king

Karolinska intensive care nephrology group

Citrate

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The goal with this lecture

1. Why is regional anticoagulation better than whole-body-anticoagulation? Citrate vs heparin…
2. How does citrate work?
3. What is CVVHD-F and where does citrate come in?
4. Can citrate spill over into the patient? How do we detect it?

Background

Dilemma!

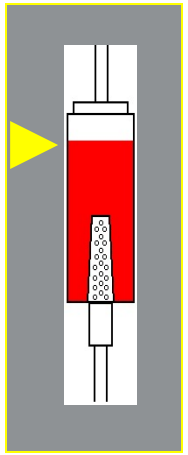
Clotting filters

Bleeding

Why anticoagulation?

Activation of coagulation

- Blood pump
- Blood-membrane
- Blood-air
- Turbulent flow (cathether, tubings)



Why not heparin?

Biggest heparin drawback: it causes systemic anticoagulation!

So heparin increases the **bleeding risk** of the patient

Critically ill patients already have increased risk of bleeding due to surgery, trauma, mucosal injuries and coagulopathy

More or less severe bleeding is reported in **10-50%** of all ICU cases, depending on population and choice of anticoagulation

Van de Wetering J et al:**Heparin use in continuous renal replacement procedures: the struggle between filter coagulation and patient hemorrhage.** *J Am Soc Nephrol* 1996, **7:**145-150; Oudemans-Van Straaten HM et al. **Anticoagulation strategies in continuous renal replacement therapy: can the choice be evidence based?** *Intensive Care Med* 2006, **32:**188-202

Why not heparin?

Heparin binds to antithrombin (AT), potentiating its anticoagulation effect AND inhibiting its anti-inflammatoric effect

Anti-inflammatory effects of AT are exerted through binding to glucosaminoglycans on endothelial membranes, enhancing the formation of prostacyclin

The binding of AT to glucosaminoglycans diminishes the adherence and migration of leukocytes, reduces platelet aggregation and decreases proinflammatory cytokine production**. Heparin binding to AT abolishes this effect**

Warren BL et al:**Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial.** *JAMA* 2001, **286:**1869-1878; Leithauser B et al: **Antithrombin attenuates microvascular leakage and leukocyte- endothelial interaction in response to endotoxin.** *Semin Thromb Hemost* 2002, **28**(Suppl 1)**:**87-94.

Why not heparin?

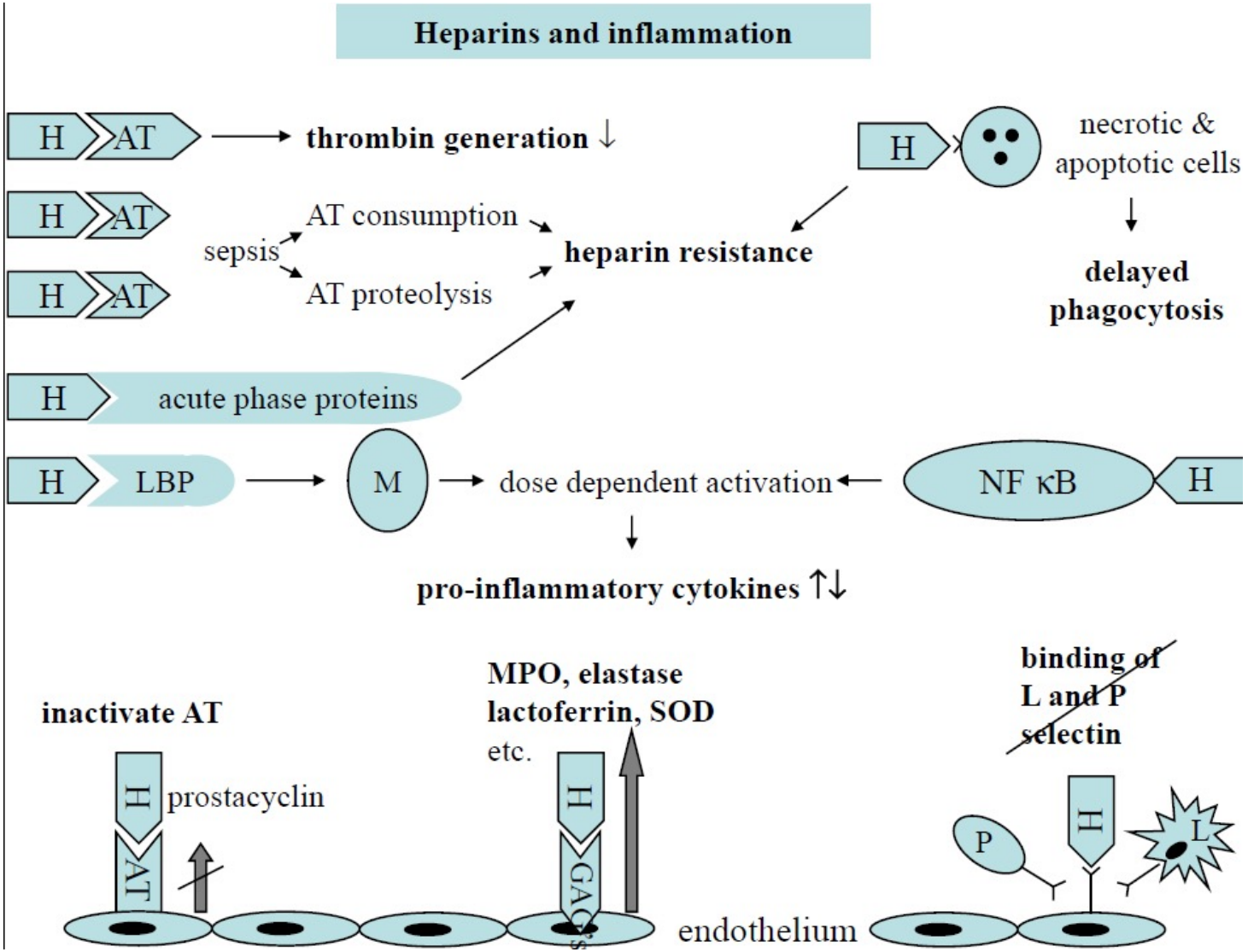
Heparin, normally potentiating AT, inactivates AT in the presence of elastase. This process leads to proinflammatory and procoagulant effects on the endothelium in sepsis, **which may compromise the microcirculation and threaten tissue perfusion** Jordan RE et al.: **Antithrombin inactivation by neutrophil elastase requires heparin.** *Am J Med* 1989, **87:**19S-22S.

