Continuous renal replacement therapy (CRRT) at Clinical Center University of Sarajevo - our experience

Amela Bećiragić

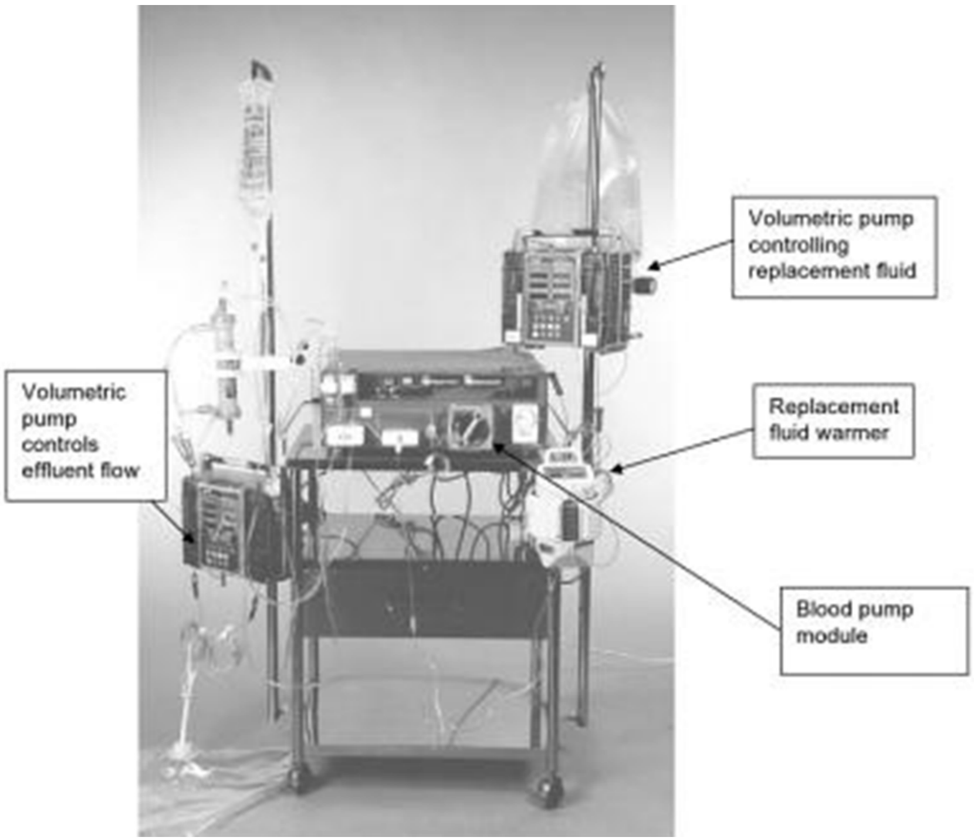
What is CRRT?

DEFINITION

- Continuous renal replacement therapy (CRRT) is indicated for continuous solute removal and/or fluid removal in critically ill patients.

- It allows for slow and isotonic fluid removal resulting in better hemodynamic tolerance even in unstable patients with shock and severe fluid overload.

- This process can be applied to both adults and children.


Volumetric pump controlling replacement fluid
Volumetric pump controls effluent flow
Replacement fluid warmer
Blood pump module

