CRRT Modalities

Farin Rashid Farokhi
Associate Professor of Nephrology
Masih Daneshvari Hospital
Shahid Beheshti University of Medical Science

Case presentation

- A 56 year-old-man with a medical history of DM, HTN, and IHD was admitted to the ICU with a diagnosis of pneumo-sepsis. His body weight at the time of hospital admission was 72 kg. He underwent mechanical ventilation and received wide spectrum antibiotics. A CT-scan with intravenous contrast had been performed before transferring to the ICU, showing bilateral ground glass opacities. At the time of nephrology consultation on the third day of ICU admission, there was anuria for the previous 24 hours. Other findings included the followings:

- BP: 80/40 (dependent to vasopressors)
- Peripheral edema: +3
- Cumulative fluid balance: +8 lit
- PH: 7.08, HCO_3: 10 mEq/L
- WBC: 14000/µL , Hgb: 10.3 g/dL, HCT: 30%
- BUN: 120 mg/dL, Creatinine: 2.2 mg/dL
- Na:134 mEq/L, K: 6 mEq/L

Case presentation

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- Na:134 mEq/L, K: 6 mEq/L

RRT (especially CRRT) is not fast enough in terms of correcting life threatening electrolyte disorders. Hyperkalemia of this patient should be medically treated as soon as possible, and the potassium level should be monitored during RRT.

CRRT was started for the presented patient with the following order

-Mode: CVVH
-Blood flow: 100 cc/min
-Replacement fluid: 1800 cc/h, post-dilution
-Net UF: 100 cc/h
-Membrane: High-flux , K_f: 80 cc/mmHg/h
-Anticoagulation: heparin 2000 IU heparin as loading dose, then 400 IU/h, adjusted by PTT

Is the above order an appropriate prescription for the patient?

Prescription of CRRT

- **Initial prescription**

- **Frequent reassessment of the the response to prescribed CRRT dose**

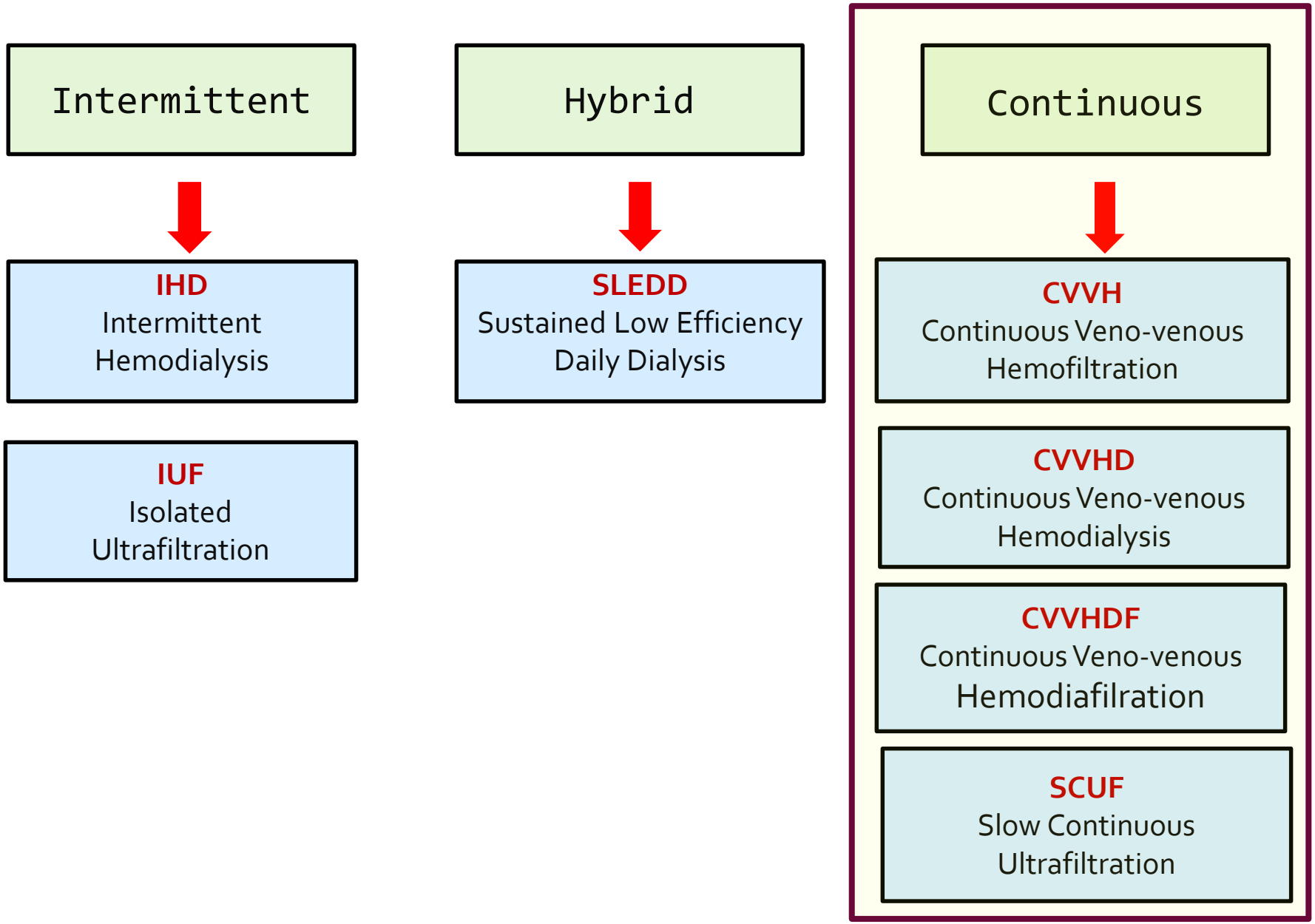
--the ratio of delivered to prescribed dose

--effective CRRT treatment time

--other measures of solute control

--additional modifications based on clinical needs

Major renal replacement therapy Methods in ICU

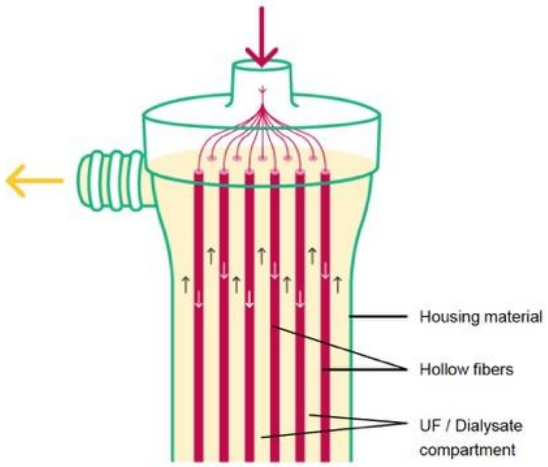


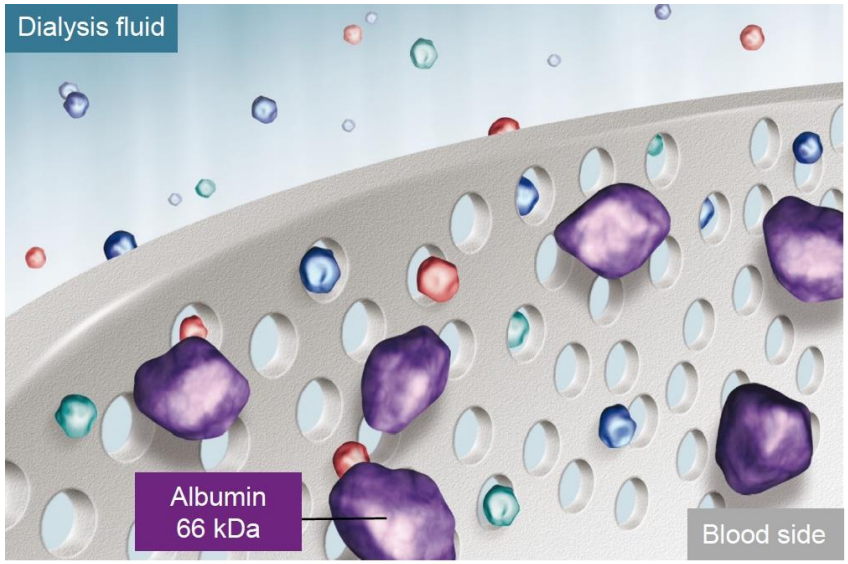
Transport mechanisms in CRRT

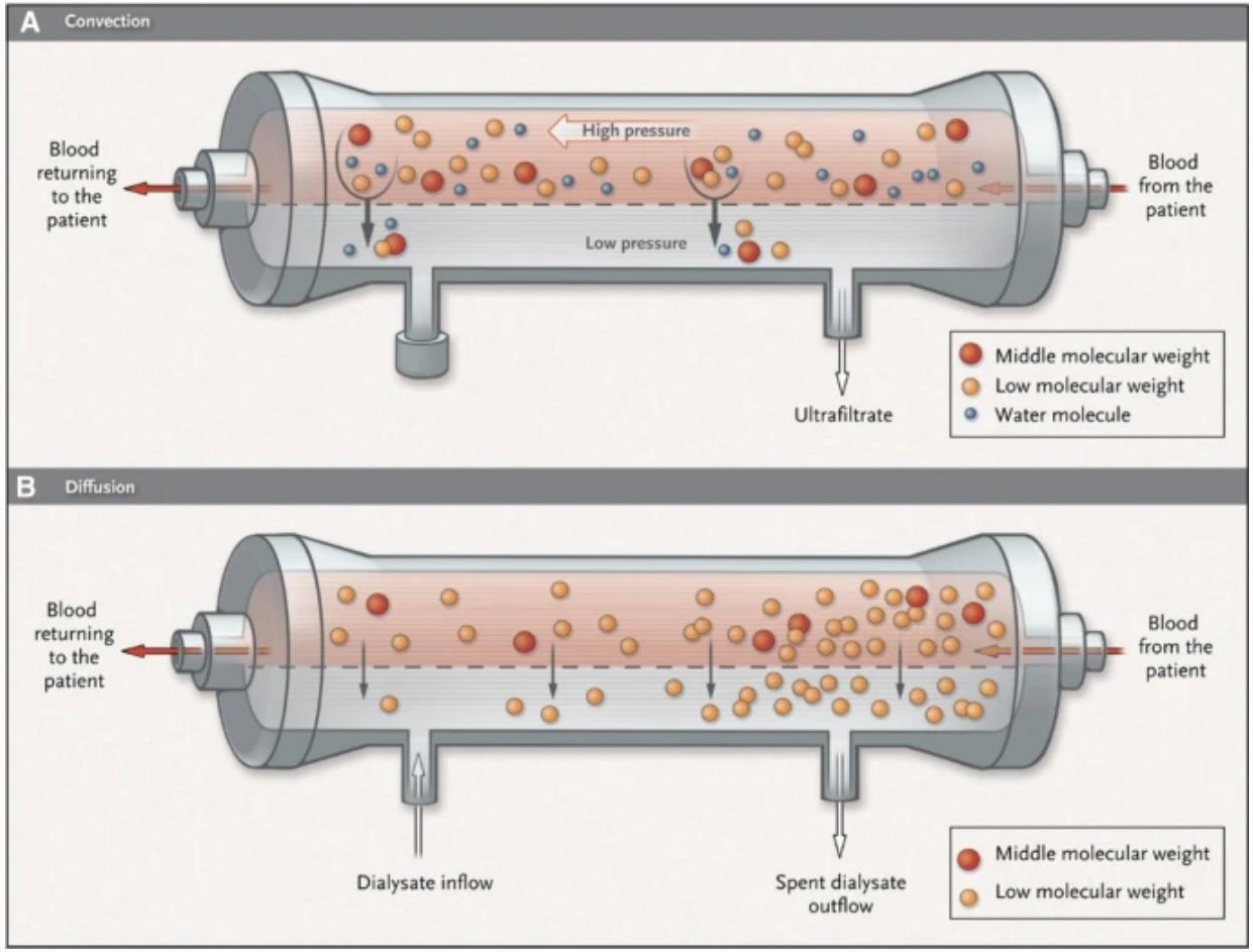
- Ultrafiltration
- Diffusion
- Convection
- Absorption

Multiple CRRT modalities differ from each other according to mechanisms of solute transport.