Heparin may thus have adverse effects on the micro-circulation in sepsis. Hoffmann JN et al: **Adverse effect of heparin on antithrombin action during endotoxemia: microhemodynamic and cellular mechanisms.** *Thromb Haemost* 2002, **88:**242-252; Heinzelmann M et al: **Heparin binds to lipopolysaccharide (LPS)-binding protein, facilitates the transfer of LPS to CD14, and enhances LPS-induced activation of peripheral blood monocytes.** *J Immunol* 2005, **174:**2280-2287

Why not heparin?

Depending on the dose and type of heparin, on the population and on the criteria used for diagnosis, **<1 to 5% of heparin-treated patients develop heparin-induced thrombocytopenia** Verma AK et al: **Frequency of heparin-induced thrombocytopenia in critical care patients.** *Pharmacotherapy* 2003, **23:**745-753; Selleng K et al: **Heparin-induced thrombocytopenia in intensive care patients.**

Crit Care Med 2007, **35:**1165-1176; Selleng S et al:**Heparin-induced thrombocytopenia in patients requiring prolonged intensive care unit treatment after cardiopulmonary bypass.** *J Thromb Haemost* 2008, **6:**428-435.



Oudemans-van Straaten *et al. Critical Care* 2010 **15**:202

	HEPARIN	CITRATE
Clinical		
Anticoagulation	Regional and systemic	Regional, not systemic
Risk of bleeding	Higher	Not increased
Circuit life	Similar or shorter	Similar or longer
Metabolic control	Good	Good if well performed
Metabolic derangements		Greater risk if not well controlled
Understanding	Easy	Difficult
Life-threatening complications	Massive bleeding	
	Heparin-induced thrombocytopenia (UFH >LMWH)	Cardiac arrest due to unintended rapid infusion
Clinical outcome		Possibly better patient* and kidney survival

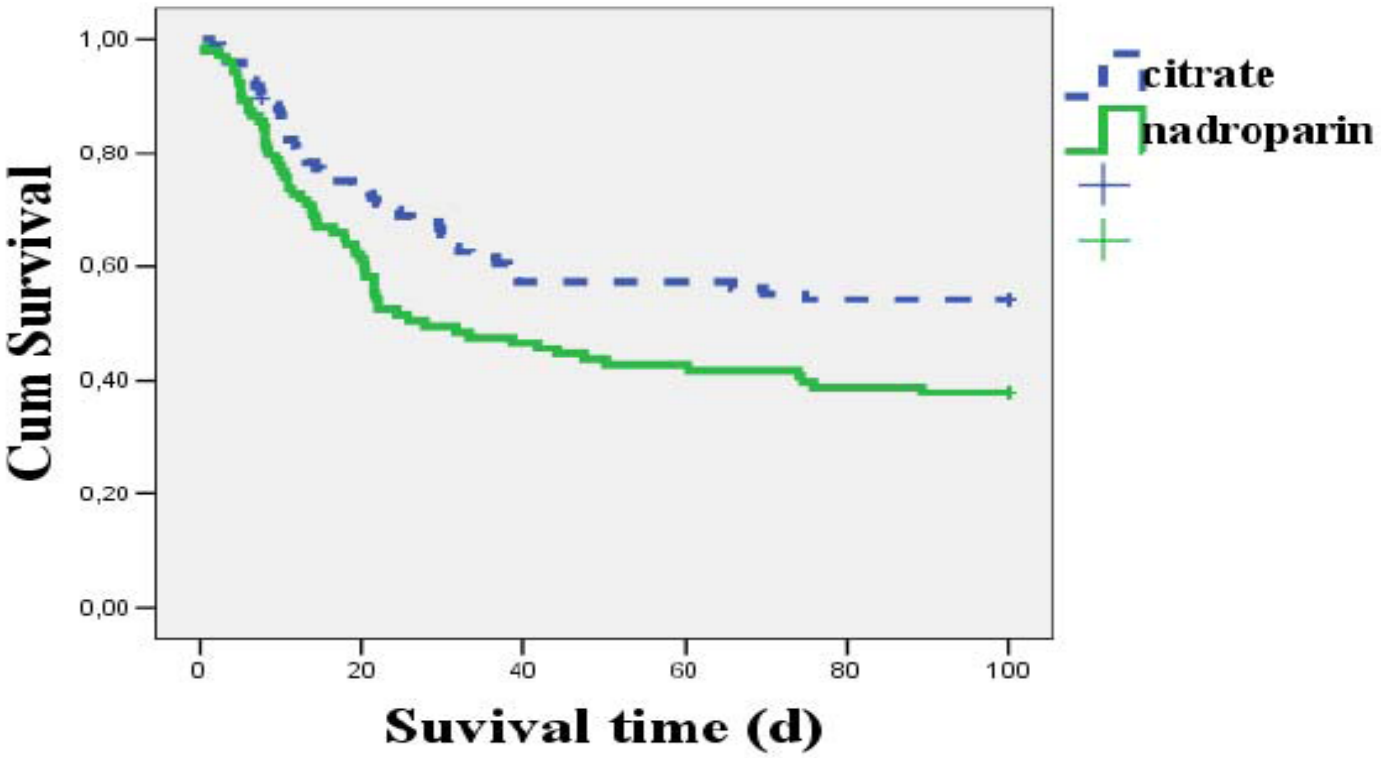
Oudemans-van Straaten *et al. Critical Care* 2010 **15**:202

Better survival with citrate?

	citrate	nadroprin	
All randomized patients	n=107	n=108	P
Mortality hospital	42%	57%	0.02
Mortality 3-months	48%	63%	0.03
Per protocol patients	n=97	n=103	
Mortality hospital	41%	57%	0.02
Mortality 3-months	45%	62%	0.02