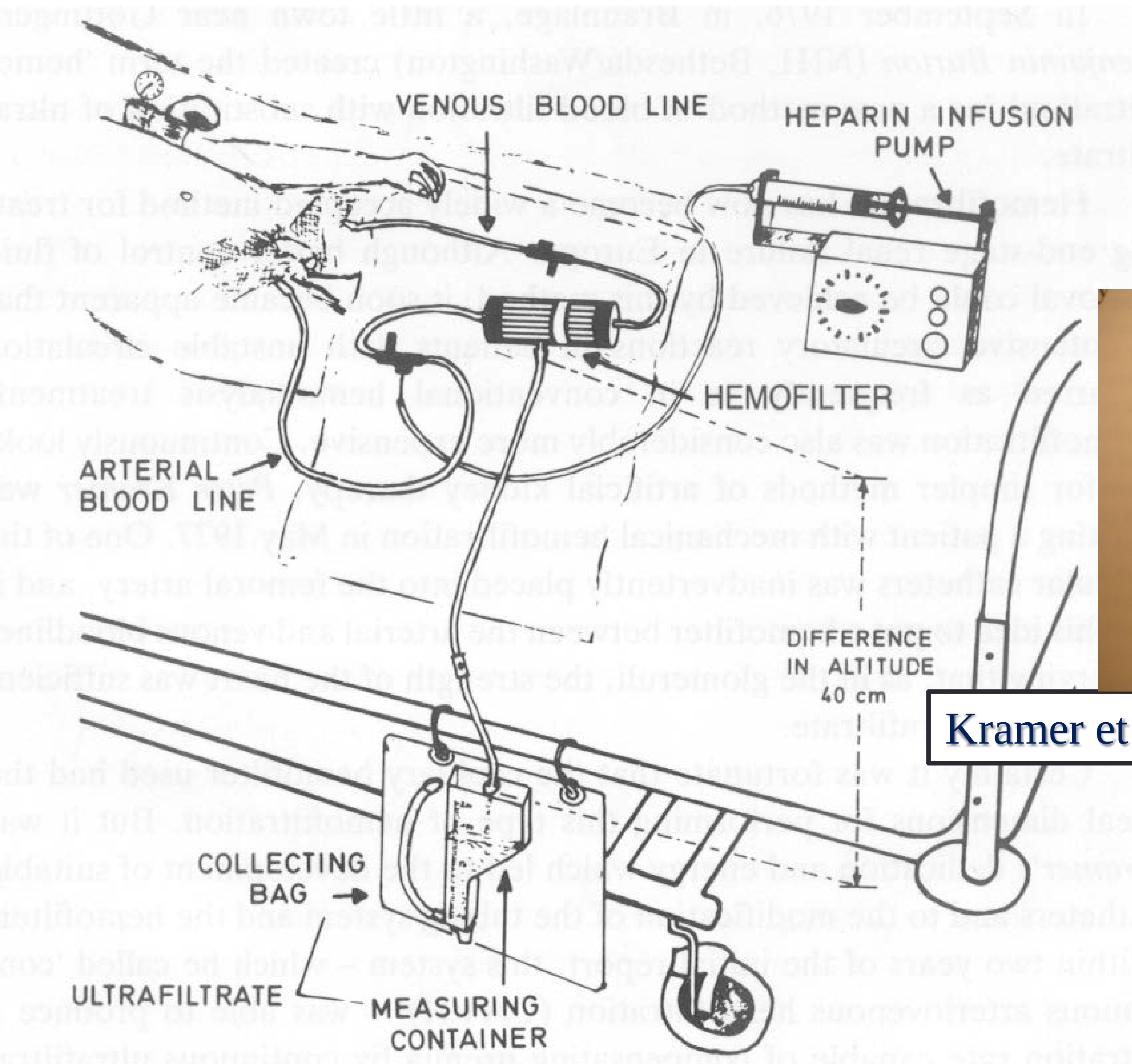

10 L

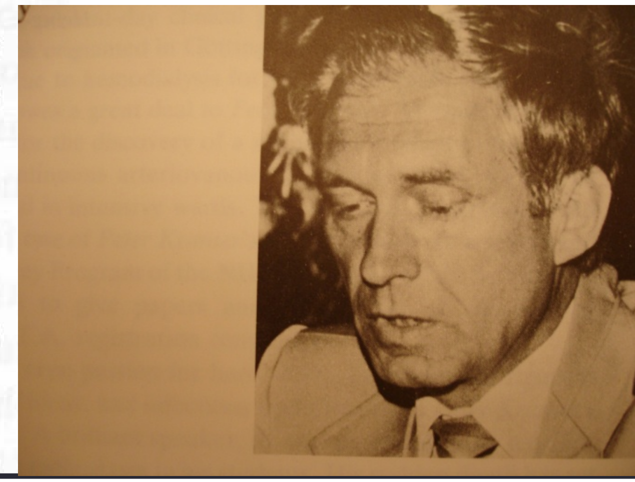
- The history of CRRT is relatively short.

- Its beginning was in 1977. when Kramer, while introducing a catheter into the femoral vein before hemodialysis, accidentally inserted the catheter into the femoral artery. He realized the possibility of using the arteriovenous gradient for filtration of blood and fluid elimination. He replaced the excessive losses by continuous infusion of substituting solutions.

- He used the term continuous arteriovenous hemofiltration (CAVH).

- This was the first step in CRRT. Over the past forty years CRRT has continued to develop and has emerged as a front line therapy for treatment of critically ill patients with acute renal failure.





Kramer et al. Int J Artif Organs 1980.

CRRT GOALS

- Removal of waste products
- Restoration of acid-base balance
- Correction of electrolyte abnormalities
- Hemodynamic stabilization
- Fluid balance
- Removal and/or modulation of septic mediators
- Nutritional support

CRRT INDICATIONS

Accepted indications are acute renal failure combined with:

- Hemodynamic instability (cardiovascular)
- Severe fluid overload unresponsive to diuretics
- Hypercatabolic states/trauma - rhabdomyolysis
- High fluid requirements (nutrition, blood products)