Diffusion flux is influenced by concentration gradient, molecular size and membrane type, blood and dialysate flow



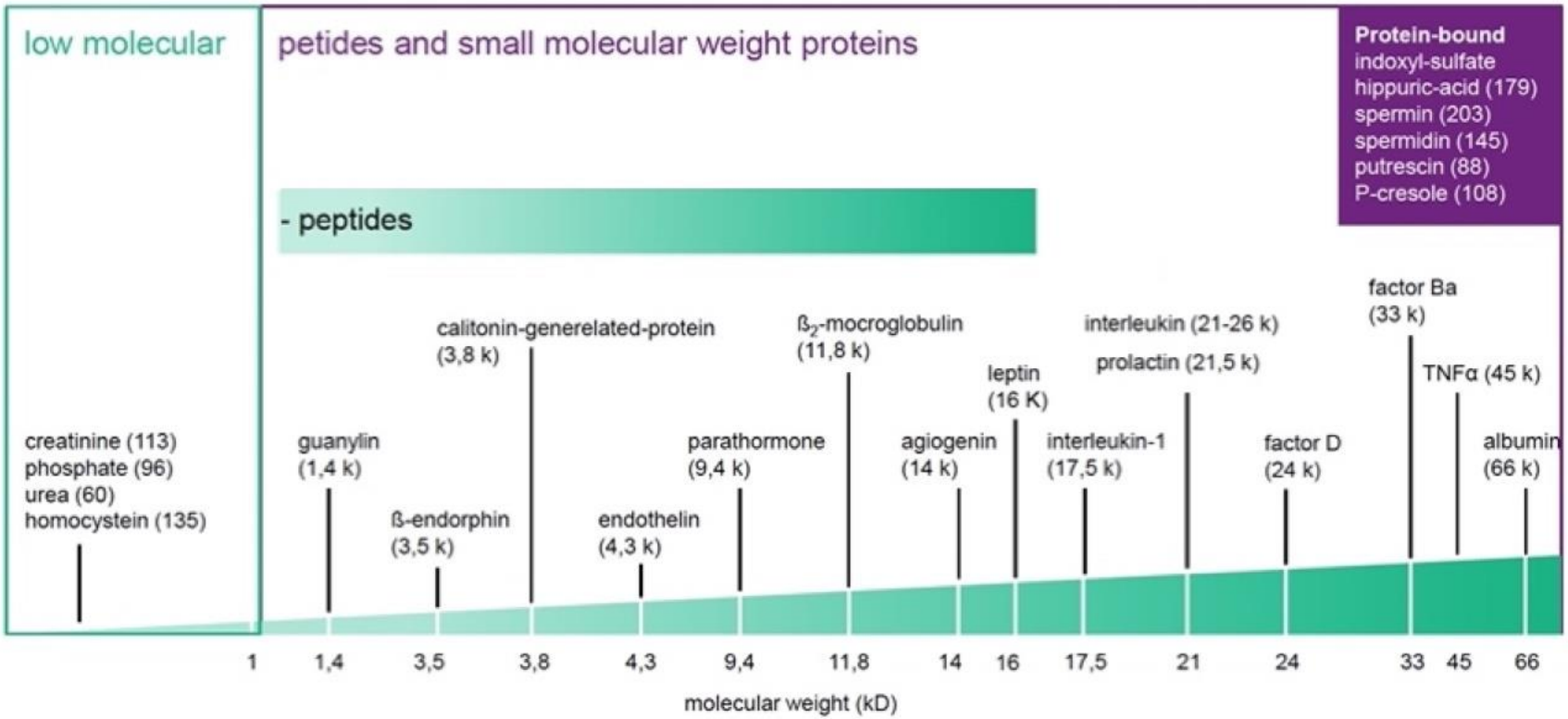



A Convection
Blood returning to the patient
High pressure
Low pressure
Blood from the patient
Ultrafiltrate
Middle molecular weight
Low molecular weight
Water molecule
B Diffusion
Blood returning to the patient
Blood from the patient
Dialysate inflow
Spent dialysate outflow
Middle molecular weight
Low molecular weight

Cut-off:

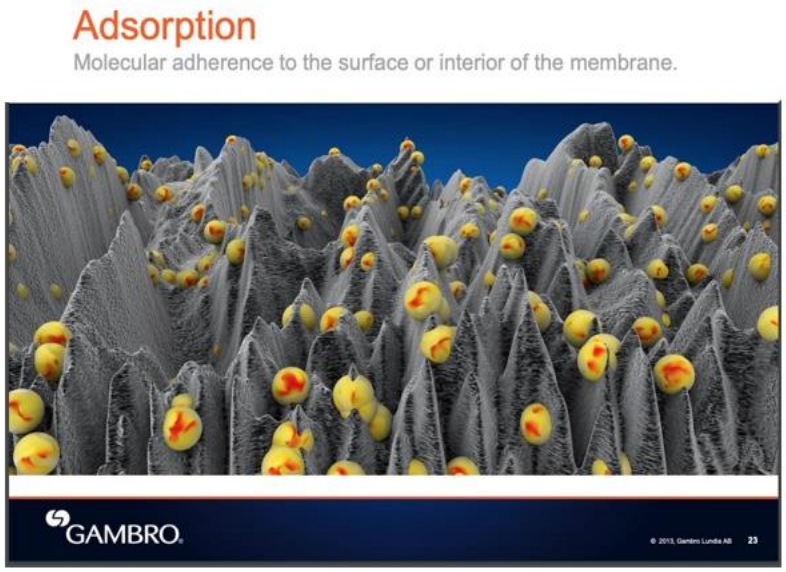
max. molecular size, which can pass through a membrane.

- In low-flux filters up to 10 kDa
- In high-flux filters up to 40-60 kDa



- **Adsorptive surface area of a membrane depends on the internal pore structures rather than its nominal surface area.**

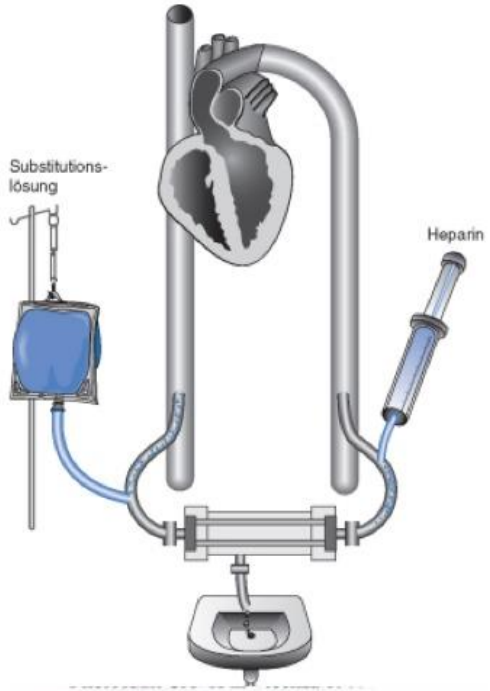
- **Adsorption of peptides and low molecular proteins to low-flux membranes is not expected to be clinically significant.**



The birth of CRRT

1960: The idea of CRRT was born, but supplies and technology were not available.

1977: An arteriovenous hemofiltration firstly described by Pitter Kramer and his colleagues.