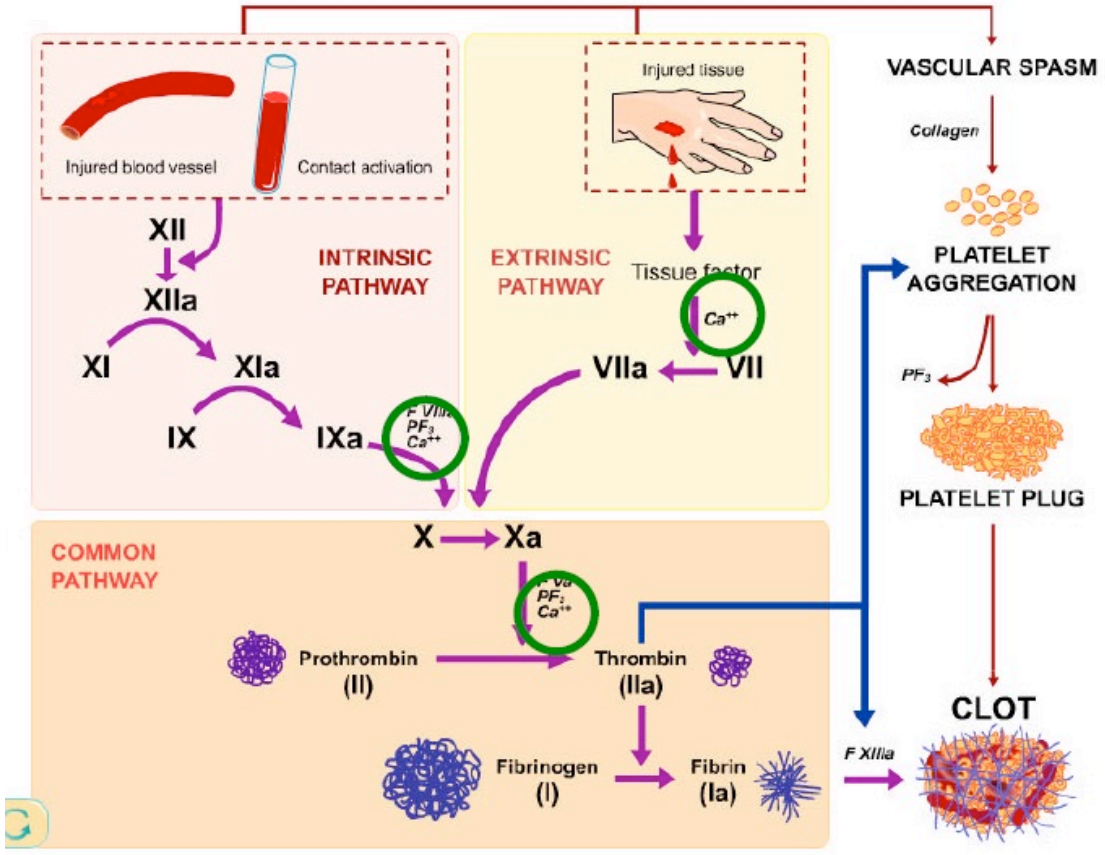
Oudemans-van Straaten *et al.* *Crit Care Med* 2009, **37:**545-552

Better survival with citrate?



Oudemans-van Straaten *et al.* *Crit Care Med* 2009, **37:**545-552

Background (2)



Background(3)

Calcium is involved in the coagulation on multiple levels.

Albumin-bound Calcium is not filtrated or dialysed, but free and ligand-bound (citrate-bound) is. Only free Calcium is active in the coagulation system

Normally 47% is ionized and free, 40% is albumin-bound and 13% is ligand-bound. **Since citrate binds calcium, addition of citrate to the blood impedes coagulation**. Less calcium is free; more is ligand-bound and inactive

Background(4)

Infusing a citrate-enhanced solution in the pre-blood-pump (PBP) allows for a **regional anticoagulation in the machine**. No systemic anticoagulation in the patient!

Citrate binds ionized calcium; the concentration of free calcium drops and coagulation is hindered

A citrate-calcium complex is formed but **30-60 % of that citrate-calcium-complex is dialyzed/filtered** and the rest is returned to the patient. Intravenous Calcium (like: Calcium-Sandoz®) is given to avoid hypocalcemia

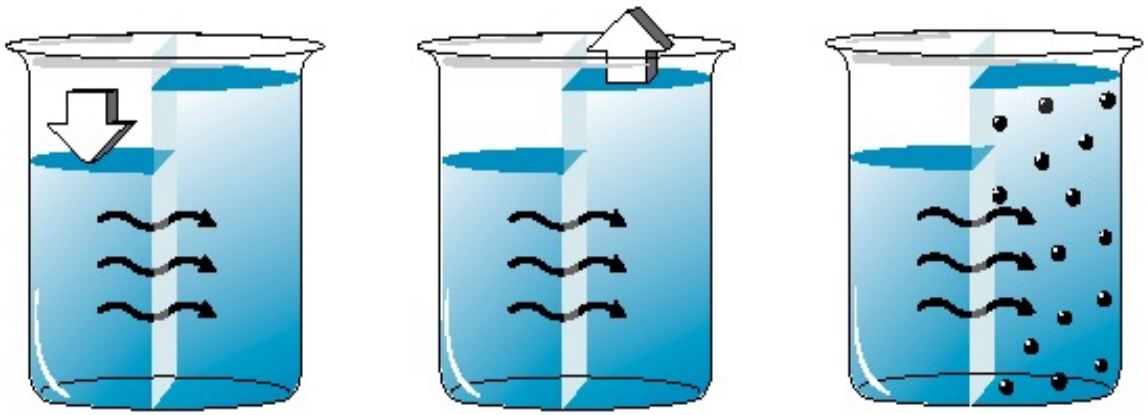
Quick break to understand RRT

Renal replacement therapy (CVVHD-F, Baxter style) uses four physical principles

1. Ultrafiltration
2. Diffusion
3. Convektion
4. Adsorption

1. Ultrafiltration

Ultrafiltration : Transporting fluid through a membrane utilizing a pressure gradient (TMP) – we use it to remove excess fluid from a patient