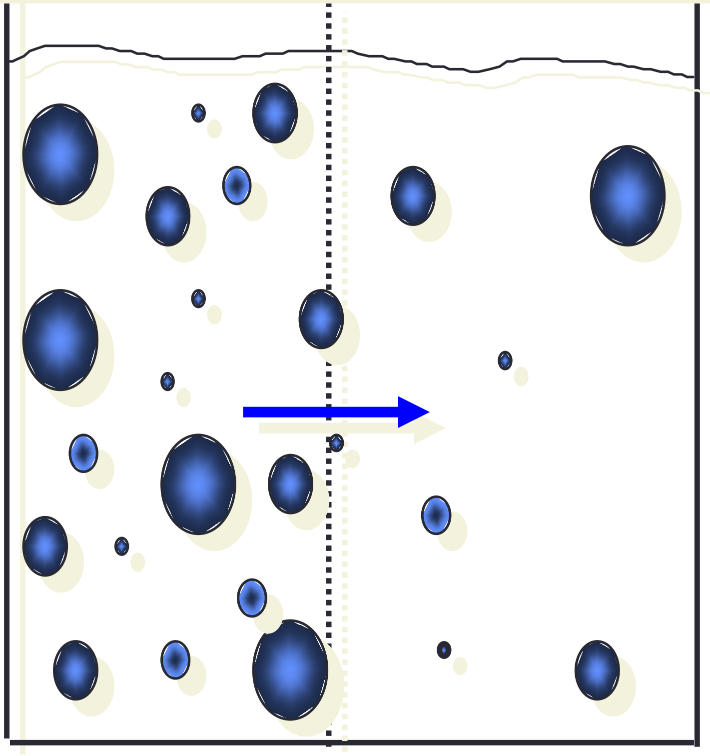
Non-renal indications:

- Sepsis, lactic acidosis, acute respiratory distress syndrome (ARDS), multiple organ dysfunction score (MODS), Chronic congestive heart failure (CHF) or decompensated CHF
- Pre-and post-cardiovascular surgery/coronary artery bypass graft (CABG)
- During extracorporeal membrane oxygenation (ECMO) for fluid management

PRINCIPLES OF CRRT / SOLUTE MANAGEMENT

DIFFUSION

- Small molecules moving at high speed
- Bigger molecules moving slower.



➢Diffusion is the movement of solutes through a semi-permeable membrane from an area of higher concentration to an area of lower concentration until equilibrium has been established.

➢In CRRT, diffusion occurs when blood flows on one side of the membrane, and dialysate solution flows counter-current on the other side.The dialysate does not mix with the blood.

➢Efficient for removing small molecules but not large molecules.

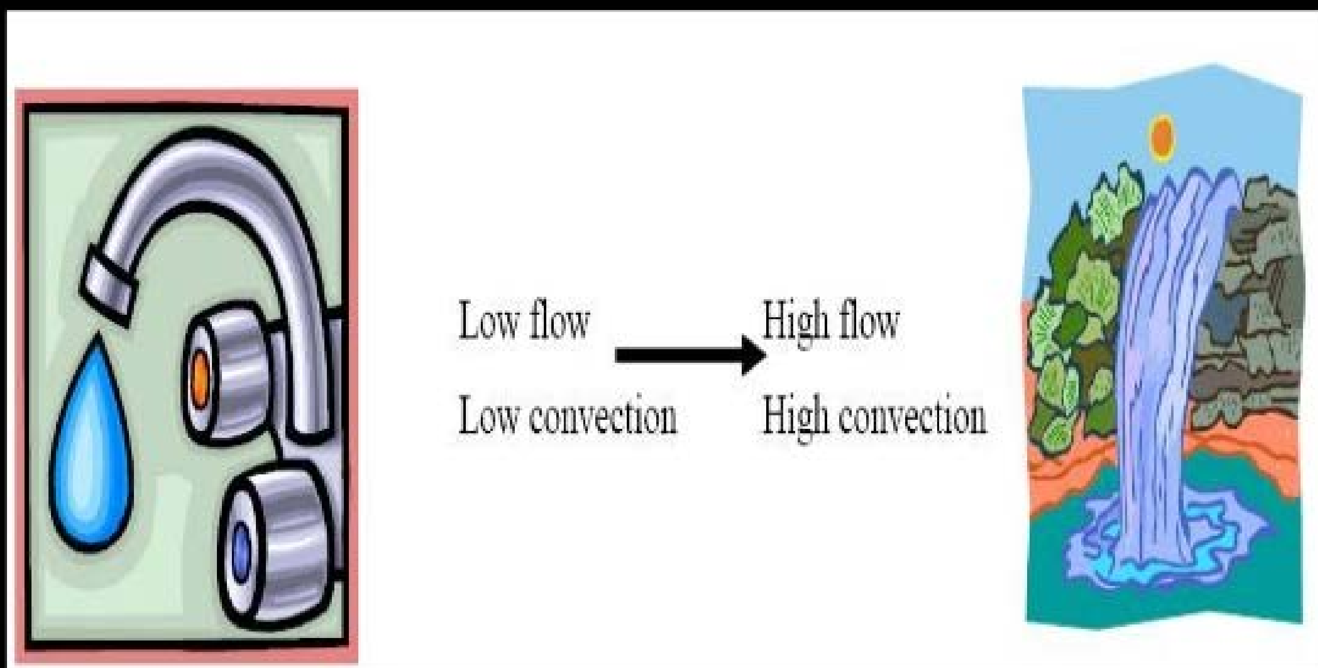
➢Molecular size and membrane type can affect clearances.