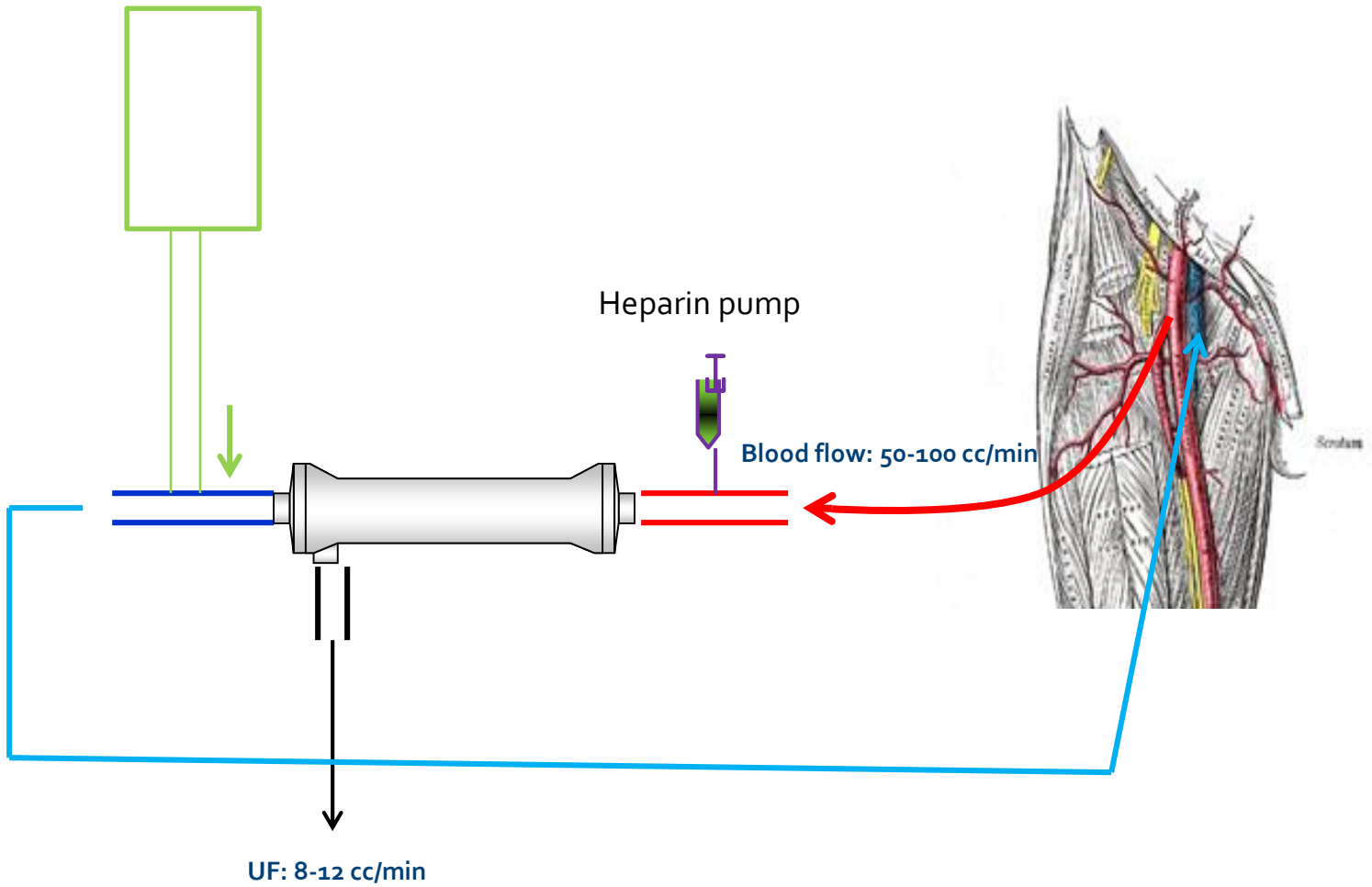


1977

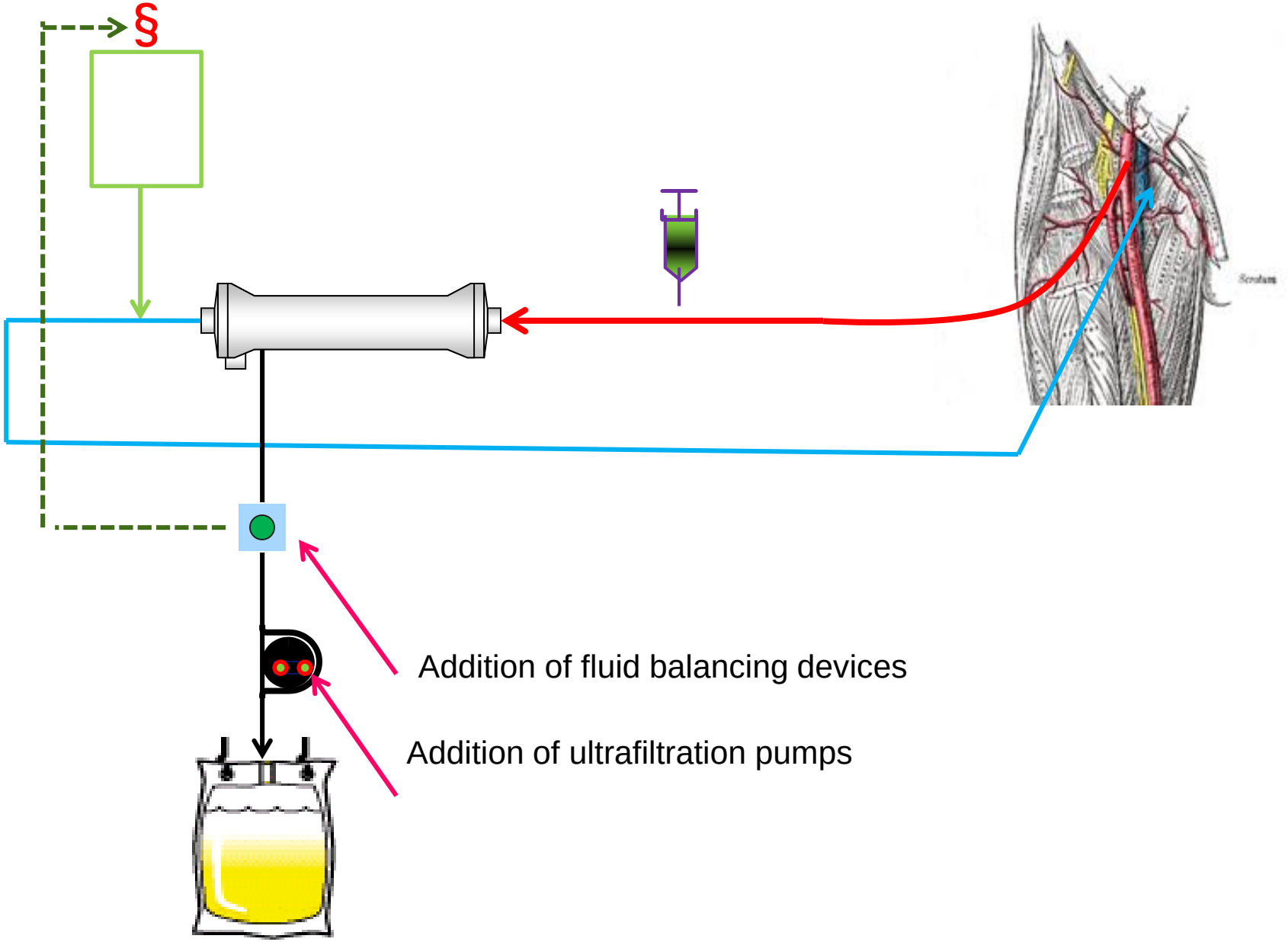
Kramer et al

The first patient treated with CAVH in Gottingen (Germany)

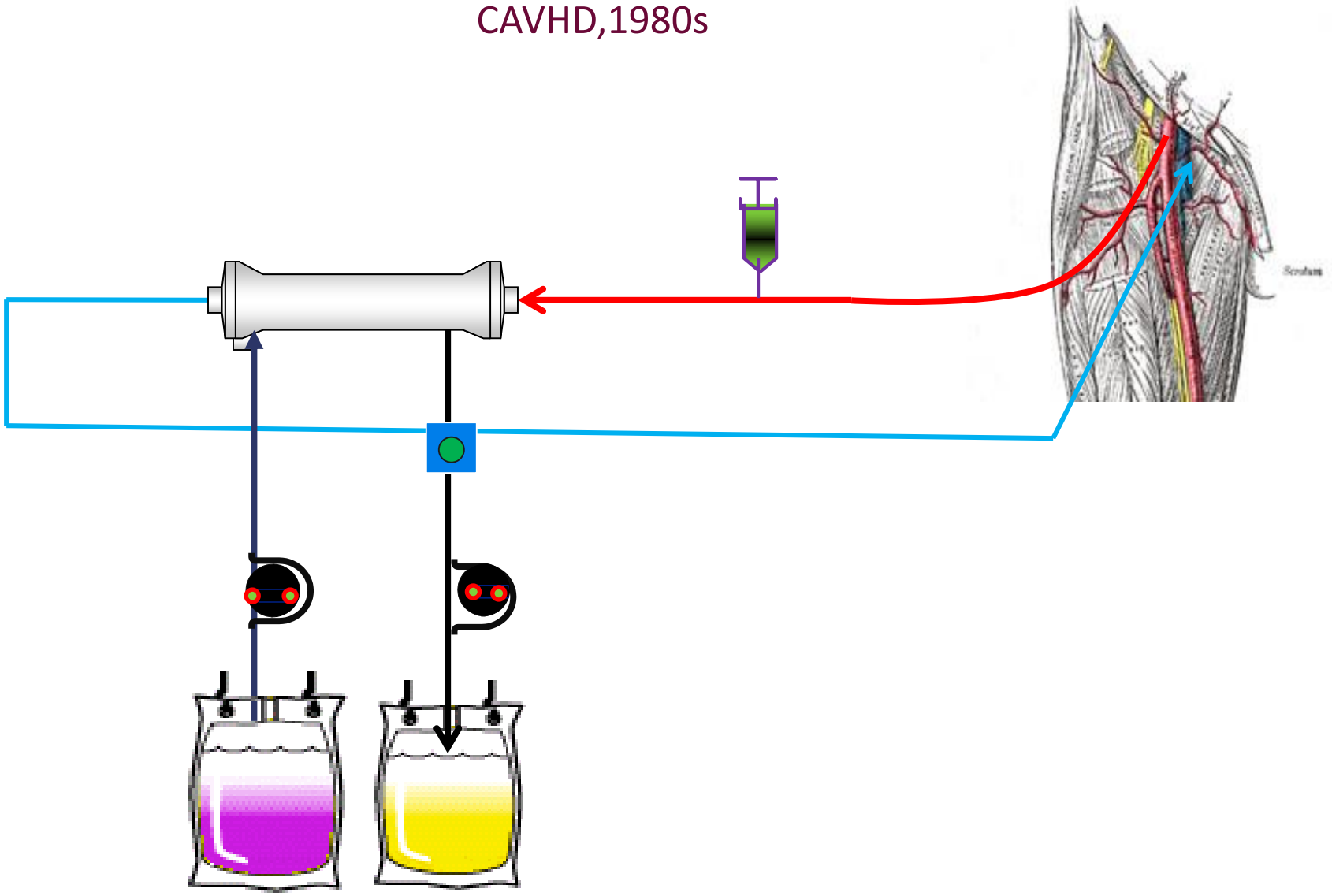
Continuous Arteriovenous Hemofiltration
CAVH



Developments of CAVH technique during 1980s



Continuous Arteriovenous Hemodialysis
CAVHD,1980s



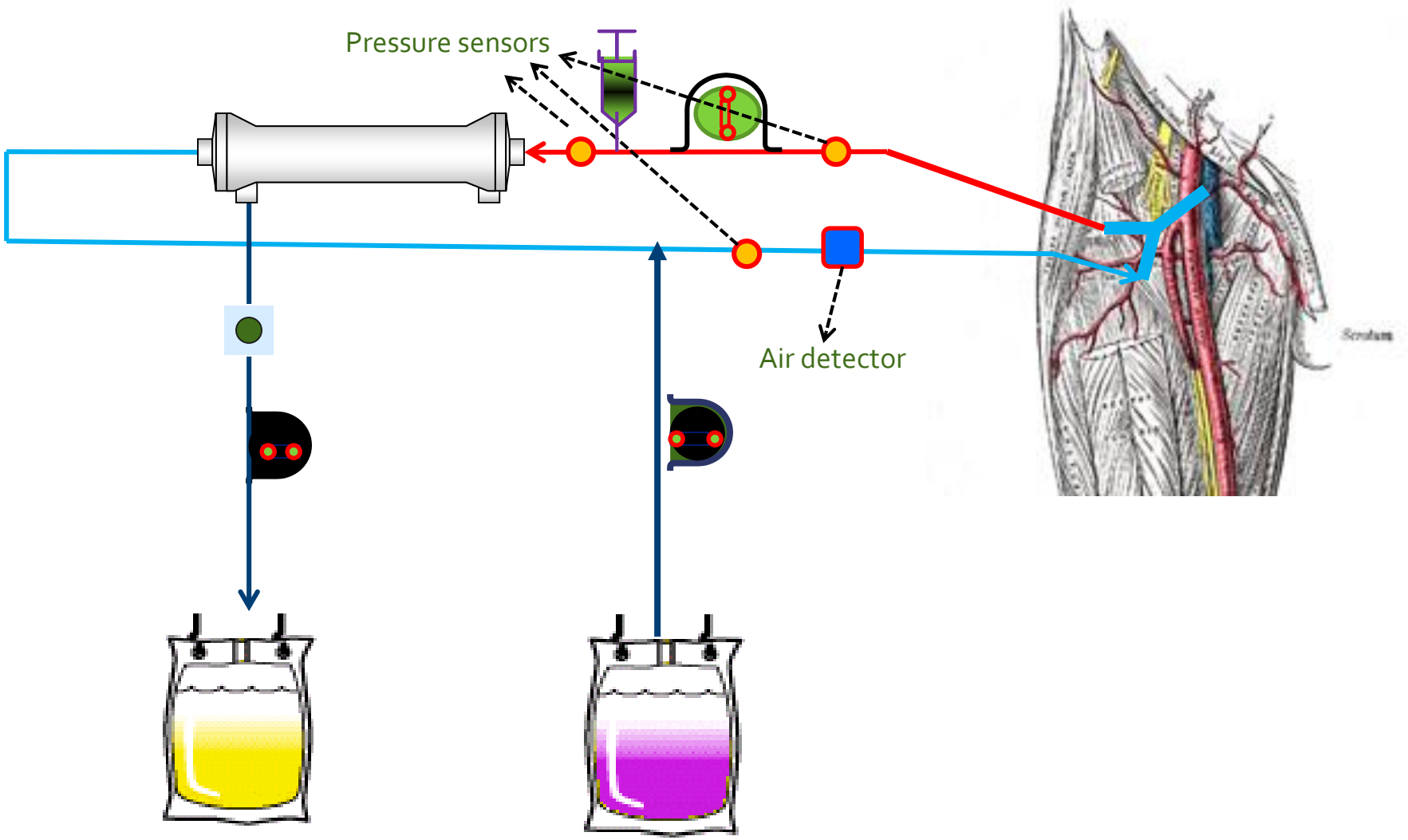
1987

Introduction of

Continuous Veno-venous Hemofiltration CVVH

by Peter Robert Uldall

(Toronto, Canada)