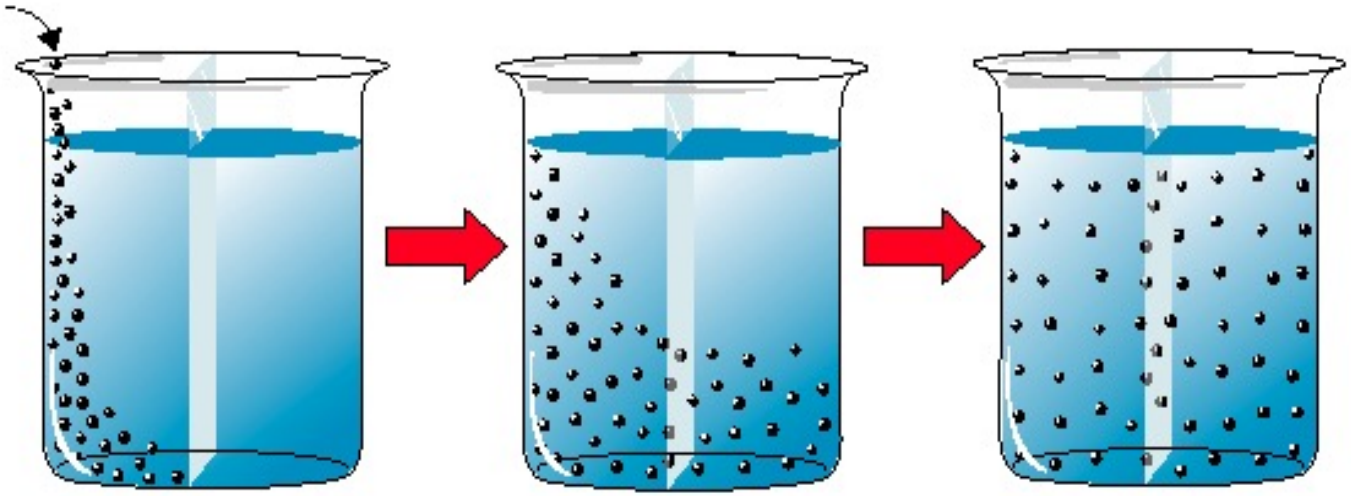


a) **positive pressure** b) **negative pressure** c) **osmotic pressure**

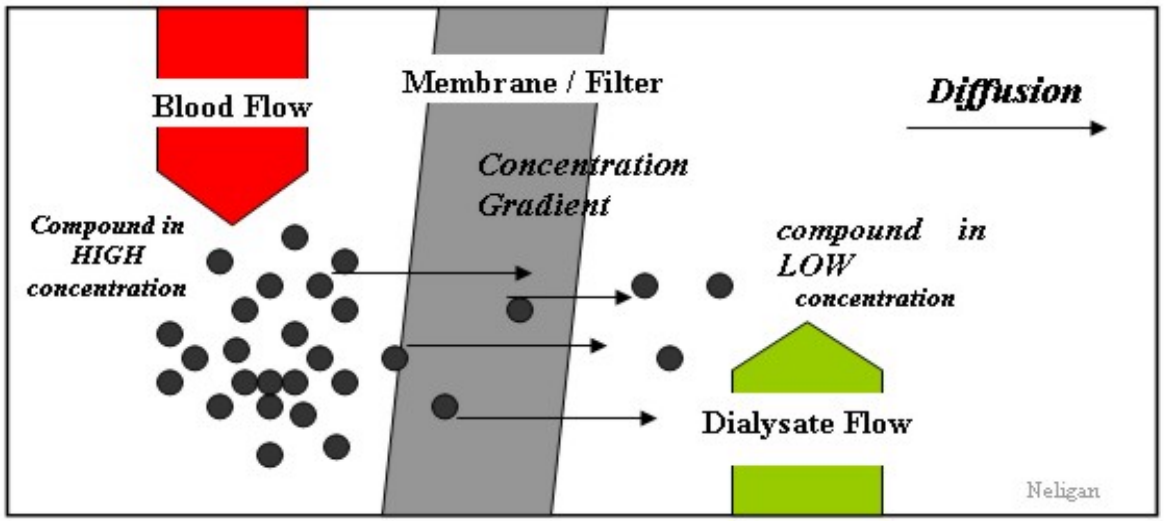
2. Diffusion

Diffusion : Molecules move from an area with high concentration to low concentration through a membrane

Most effective for small molecules, like urea and electrolytes such as potassium, K^+