CONVECTION

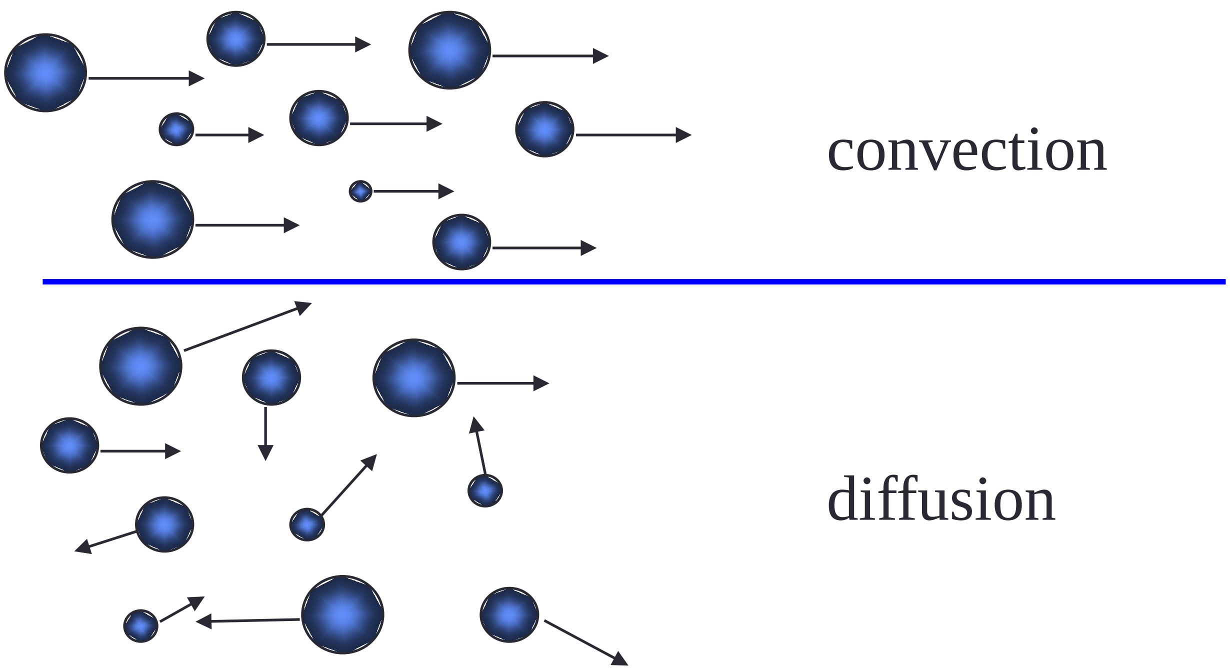
Convection is the one-way movement of solutes through a semi-permeable membrane with a water flow.

- Efficient for both larger and smaller molecules.
- The faster the substitution flow rate, the higher the clearance.
- Pressure difference between the blood and ultrafiltrate causes plasma water to be filtered across. This causes solvent drag for small and large molecules across the membrane leading to removal from the blood. The ultrafiltrate containing the solute should be replaced by substitution solutions.
- Substitution solutions must have near physiological levels of electrolytes and buffer, and be sterile. Solute molecular size and membrane type can affect clearances.