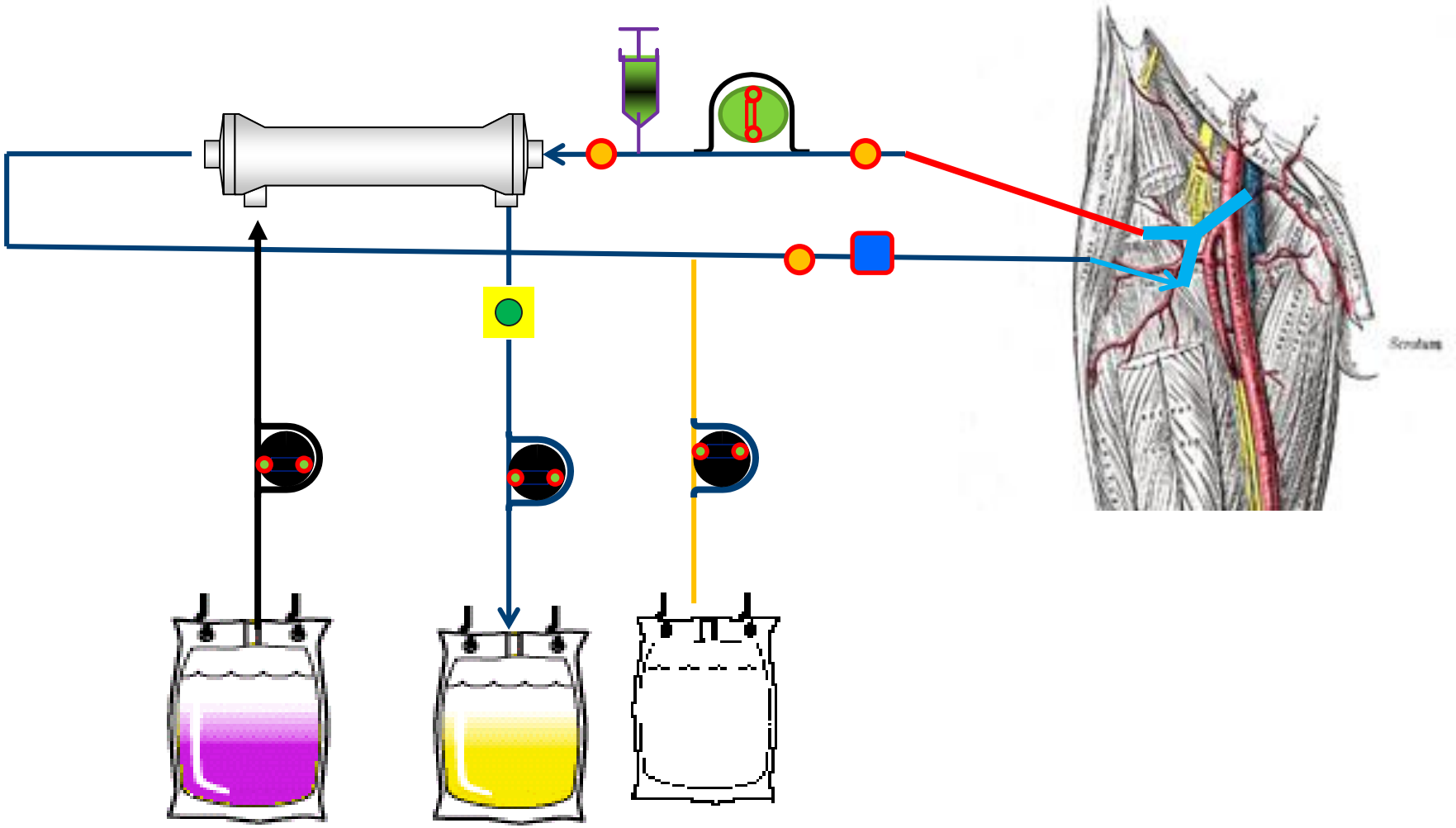


Advantages of continuous veno-venous hemofiltration to arterio-venous hemofiltration

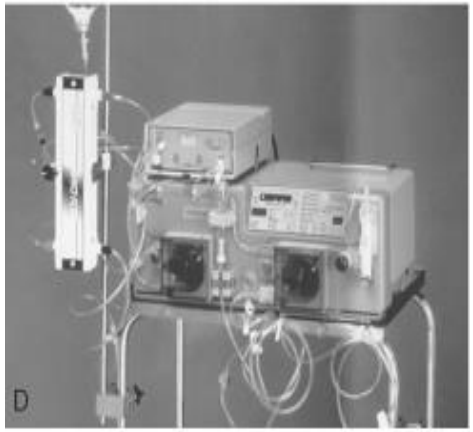
- Higher blood flow
- constant blood flow
- Eliminated risk of arterial bleeding and embolization
- Less anticoagulation requirement

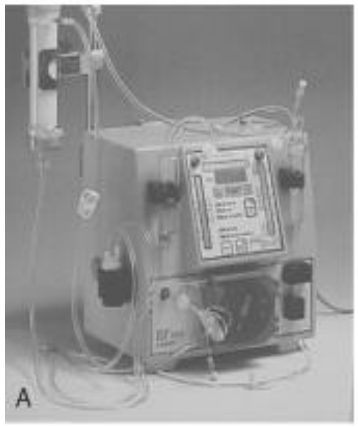
Continuous Venovenous Hemodiafiltration

CVVHDF

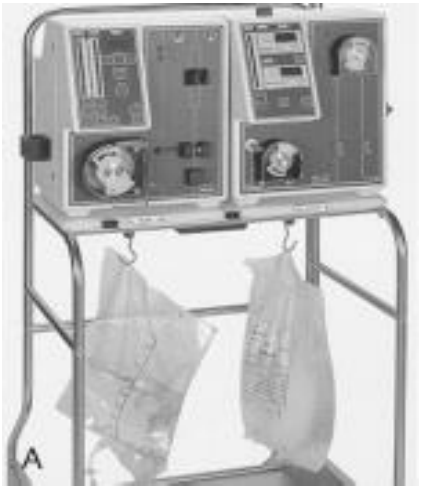


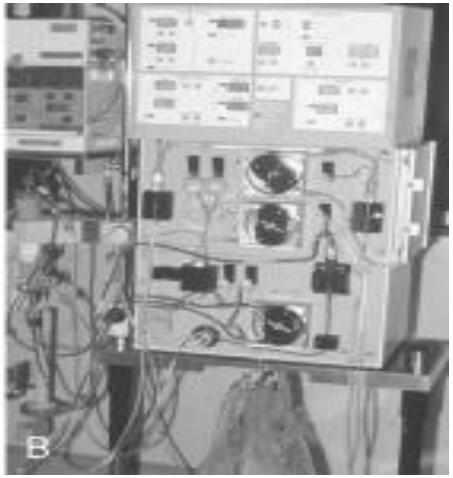
Pumps and ultrafiltration control system for CRRT





First generation machines for CRRT, late 1980s



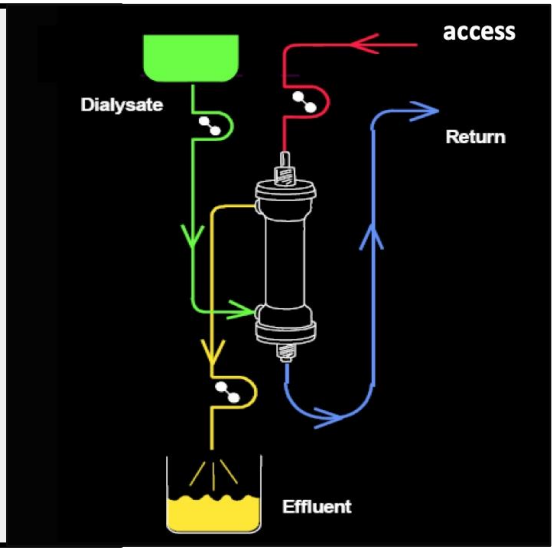


Recent generation of machines for CRRT

- Safe, reliable and easy performance
- Automatically priming

Continues Veno-venous Hemodialysis (CVVHD)

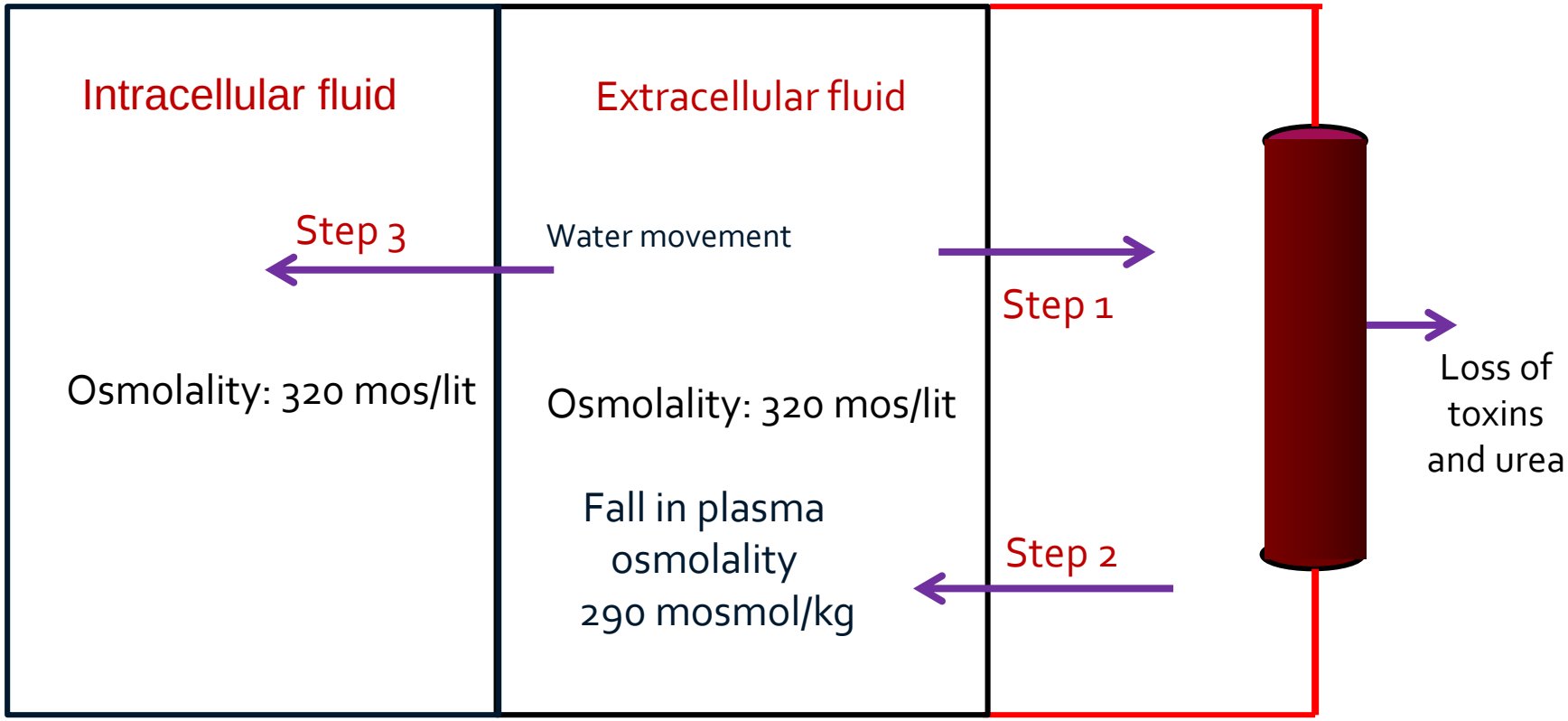
- ✓ **Duration**: 24 hours to several days
- ✓ **Membrane:** high-flux/low-flux
- ✓ **Blood flow rate**: 100-250 cc/min
- ✓ **Net UF rate:** 0-300cc/hour
- ✓ **Dialysate fluid rate:** 1000-2000 cc/h
- ✓ **Replacement fluid rate:** 0



effluent flow rate = net ultrafiltration+ dialysate flow rate
filter clearance= effluent flow rate x sieving coefficient
sieving coefficient = the ratio of solute concentration in the ultra-filtrate to plasma

Mechanism of solute transport in CVVHD is diffusion.

Intracellular shift of water during conventional hemodialysis may aggravate volume depletion



There is no rapid change in osmolality during CRRT. Thus, hypotension is not aggravated by intracellular fluid shift.