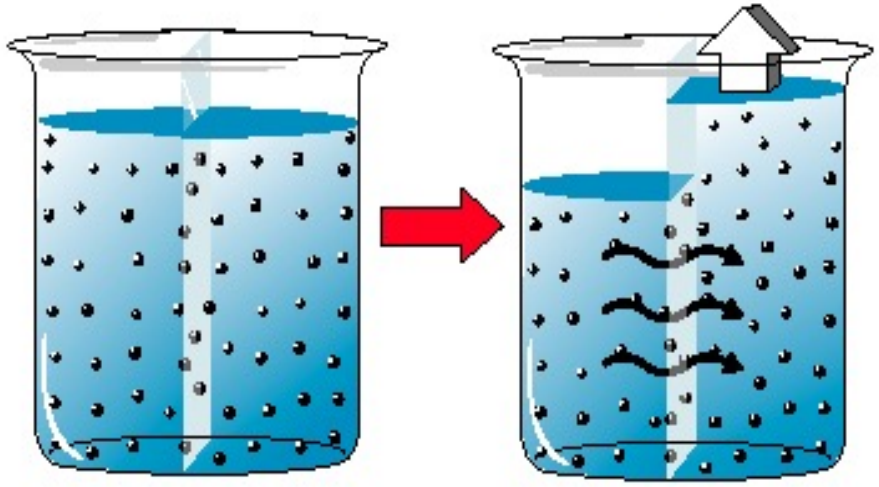
2. Diffusion=dialysis



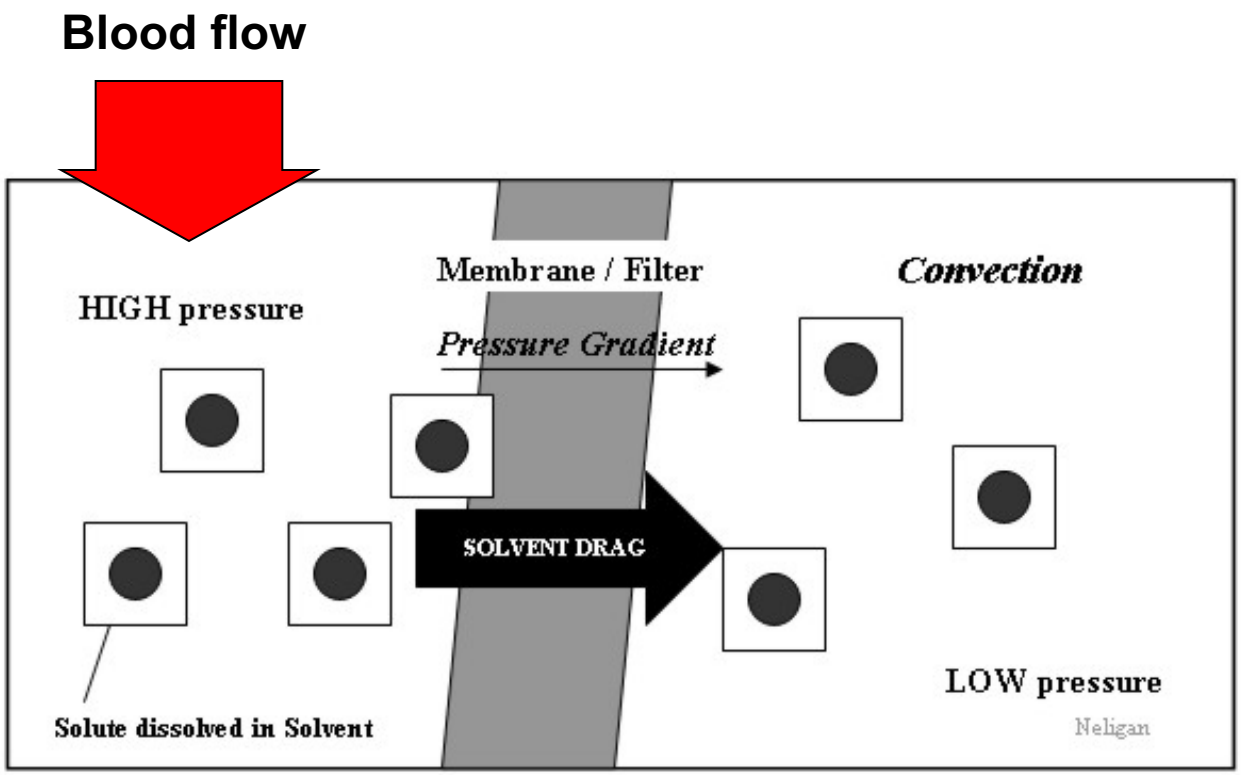
3. Convection

Molecules move with a water flow through a membrane, “solvent drag”

Better for removal av midsize/larger molecules (like myoglobin)



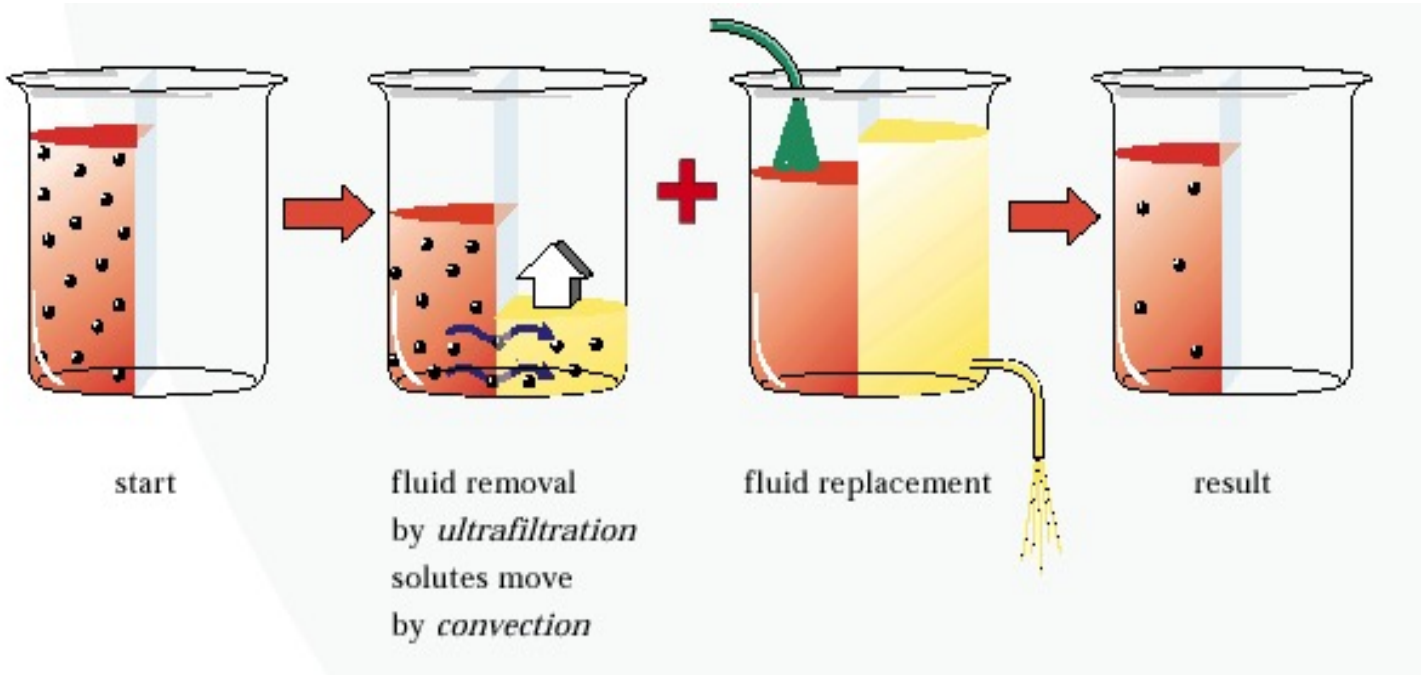
3. Convection – TMP is used



TMP

(**trans**membrane**p**ressure)

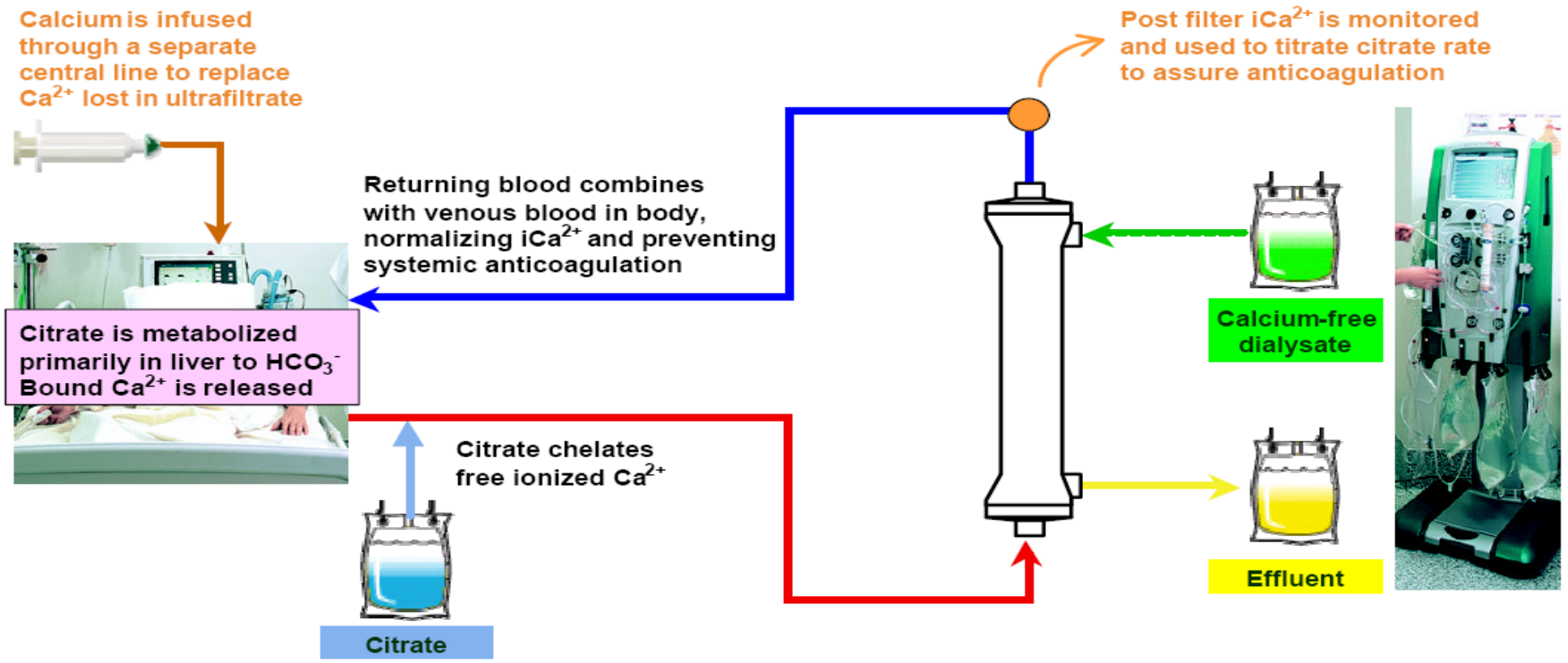
3. Convection – citrate!