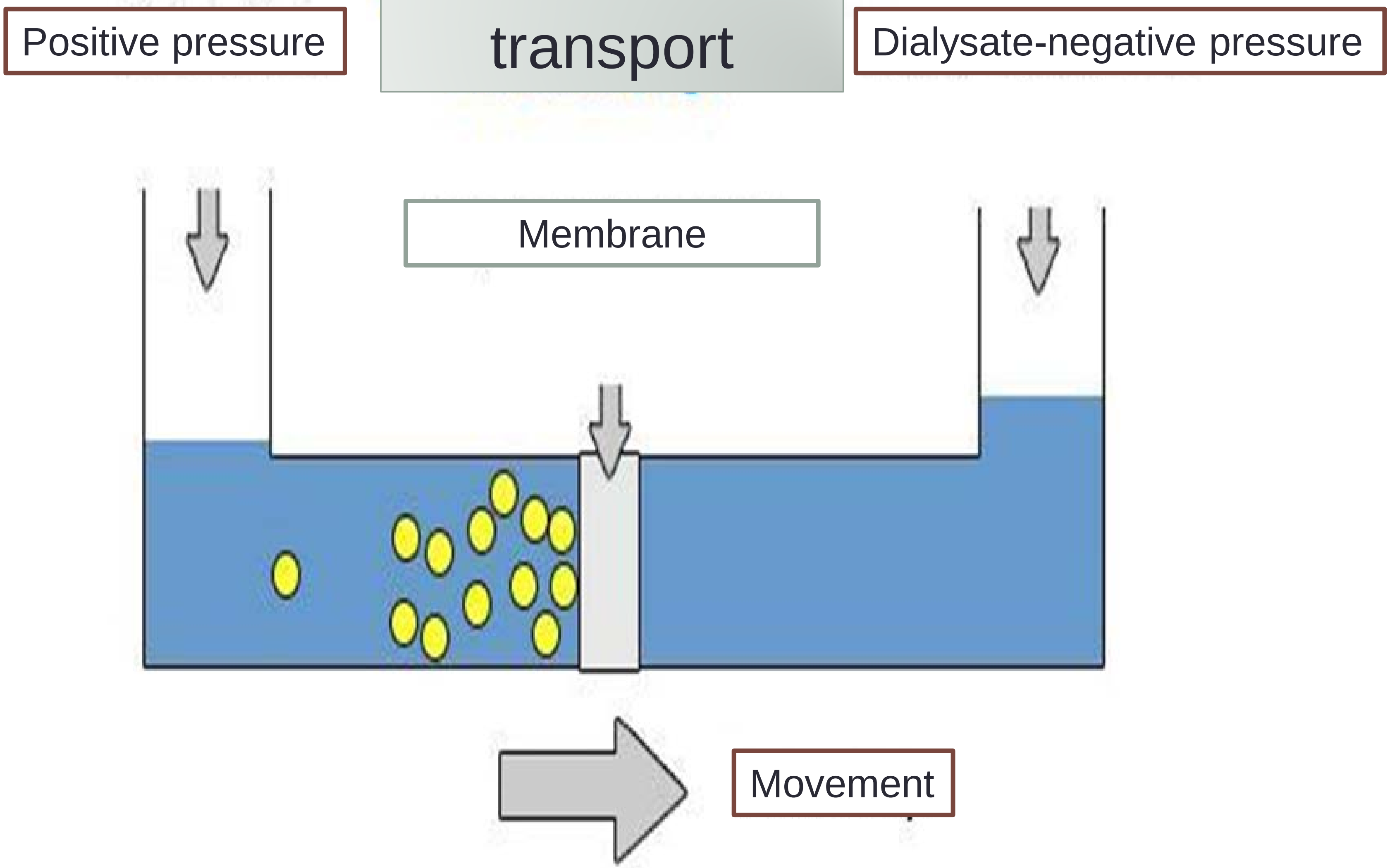
Convection



CONVECTION



Convective transport

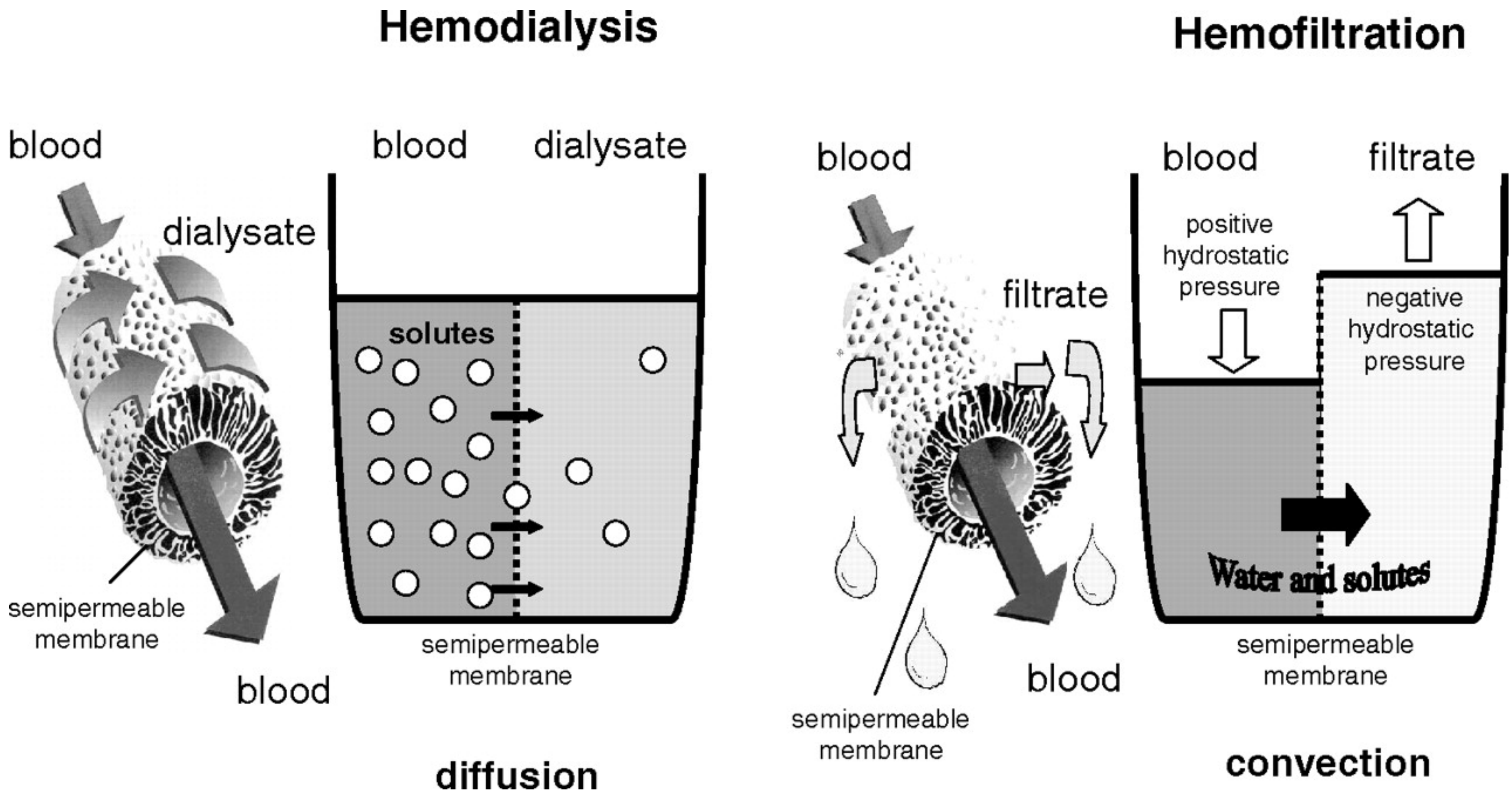


ULTRAFILTRATION

- Ultrafiltration is the movement of fluid through a semi-permeable membrane along a pressure gradient.
- Positive pressure is generated on the blood side of the membrane and negative pressure is generated on the fluid side.
- This gradient, positive to negative, influences the movement of fluid from the blood side to the fluid side, resulting in a net removal of fluid from the patient.
- The ultrafiltration rate depends on the pressure applied to the filter, inside and outside the fibers.
- Minimal solute clearance happens by convection during ultrafiltration.

ADSORPTION

- Adsorption is the adherence of solutes and biological matter to the surface of a membrane.
- High levels of adsorption can cause certain filters to clog and become ineffective.
