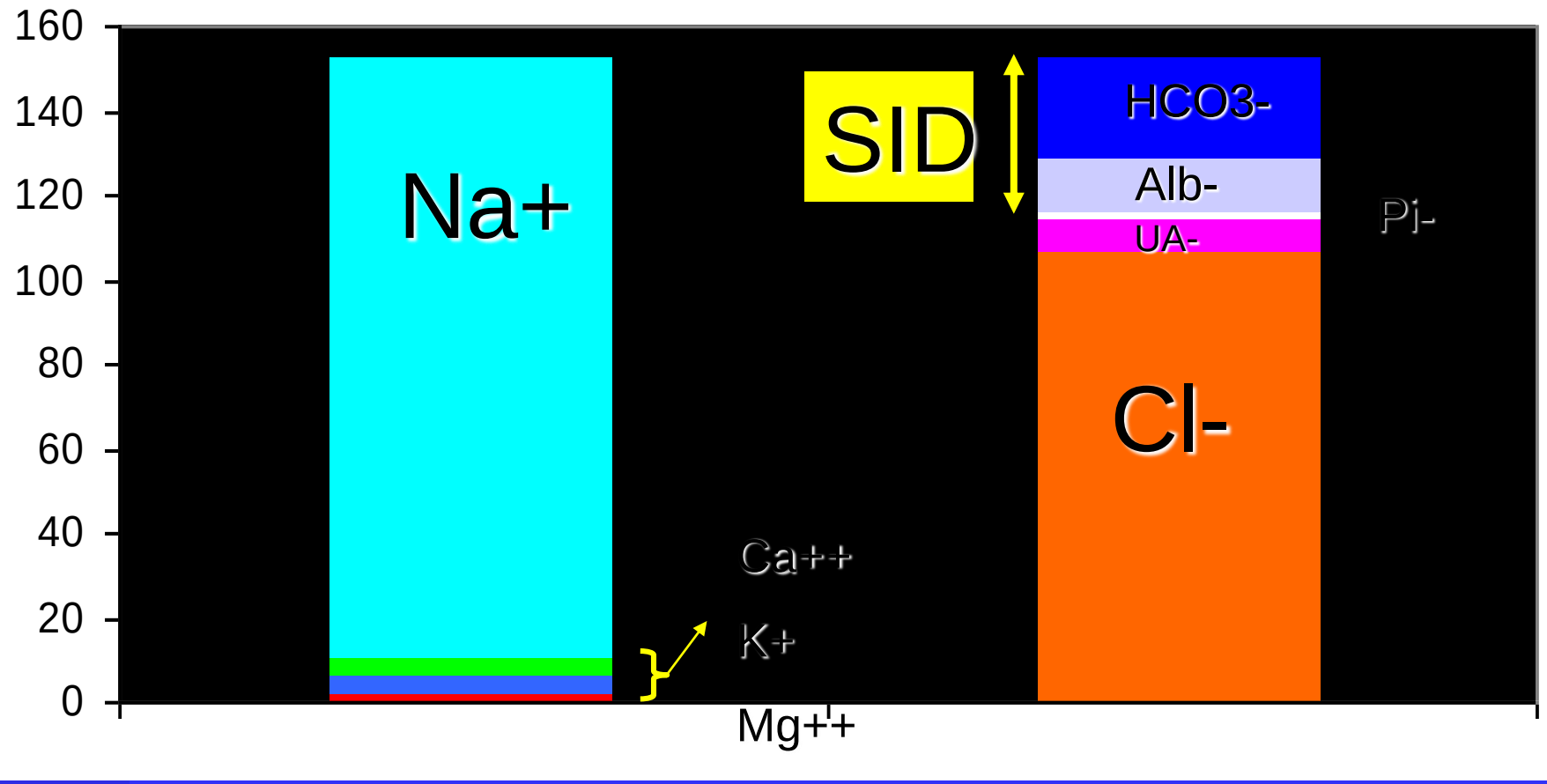


Tripathy S.Indian Crit Care Med 2009;13:217-220

Honore PM et al.Crit Care Med 2008;36:1665-1666

Jacobs R, Honore PM et al.BMC Nephrol 2016;17:119-

Plasma Electro-Neutrality



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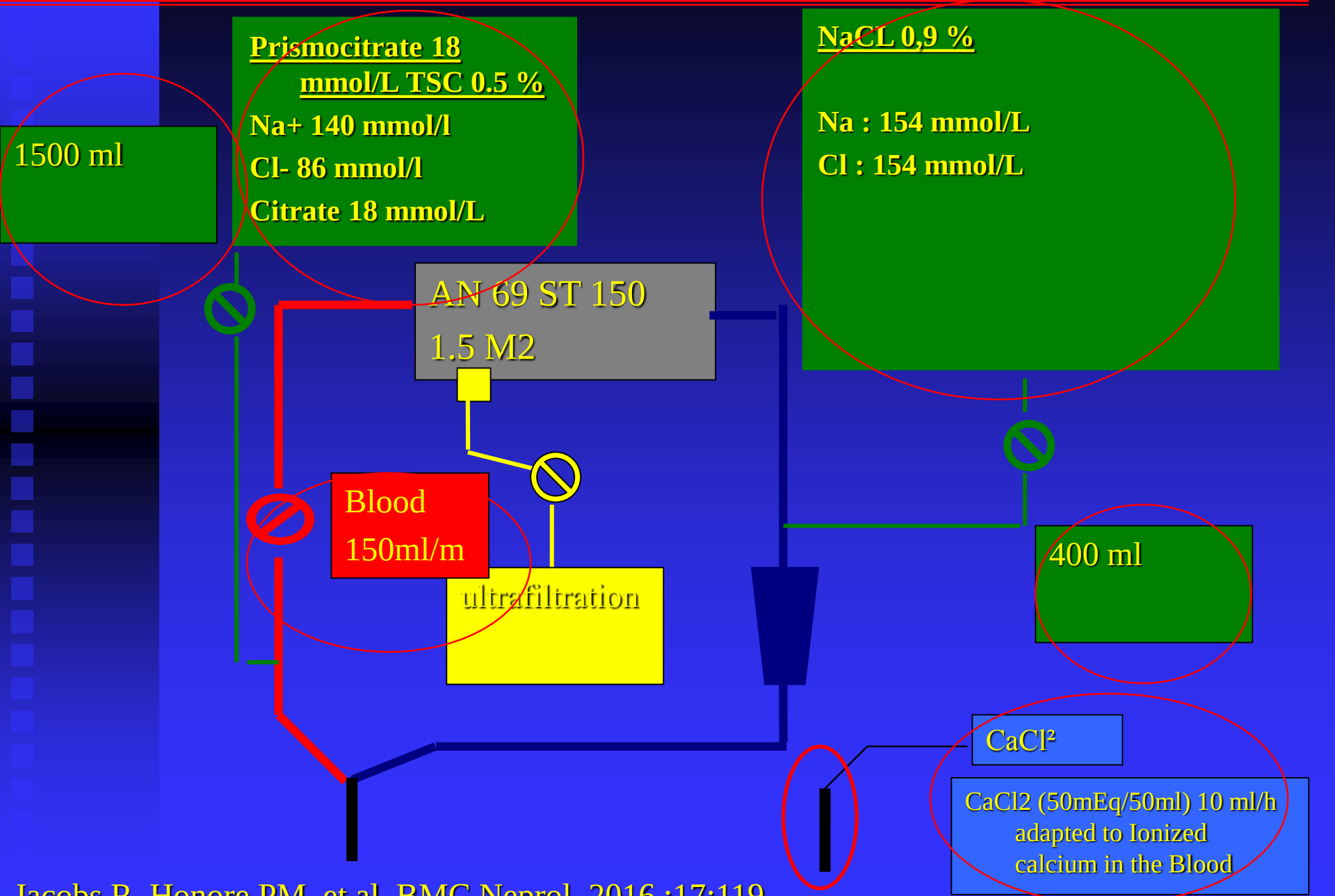

Jacobs R, Honore PM et al. BMC Neprol 2016 :17:119-

Calcium infusion MUST via **CVC** !!

One lumen of the CVC is occupied

Calcium extravasation causing tissue necrosis

Conclusions & Perspectives

- New Diluted Citrate Formulations are Now Commercially Available (and not anymore homemade)
- Electrolytes at Physiological [],Diluted Citrate (0.5 %) and only Two Solutions do reduce Dramatically the Risk of Errors and Dangerous Side Effects..
- We did Chose to go for a Monitored System as this will allow us to adapt to each patient and also to detect Citrate Accumulation..Also Recommended by ADQI XVII
- The VUB Protocol do Use: Diluted Citrate 0.5, CVVH, only 2 bags, monitoring & dose of 35 ml via a sliding scale
- Increase Chloride Concentrations will Fix Metabolic Alkalosis Induced by CRRT with RCA and PC 18