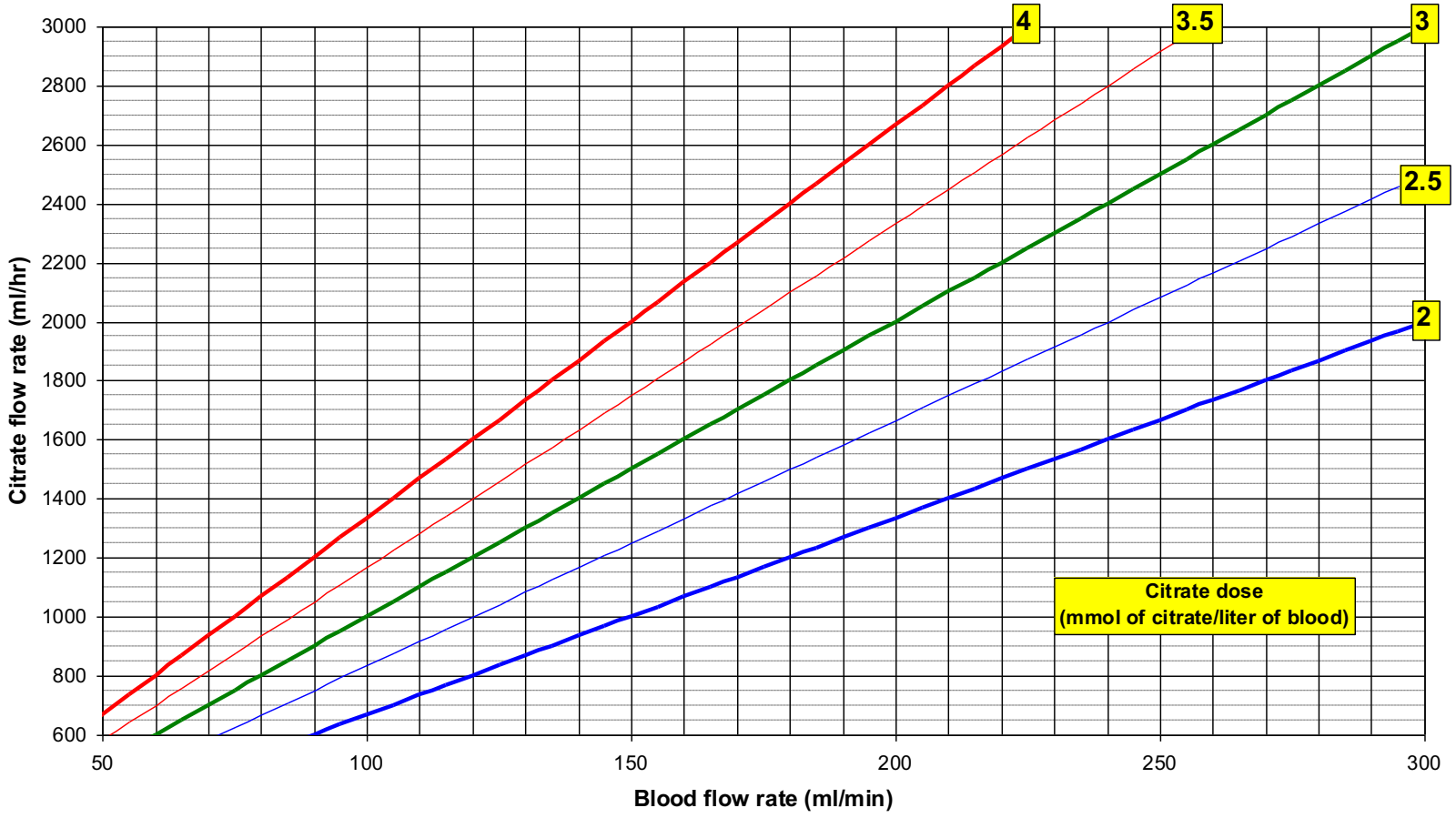
Summary

Citrate anticoagulation

- **Action in circuit - Summary**



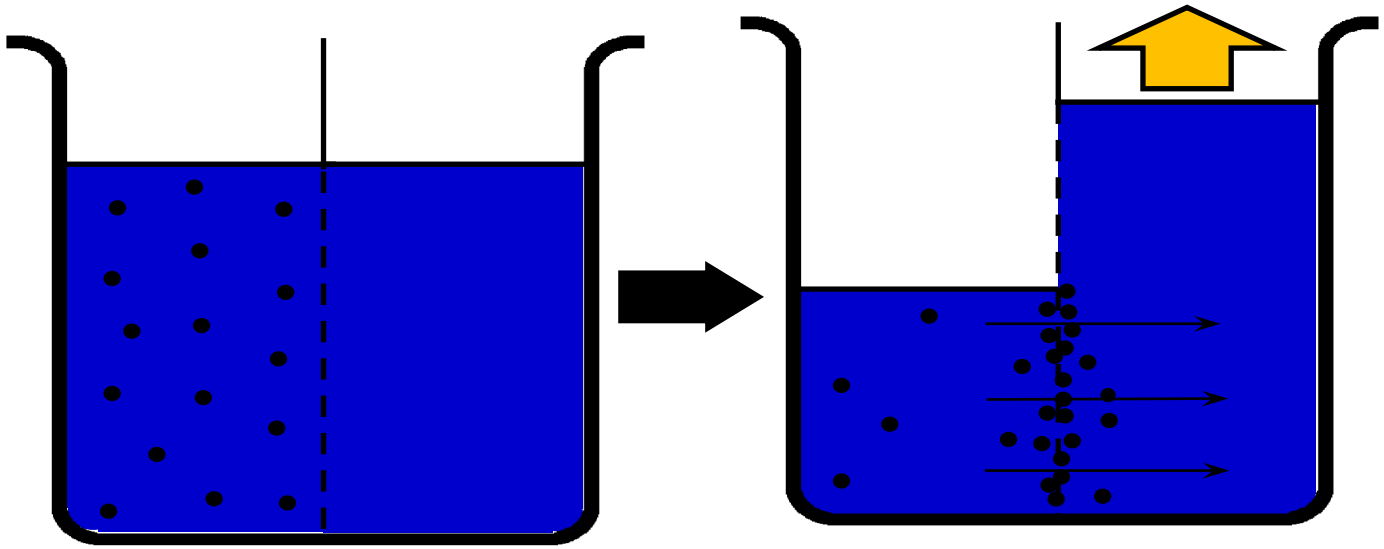
Citrate dose using Regiocitrate18/0



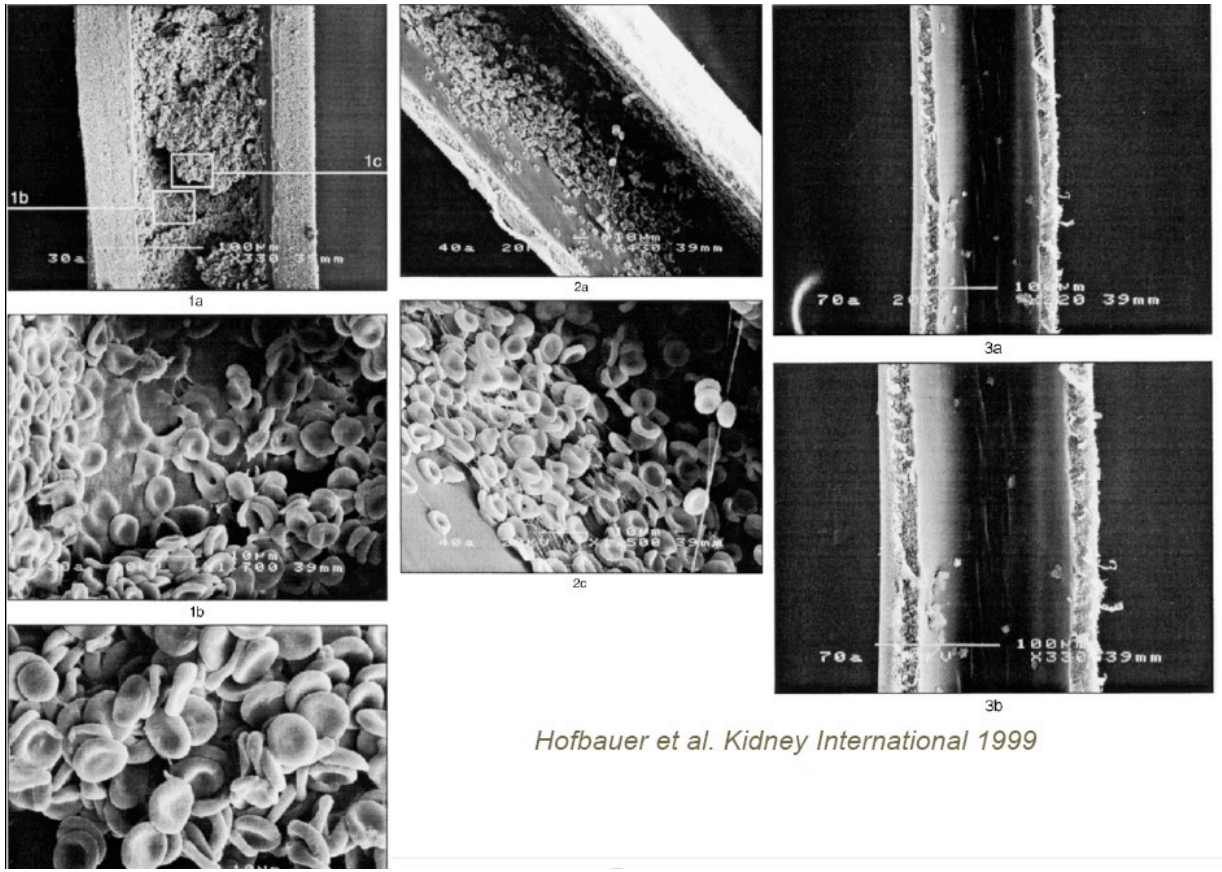
4. Adsorbtion (like Oxiris)