- Membrane type affects adsorptive tendencies/effectiveness.
- Adsorption may also cause limited removal of some solutes (e.g.,ß2 microglobulins) from the blood.

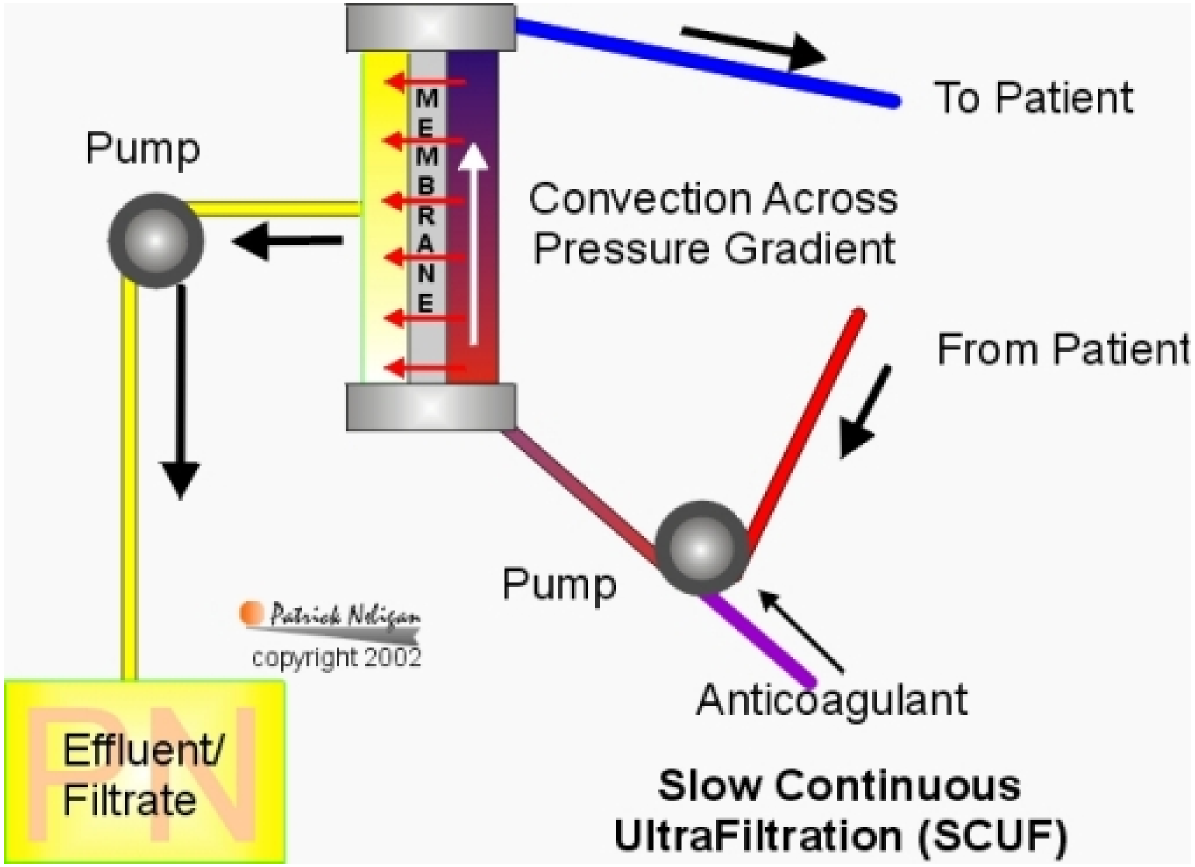

Hemodialysis
blood
dialysate
blood
blood
dialysate
solutes
semipermeable membrane
semipermeable membrane
diffusion
Hemofiltration
blood
filtrate
blood
blood
filtrate
positive hydrostatic pressure
negative hydrostatic pressure
Water and solutes
semipermeable membrane
semipermeable membrane
convection

TYPES OF CRRT

SLOW CONTINUOUS ULTRAFILTRATION (SCUF)

- Primary therapeutic goal: safe management of fluid removal.
- Primary indications: fluid overload without significant electrolyte imbalance.
- Principle used: ultrafiltration
- Therapy characteristics: no dialysate or substitution solutions. Fluid removal only.