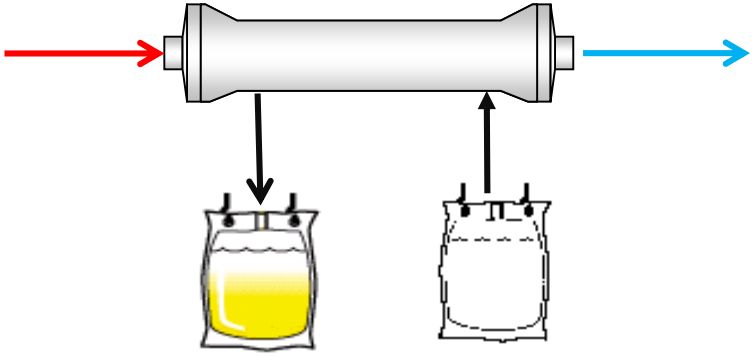
Advantages of CRRT as compared with intermittent RRT in critically ill patients

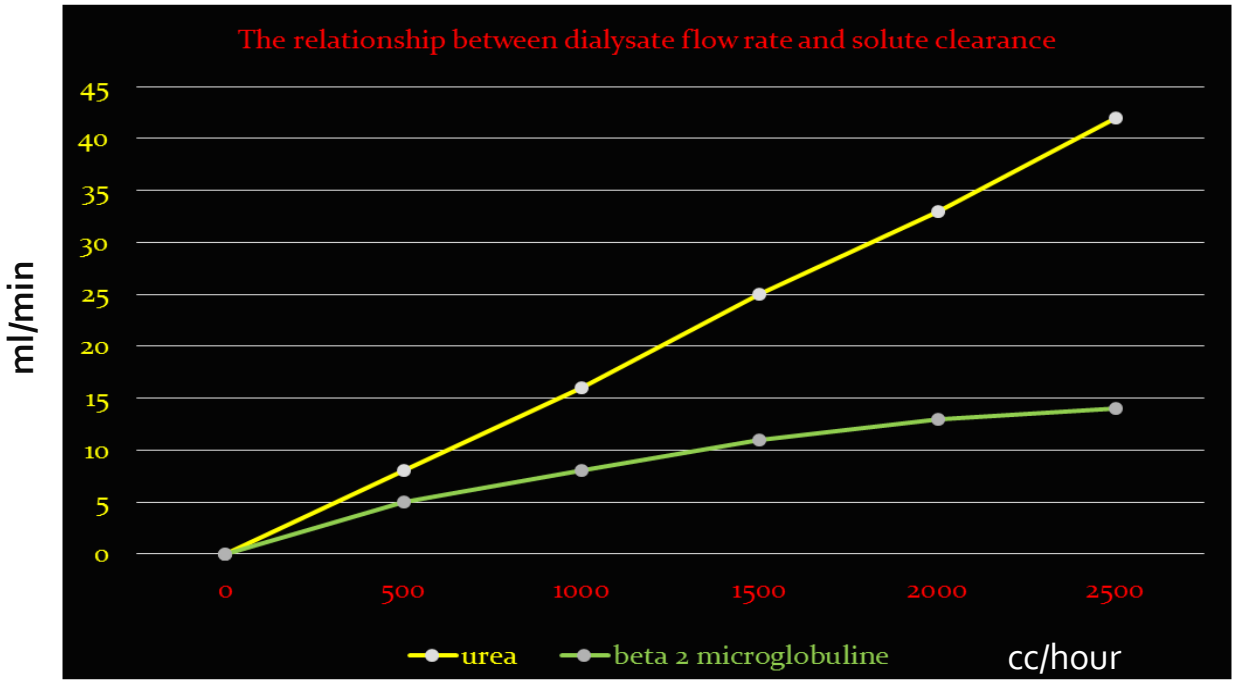
- Slow and smooth removal of fluid removal and excess uremic toxins
- Continuous function, simulating normal kidney function
- Decreased rate of intradialytic hypotension
- Superiority in patients with hemodynamic instability, high intracranial pressure, and acute brain injury
- Lower risk of kidney non-recovery?
- Reduced risk of dialysis dependence among survivors?

Studies designed to compare continuous versus intermittent therapies have not shown a beneficial effect on mortality.

Disadvantages of CRRT

- Continuous anticoagulation and increased risk of bleeding
- Drug removal
- Immobilization of patients for prolonged time
- Increased cost?

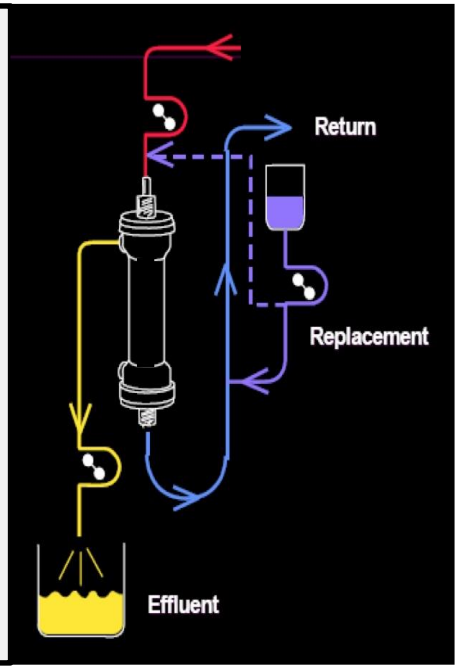




Solute clearance increases by blood flow rate during conventional intermittent hemodialysis. But in CVVHD, it depends on dialysate flow rate.

Continues Veno-venous Hemofiltration (CVVH)

- ✓ **Duration**: 24 hours to several days
- ✓ **Membrane:** high-flux
- ✓ **Blood flow rate**: 100-250 cc/min
- ✓ **Net UF rate:** 0-300 cc/hour
- ✓ **Dialysate fluid rate:** 0
- ✓ **Replacement fluid rate:** 1000-2000 cc/hour
- ✓ **Replacement fluid infusion site**: predilution and/or postdilution



- **Mechanism of solute transport in CVVH is convection that is associated with greater clearance of higher molecular weight solutes.**
- **Membrane survival is worse than CVVHD because in CVVH water loss toward the end of hemofilter can induce hemoconcentration and membrane clothing.**

-Mode: CVVH
-Blood flow: 100 cc/min
-Replacement fluid: 1800 cc/h, post-dilution
-Net UF: 100 cc/h
-Membrane: High-flux , K_f: 80 cc/mmHg/h
-Anticoagulation: heparin 2000 IU heparin as loading dose, then 400 IU/h, adjusted by PTT

-Mode: CVVH
-Blood flow: 100 cc/min
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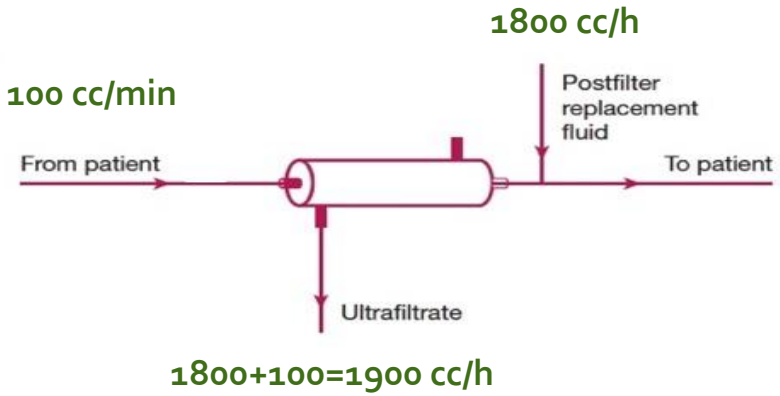


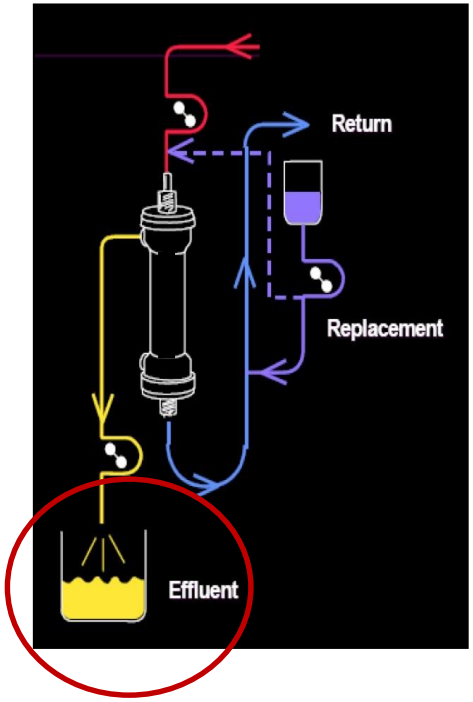
effluent rate = K_f X TMP

- K_f: ultrafiltration coefficient of membrane
- TMP: transmembrane pressure
- 1800 cc/h+100 cc= 80 cc/mmHg/h x TMP mmHg
- TMP= 24 mmHg

Is the following prescription appropriate to met adequate dose of CRRT?

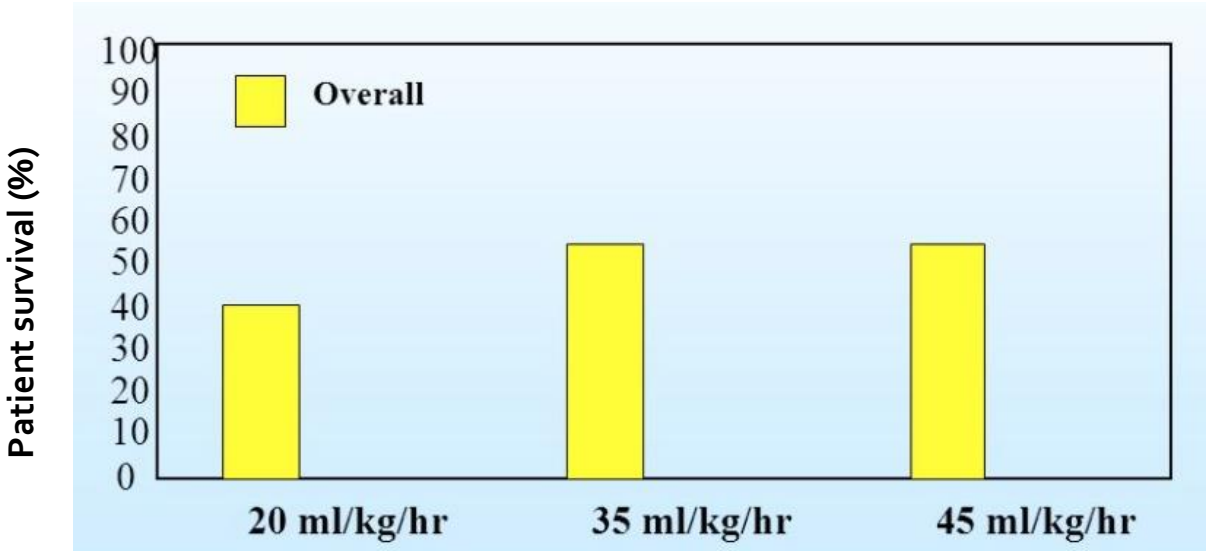
-Mode: CVVH
-Blood flow: 100 cc/min
-Replacement fluid: 1800 cc/h, post-dilution
-Net UF: 100 cc/h
-Membrane: High-flux , K_f: 80 cc/mmHg/h
-Anticoagulation: heparin 2000 IU heparin as loading dose, then 400 IU/h, adjusted by PTT

- The adequate dose of CRRT may be represented by the volume of blood purified per unite of time.
- In clinical practice the dose of CRRT is the effluent flow rate.



effluent flow rate = net ultrafiltration+ replacement flow rate
filter clearance= effluent flow rate x sieving coefficient
sieving coefficient = the ratio of solute concentration in the ultra-filtrate to plasma

In 2000, Ronco et al have shown that the higher delivered dose of CRRT is superior to 20 cc/kg/h in improving the survival rate.



Rnco C, et al., Lancet 2004

The following major multi-centric RCTs showed that increasing dose intensity above 20-25 mL/kg/h dose not deliver clinical benefits to critically ill patients

- ATN-CVVHDF in the USA (2008)
- RENAL-CVVH in Australia and New Zealand (2009)
- IVOIRE-CVVHF in France, Belgium, Netherland (2013)

Rnco C, et al., Lancet 2004

Interruption of CRRT treatment due to the following reasons can have a substantial impact on the actual delivered dose of CRRT.

- Circuit clotting
- Machine alarms
- Change of replacement solutions
- Radiologic investigations and/or surgical procedures

In clinical practice, in order to achieve a delivered dose of 20-25 cc/kg/h, it is necessary to prescribe CRRT in a range of 25-30 cc/kg/h

Is the following prescription appropriate to met adequate dose of CRRT?

Yes, it is.