Adsorption: Molecules adhere to the membrane (inside or on the surface)

Works best for larger molecules



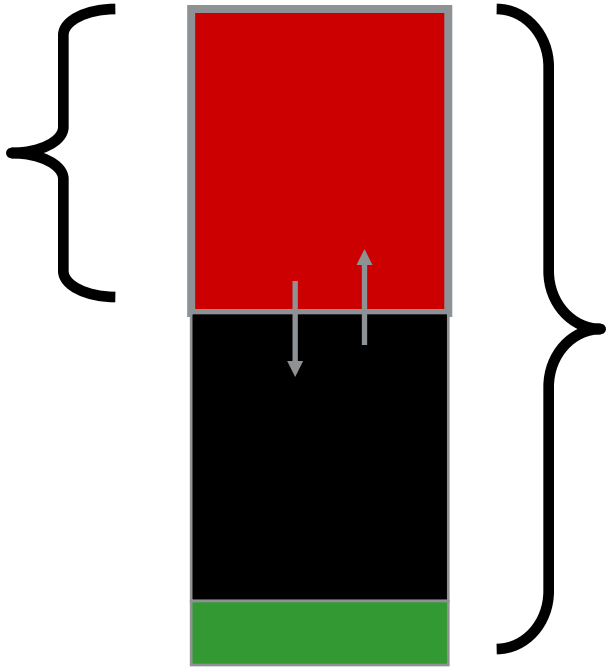
Heparin compared to citrate



Hofbauer et al. Kidney International 1999

Calcium distribution

Ionized Calcium:



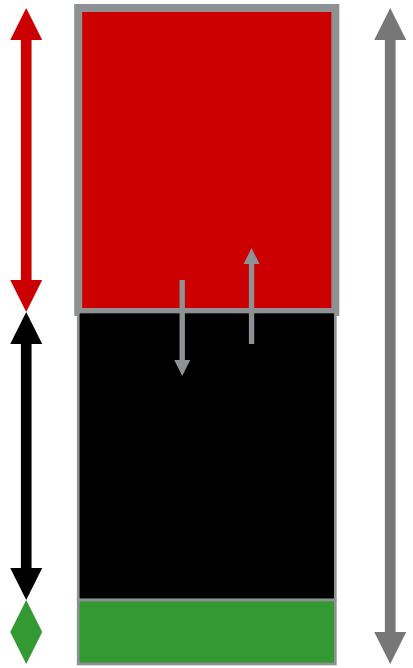
Total Calcium:

Calcium in Plasma

Ionized Ca (~50%)
~ 1.17 – 1.3 mmol/L

Protein bound Ca (~40%)
~ 0.95 – 1.2 mmol/L

Complex bound Ca (~10%)
~ 0.05 mmol/L



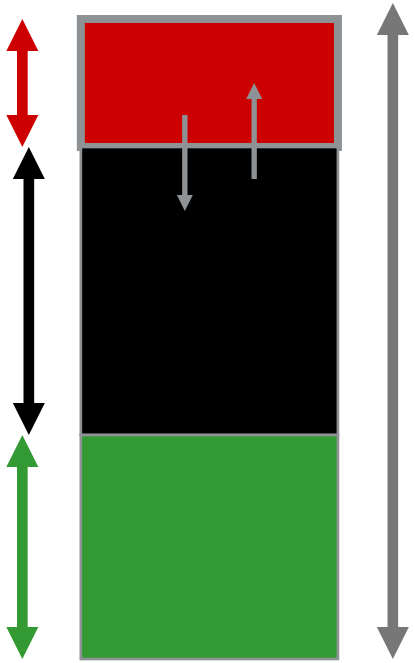
Total Ca
~ 2.2 - 2.6 mmol/L

Calcium with Citrate➔

Ionized Ca (~25%)
~ 0,3 – 0,4 mmol/L

Protein bound Ca (~40%)
~ 0.95 – 1.2 mmol/L

Complex bound Ca (~35%)
~ 0.175 mmol/L

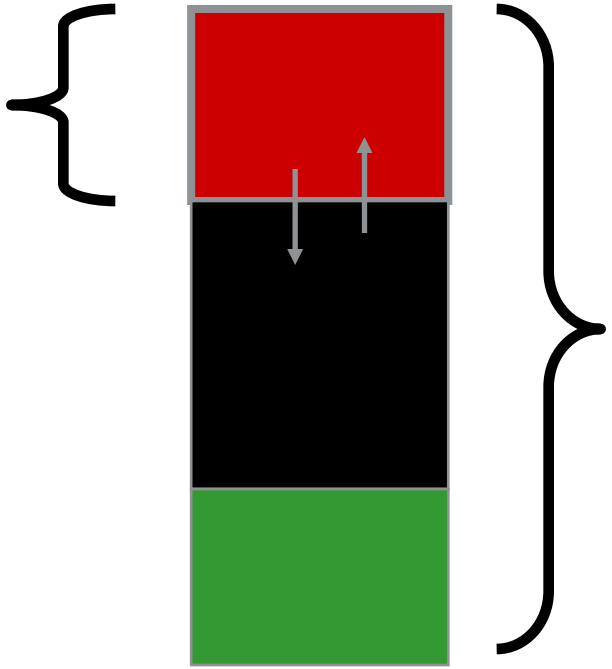


Total Ca
~ 2.2 - 2.6 mmol/L

Is Citrate metabolised?
Calcium gap

Ionized Calcium:

Plasma concentration ↓



Total Calcium:

$$\frac{Ca_{tot}}{Ca_{Ion}} = \uparrow$$

- **Ratio total-Ca (=S-Ca)/ ionized Ca should not surpass 2.5**

Ordinationsjournal för CVVHDF via Prismaflex

År		CDK		Pat id
Antikoagulantia	**Modalitet**	**Indikation**		
Citrat ☐	CVVHDF ☐	Uremi ☐		
Heparin ☐	CVVH ☐	Anuri ☐		
Ingen ☐	CVVHD ☐	Hypervolemi ☐		
Annat:	SCUF ☐	Elektrolytrubbning ☐		
		Acidos ☐		
		Sepsis ☐		
		Hypertermi ☐		

Startvärden	Datum								
	Tid								
	Aktuell vikt (kg)								
	P-Kreatinin (µmol/L)								
	P-Cystatin C (mg/L)								
	P-Urea (mmol/L)								
Ordinationer	**Filter** (ST150 el. Oxiris)								
	Ordinerad dos (mL/kg/h)								
	Heparin i primning Ja/Nej								
	Blodflöde (mL/min)								
	Citratdos (mmol/L) (vanligen 3 mmol/L)								
	Ca^{2+}-inf. ord i clinisoft	☐	☐	☐	☐	☐	☐	☐	☐
	PBP-flöde (mL/h) **på vit våg**								
	Prismocitrat 18/0	☐	☐	☐	☐	☐	☐	☐	☐
	Phoxilium	☐	☐	☐	☐	☐	☐	☐	☐
	Prismasol 4	☐	☐	☐	☐	☐	☐	☐	☐
	Natriumtillsats (mmol/5 L)								
	Dialysatflöde (mL/h) **grön våg**								
	Prism0Cal B22	☐	☐	☐	☐	☐	☐	☐	☐
	Phoxilium	☐	☐	☐	☐	☐	☐	☐	☐
	Prismasol 4	☐	☐	☐	☐	☐	☐	☐	☐
	Natriumtillsats (mmol/5 L)								
	Ersättningsflöde (mL/h) Ange före eller efter på lila våg								
	Phoxilium	☐	☐	☐	☐	☐	☐	☐	☐
	Prismasol 4	☐	☐	☐	☐	☐	☐	☐	☐
	Natriumtillsats (mmol/5 L)								
	Signatur läkare								
	Avflödes dos (mL/kg/h) **Faktisk behandlingstid** h/min								