SCUF



To Patient
Pump
M E M B R A N E
Convection Across Pressure Gradient
From Patient
Pump
Patrick Neligan
copyright 2002
Anticoagulant
Effluent/ Filtrate
Slow Continuous UltraFiltration (SCUF)

CONTINUOUS VENO-VENOUS HEMOFILTRATION (CVVHD)

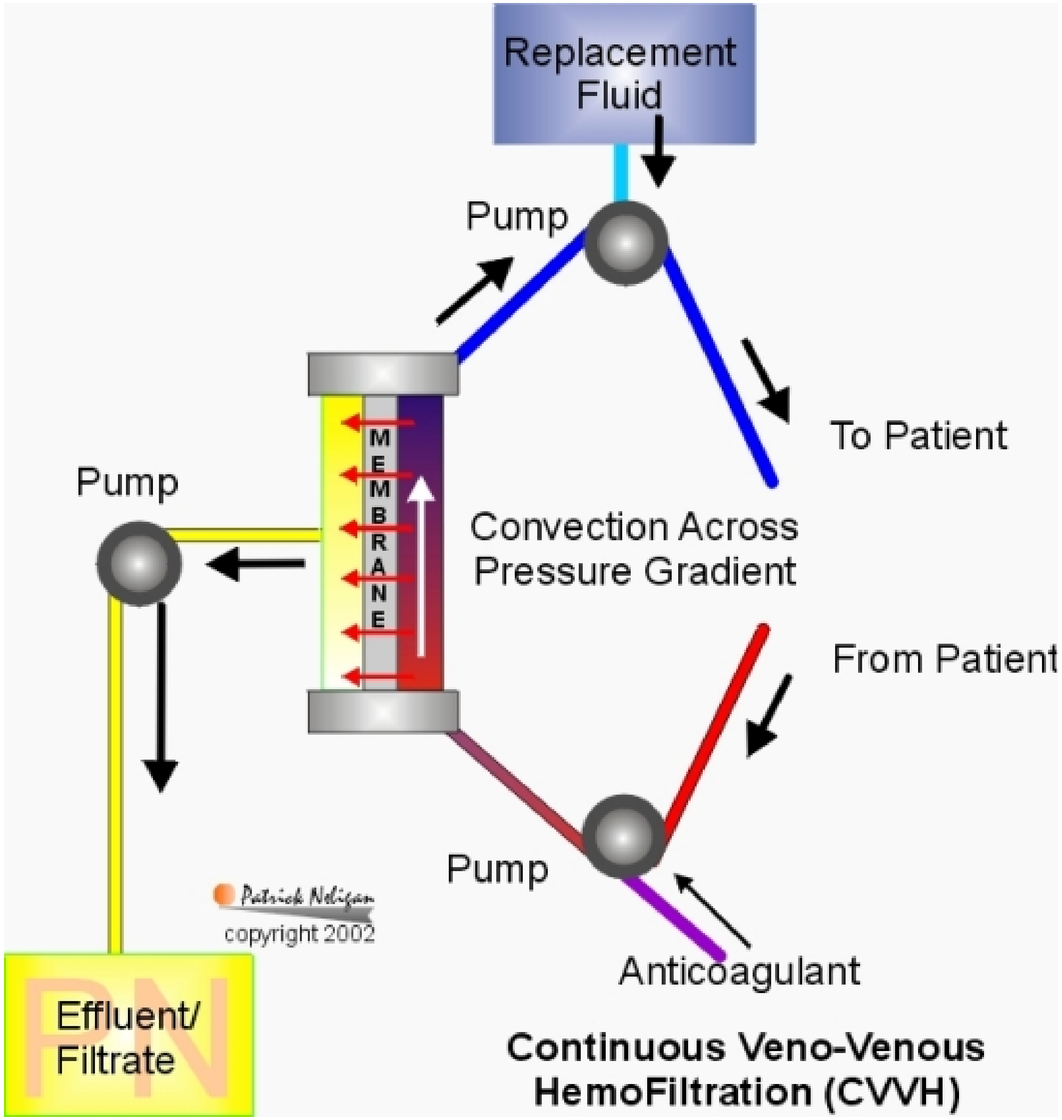
- Primary therapeutic goal: solute removal and safe management of fluid volume.

- Primary indications: uremia, severe acid/base or electrolyte imbalance.

- Principle used: convection.

- Therapy characteristics: Requires substitution solution to drive convection. No dialysate solution. Effective at removing small and large molecules.