-Mode: CVVH
-Blood flow: 100 cc/min
-Replacement fluid: 1800 cc/h, post-dilution
-Net UF: 100 cc/h
-Membrane: High-flux , K_f: 80 cc/mmHg/h
-Anticoagulation: heparin 2000 IU heparin as loading dose, then 400 IU/h, adjusted by PTT

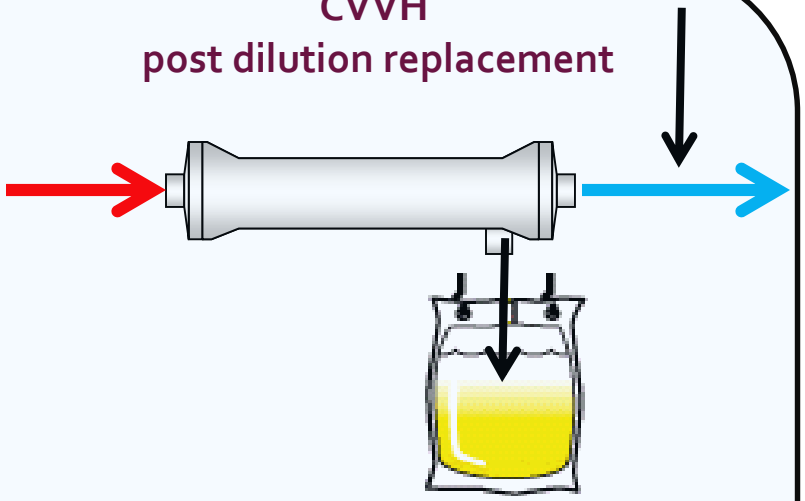
effluent flow rate = net ultrafiltration+ replacement flow rate
effluent flow rate= 100+1800=1900 cc
Effluent flow rate/Body weight =1900/72= 26.4 cc/kg/h

In clinical practice, in order to achieve a delivered dose of 20-25 cc/kg/h, it is necessary to prescribe CRRT in a range of 25-30 cc/kg/h

What is the difference between pre and post-dilution?

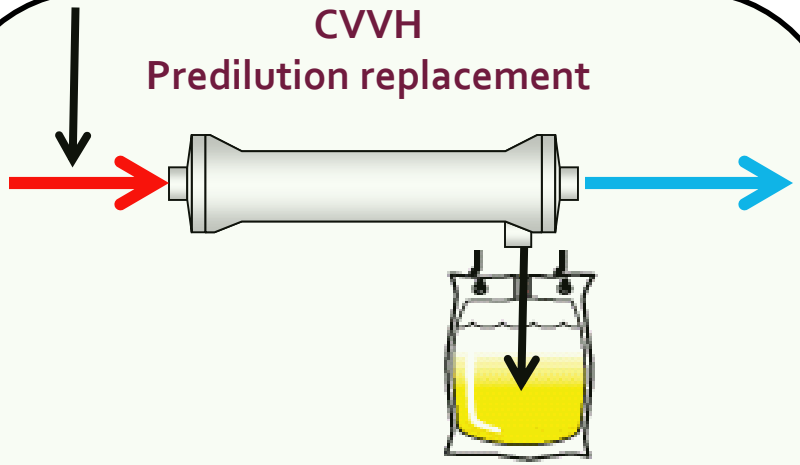
-Mode: CVVH
-Blood flow: 100 cc/min
-Replacement fluid: 1800 cc/h, post-dilution
-Net UF: 100 cc/h
-Membrane: High-flux , K_f: 80 cc/mmHg/h
-Anticoagulation: heparin 2000 IU heparin as loading dose, then 400 IU/h, adjusted by PTT

CVVH
post dilution replacement



- Increased risk of coagulation
- Lower circuit survival
- Better convective clearance

CVVH
Predilution replacement



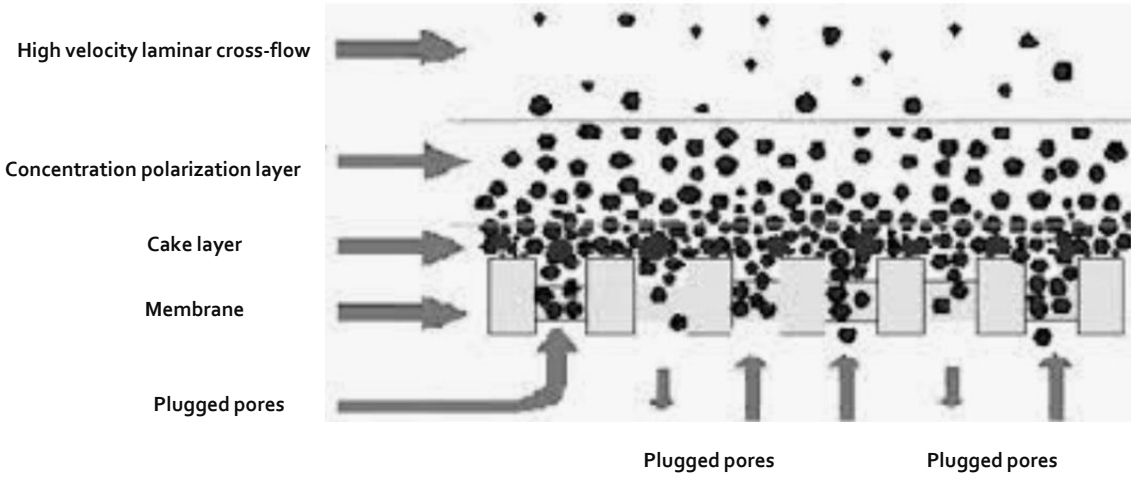
- Reduced risk of coagulation
- Longer circuit survival
- Reduced convective clearance
- Better membrane performance by reducing protein adsorption and concentration polarization
- More solute movement out of RBC due to creating concentration gradient

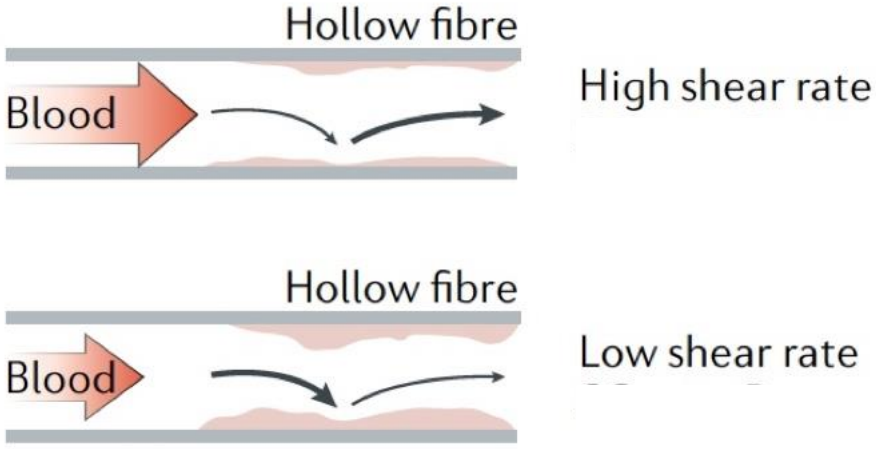
A combination of predilution and post dilution can be considered

Concentration polarization

- In patients with a high effluent rate to plasma flow (>30%), some loss of clearance will occur as proteins and cells are pushed against the membrane by TMP and formed a proteinaceous layer (so called concentration polarization).

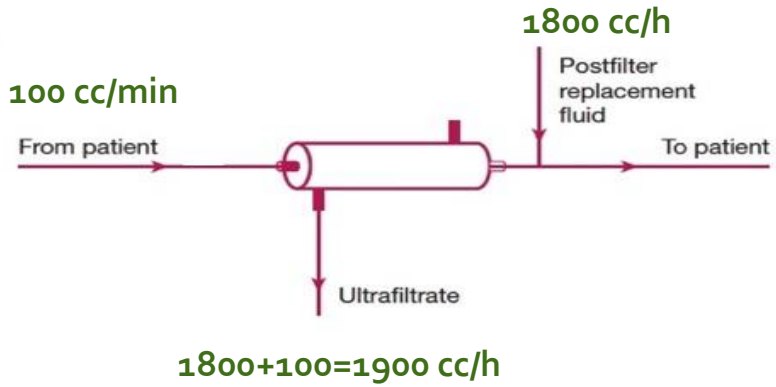
- Concentration polarization decreases membrane permeability due to lowering pores' sizes and numbers.





Augmented blood flow in pre-dilution method create a relatively high membrane shear rate, which reduces solute membrane interaction.

Ronco C, and Clark RC. Nature Reviews Nephrology 2018; 14: 394-410



Blood flow rate: 100 cc/min
HCT: 30%

→ Plasma flow: Blood flow rate (1-HCT)= 100 (1-0.3)= 70 cc/min

effluent rate: 1900 cc/hour or 1900/60= 32 cc/min

effluent rate to plasma flow rate= 32/70= 45%
filtration fraction= 45%

Filtration fraction should not exceed 20-25%. High filtration fraction correspond to higher hematocrit toward end of membrane, which decrease the life of the filter and promote clot formation.

How we can correct this prescription to reduce filtration fraction?

-Mode: CVVH
-Blood flow: 100 cc/min
-Replacement fluid: 1800 cc/h, post-dilution
-Net UF: 100 cc/h
-Membrane: High-flux , K_f: 80 cc/mmHg/h
-Anticoagulation: heparin 2000 IU heparin as loading dose, then 400 IU/h, adjusted by PTT

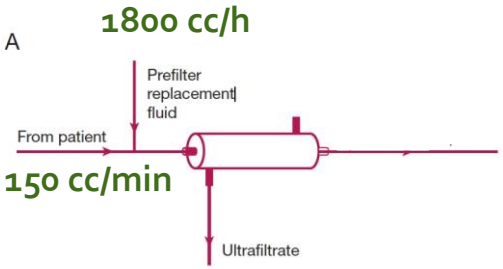
- Increasing blood flow rate
- Applying pre-dilution

-Mode: CVVH
-Blood flow: 150 cc/min
-Replacement fluid: 1800 cc/h, pre-dilution
-Net UF: 100 cc/h
-Membrane: High-flux , K_f: 80 cc/mmHg/h
-Anticoagulation: heparin 2000 IU heparin as loading dose, then 400 IU/h, adjusted by PTT

Blood flow rate: 150 cc/min
HCT: 30%

→ Plasma flow: Blood flow rate (1-HCT)= 150(1-0.3)= 105 cc/min

Replacement flow rate: 1900 cc/hour or 1900/60= 32 cc/min
Plasma flow + pre-filter replacement flow=105+32=137 cc/min
filtration fraction = 32/137 = 23%



1800+100=1900 cc/h

How the new prescription can affect CRRT adequacy?

-Mode: CVVH
-Blood flow: 150 cc/min
-Replacement fluid: 1800 cc/h, pre-dilution
-Net UF: 100 cc/h
-Membrane: High-flux , K_f: 80 cc/mmHg/h
-Anticoagulation: heparin 2000 IU heparin as loading dose, then 400 IU/h, adjusted by PTT

Urea clearance with previous order: 1.9 lit/hour
Urea clearance with the new order:1.44 lit/hour

105 / (105+32) =76%
1.9 x 76%= 1.44 lit/hour=1440 cc/h
1440/72= 20 cc/kg/h

In clinical practice, in order to achieve a delivered dose of 20-25 cc/kg/h, it is necessary to prescribe CRRT in a range of 25-30 cc/kg/h

How the new prescription can affect CRRT adequacy?

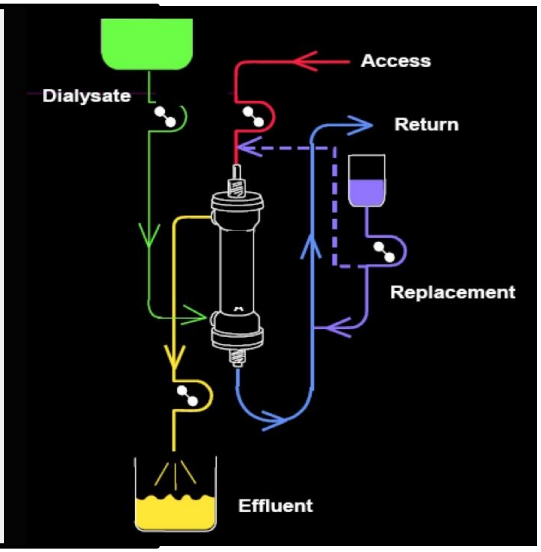
-Mode: CVVH
-Blood flow: 250 cc/min
-Replacement fluid: 1800 cc/h, pre-dilution
-Net UF: 100 cc/h
-Membrane: High-flux , K_f: 80 cc/mmHg/h
-Anticoagulation: heparin 2000 IU heparin as loading dose, then 400 IU/h, adjusted by PTT

Urea clearance with the new order:1.6 lit/hour

175/ (175+32) =84.5%
1.9x84.5%= 1.6 lit/hour=1600 cc/h
1600/72= 22.2 cc/kg/h

Continues Veno-venous Hemodiafiltration (CVVHDF)

- ✓ **Duration**: 24 hours to several days
- ✓ **Membrane:** high-flux
- ✓ **Blood flow rate**: 100-250 cc/min
- ✓ **Dialysate flow:** 1000-2000 cc/hour
- ✓ **Net UF rate:** 0-300 cc/hour
- ✓ **Replacement fluid volume:**1000-2000 cc/hour
- ✓ **Replacement fluid infusion site**: predilution and/or postdilution

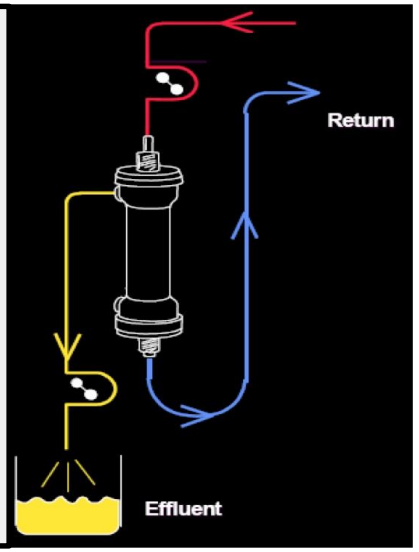


effluent flow rate = net ultrafiltration + replacement flow rate + dialysate flow rate

Mechanism of solute transport in CVVHDF is combination of convection and diffusion.

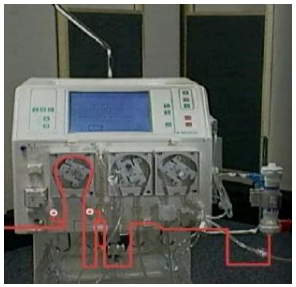
Slow Continuous Ultrafiltration (SCUF)

- ✓ **Duration**: usually 24 hours
- ✓ **Angioaccess:** central vein catheters, possibly peripheral vein
- ✓ **Membrane:** high-flux
- ✓ **Blood flow rate**: 50-100 cc/min
- ✓ **UF rate:** 2-8 cc/min, typically<8 lit/day

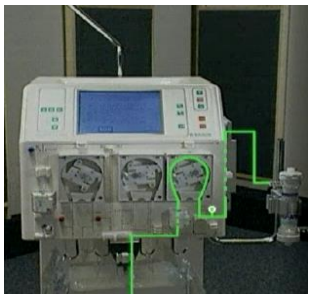


- **SCUF** is being used increasingly as an adjunctive therapy in patients with refractory heart failure.
- During hemofiltration a maximum filtration fraction of 25% is usually considered to prevent hemoconcentration and the resulted filter clotting.
- As in **SCUF** the Uf rate is less than 10 cc/min, a blood flow rate of 50 cc/min may be adequate to maintain the filtration fraction less than 25%

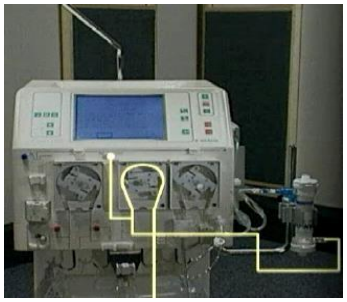
Blood flow pump



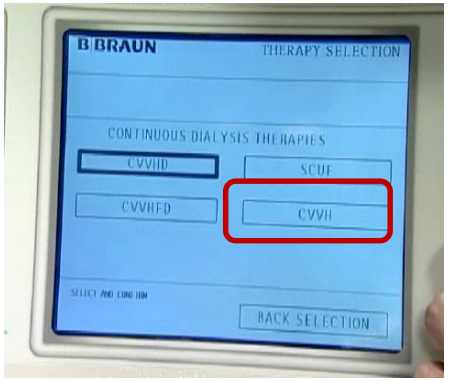
Dialysate/replacement fluid pump

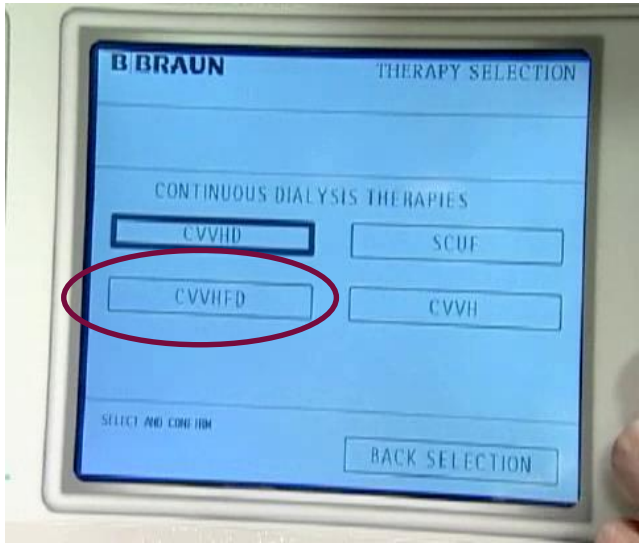


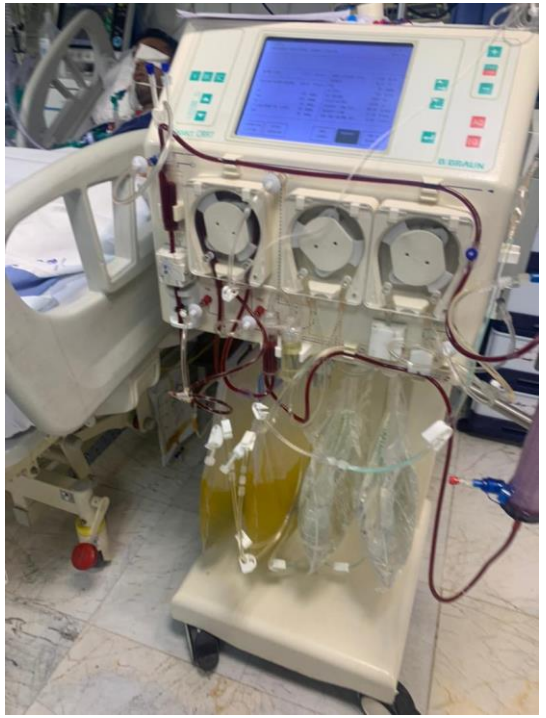
Ultrafiltration pump



Balancing systems provide ultrafiltration control



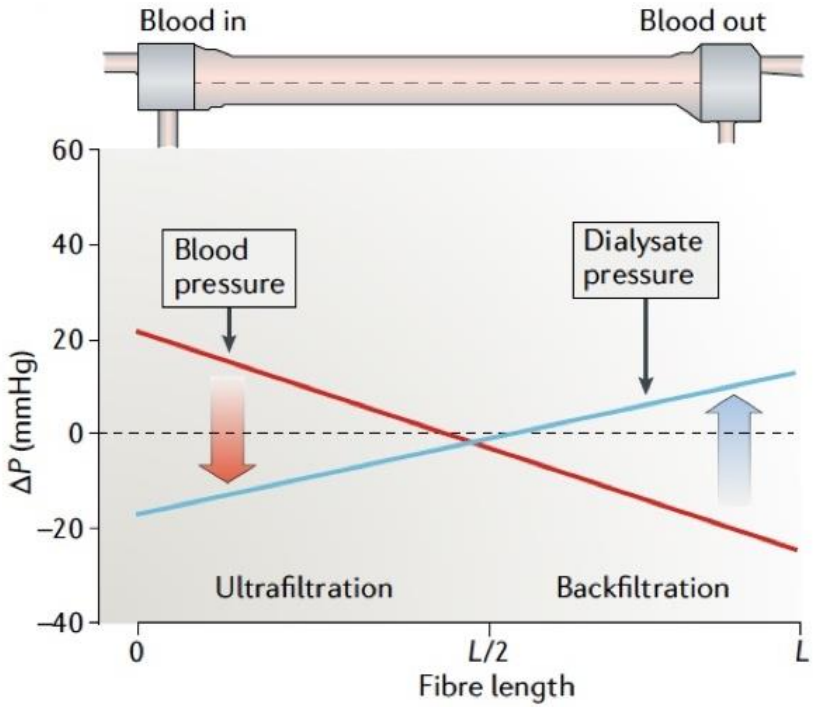




CVVHDF (continuous veno-venous high-flux dialysis)

vs

CVVHDF (continuous veno-venous hemo-diafiltration)



CVVHDF (continuous veno-venous high-flux dialysis)

- In addition to diffusive clearance, there is ultrafiltration and convective clearance in the proximal part of the dialyzer and back filtration more distally (like replacement fluid in CVVHDF)

Ronco C, and Clark RC. Nature Reviews Nephrology 2018; 14: 394-410

Friedrich et al. Critical Care 2012, 16:R146
http://ccforum.com/content/16/4/R146

CRITICAL CARE

RESEARCH Open Access

Hemofiltration compared to hemodialysis for acute kidney injury: systematic review and meta-analysis

Jan O Friedrich[1,2,3,4,5*], Ron Wald[1,2,4], Sean M Bagshaw[6], Karen EA Burns[1,2,3,4,5] and Neill KJ Adhikari[1,5,7]

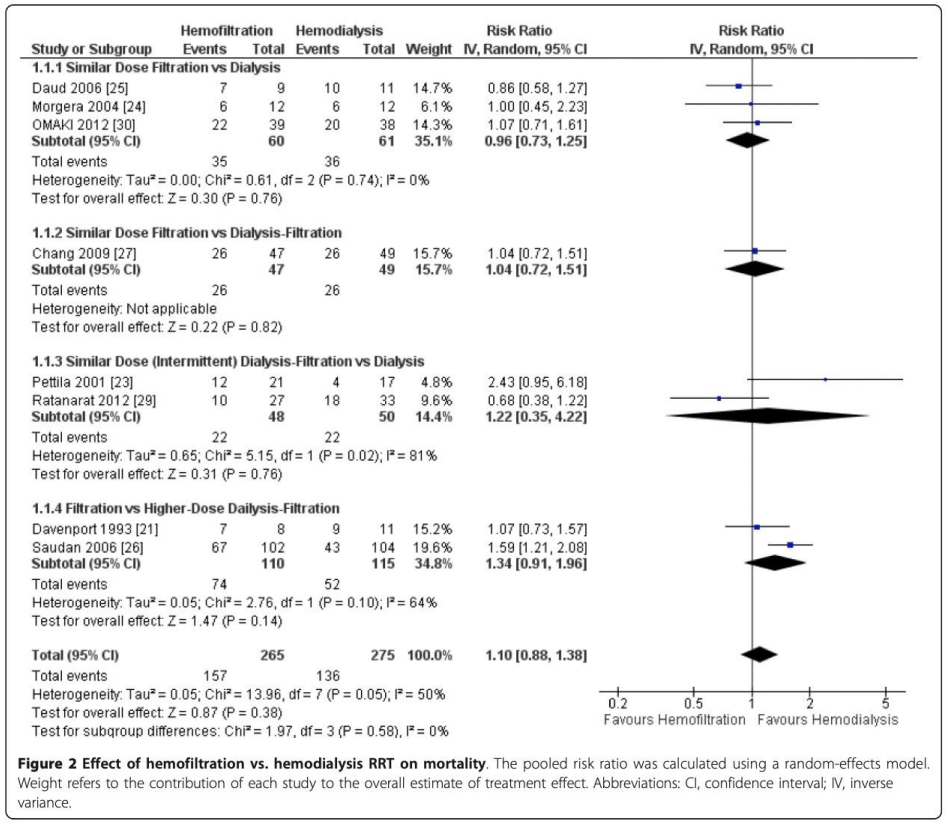


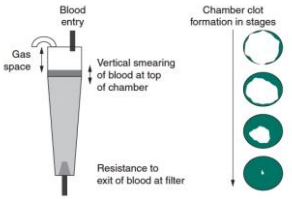
Figure 2 Effect of hemofiltration vs. hemodialysis RRT on mortality. The pooled risk ratio was calculated using a random-effects model. Weight refers to the contribution of each study to the overall estimate of treatment effect. Abbreviations: CI, confidence interval; IV, inverse variance.

Anticoagulation in CRRT:

- Disturbed hemostasis in patients receiving CRRT is the consequence of a complex interaction of critical illness, uremia, and extra-corporal circuit.

- The goals of ideal anticoagulation are the followings
  - optimized circuit patency
  - reduced risk of bleeding
  - easy monitoring
  - minimal side effects
  - available antidotes

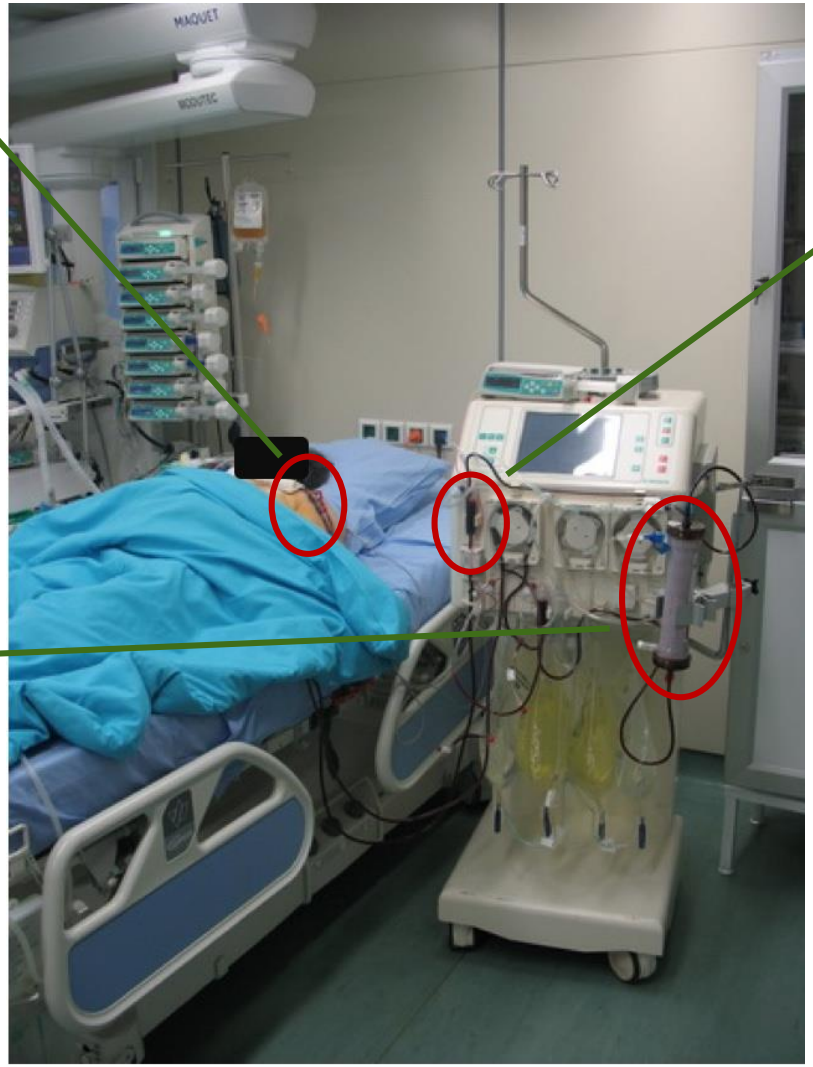
Most common sites for potential thrombosis



Venous access

Preventive strategies:

- The use of large-bore central vein catheters in the in right jugular or right/left femoral positions is recommended.
- The length of femoral catheters for optimal flow rate should be 25-35 cm.
- The right position for the tip of catheter is inferior vena cava for femoral and right atrium for jugular catheters.



Venous air trap

Preventive strategies:
Lack of supportive evidence

- Keep venous chamber full of blood, minimizing the gas packet
- Add post dilution fluids directly into this chamber
- Add heparin into chambers during the priming procedure

Dialyzer

Preventive strategies:

- The use of biocompatible membrane
- Pre-dilution, saline flushes, higher blood flow rate and lower filtration fracture
- Surface coating with heparin membranes
- Citrate anticoagulation

Advantages and disadvantages of various anticoagulation during CRRT

Drug	Advantages	Disadvantages
Unfractionated heparin	Widely used, less expensive, shorter half-life, reversible, easy monitoring (aPTT or ACT)	Risk for bleeding, unpredictable action, heparin resistance, HIT
Low-molecular-weight heparin	More reliable anticoagulation, reduced risk for HIT	Cumulative effect, expensive, anti-Xa monitoring needed
Citrate	Regional anticoagulation, low bleeding risk	Metabolic acidosis and hypocalcemia (especially in hepatic failure patients), hypernatremia, metabolic alkalosis
Alternative agents		
Argatroban		
Danaparoid	Safe and effective	Cost
Recombinant hirudin	Lack of experience in most centers	

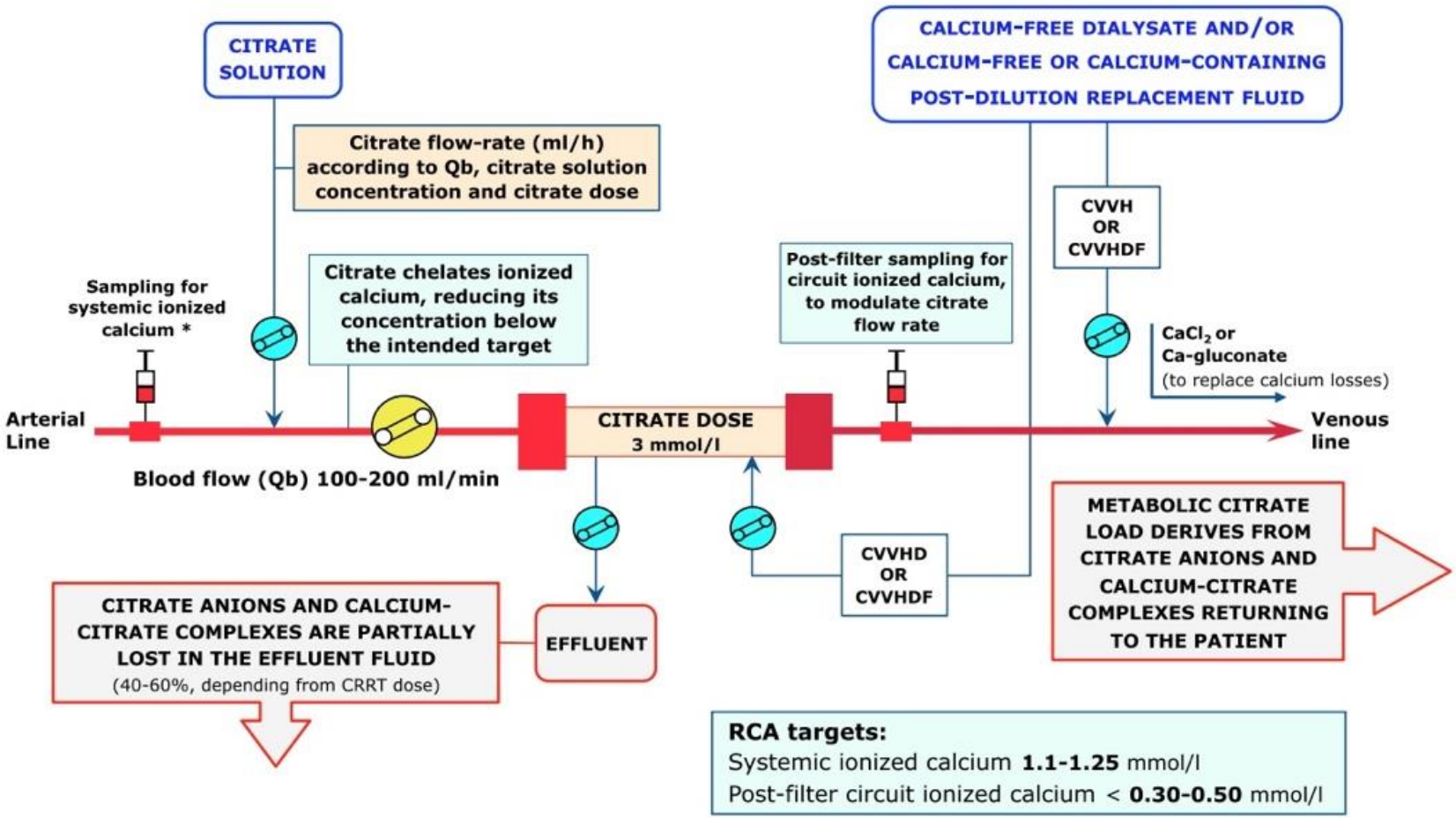
Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; CRRT, continuous renal replacement

Am J Kidney Dis. 2016;68(4):645-657

Dosing and Monitoring of Anticoagulation

	LOADING DOSE	MAINTENANCE DOSE	MONITORING	TARGET
Systemic Anticoagulation				
Unfractionated heparin	2000–5000 IU	5–10 IU/kg/hr	APTT	1–1.4 times normal
Low-Molecular-Weight Heparins				
Dalteparin	15–25 IU/kg	5 IU/kg/hr	Anti-Xa	0.25–0.35 IU/mL
Nadroparin	15–25 IU/kg	5 IU/kg/hr	Anti-Xa	0.25–0.35 IU/mL
Enoxaparin	0.15 mg/kg	0.05 mg/kg/hr	Anti-Xa	0.25–0.35 IU/mL
Alternative Anticoagulants in Case of HIT(T)				
Argatroban	100 µg/kg	0.25–1 µg/kg/min	APTT	1–1.4 times normal
Fondaparinux	No loading	2.5 mg/day 1.25 mg/day after 1–2 days	Anti-Xa	Anti-Xa 0.25–0.35 IU/mL
Danaparoid	750 U	1–2 U/kg/hr	Anti-Xa	Anti-Xa 0.25–0.35 IU/mL
Nafamostat	No loading	0.1–0.5 mg/kg/hr	APTT	1–1.4 times normal
Anticoagulation for Combined Kidney and Liver Failure and an Increased Bleeding Risk				
Prostacyclin	No loading	3–5 ng/kg/min	Thromboelastography	
Regional Anticoagulation				
Sodium citrate	No loading	2.5–4 mmol/L blood flow	Postfilter iCa or fixed dose	0.25–0.35 mmol/L

APTT, Activate partial thromboplastin time; *HIT(T),* heparin-induced thrombocytopenia (and thrombosis).



The KDIGO guidelines suggested regional citrate anticoagulation rather than heparin in patients with no contraindication for citrate.

Morabito S, et al. Clin J Am Soc Nephrol 2014; 9: 2173-2188

- Citrate anticoagulation is the first choice anticoagulation during CRRT.
- It is associated with decreased risk of bleeding.
- The membrane life is longer with citrate anticoagulation.
- The main limitation of citrate anticoagulation is accumulation, developing in case of hypoperfusion or liver dysfunction.
- Citrate accumulation is associated with a decrease in iCa, a rise in total Ca, increase in total/iCa, and metabolic acidosis.
- If total Ca/iCa >2.5, citrate should be reduced or discontinued

Examples of available replacement/dialysate fluids for CRRT

	Gambro (Baxter)		NxStage	B. Braun
	[a]PrismaSol BGK/B22K/ BK	[b]PrismaSATE BGK/B22K/ BK	[b]RFP 400-456	[b]Duosol 4551-4556
Na^+, mEq/L	140	140	130-140	140-136
K^+, mEq/L	0-4	0-2-4	0-4	0-4
Cl^-, mEq/L	108-113	108-120.5	108.5-120.5	109-117
Lactate, mEq/L	3	3	0	0
Bicarbonate, mEq/L	22-32	22-32	25-35	35-25
Ca^{2+}, mEq/L	0-2.5-3.5	0-2.5-3.5	0-3	3-0
Mg^+, mEq/L	1.0-1.2-1.5	1.0-1.2-1.5	1-1.5	1-1.5
Dextrose, g/dL	0-1	0-1.1	1	1-0

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