CVVHD

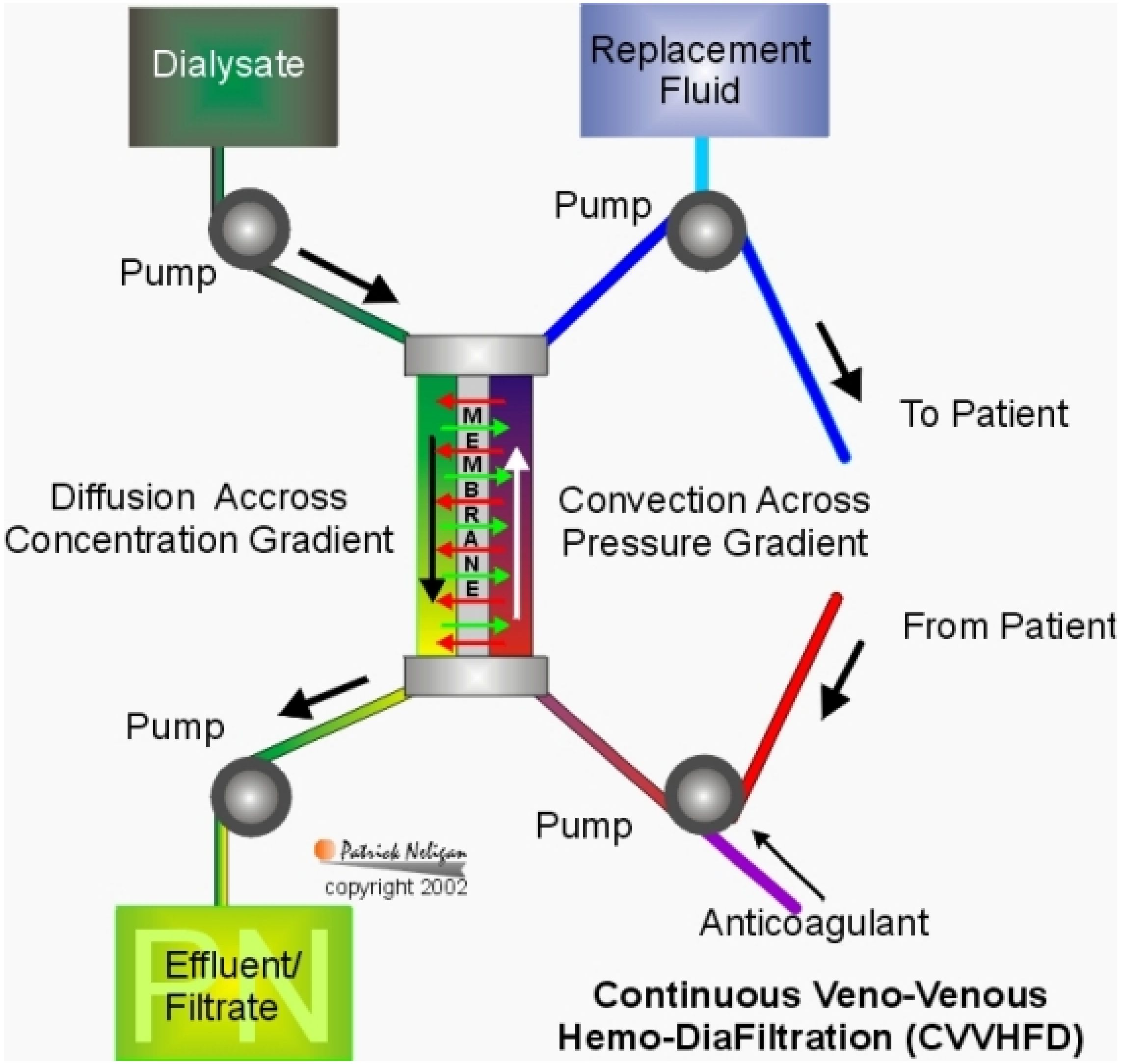


Replacement Fluid
Pump
To Patient
Pump
Convection Across Pressure Gradient
MEMBRANE
From Patient
Pump
Patrick Neligan
copyright 2002
Anticoagulant
Effluent/ Filtrate
Continuous Veno-Venous HemoFiltration (CVVH)

CONTINUOUS VENO-VENOUS HEMODIAFILTRATION (CVVHDF)

- Primary therapeutic goal: solute removal and safe management of fluid volume.
- Primary indications: uremia, severe acid/base or electrolyte imbalance.
- Principle used: diffusion and convection
- Therapy characteristics: requires dialysate fluid and substitution solution to drive diffusion and convection. Effective at removing small, medium and large molecules.

CVVHDF



Dialysate
Replacement Fluid
Pump
Pump
To Patient
M E M B R A N E
Diffusion Accross Concentration Gradient
Convection Across Pressure Gradient
From Patient
Pump
Pump
Patrick Neligan
copyright 2002
Anticoagulant
Effluent/ Filtrate
Continuous Veno-Venous Hemo-DiaFiltration (CVVHFD)

COMPONENTS OF A CRRT PROGRAM

- Vascular access
- Anticoagulation
- CRRT system (machine, hemofilters, line sets, accessories)
- Fluid management
- Team

VASCULAR ACCESS

- Vascular access is a basic prerequisite to perform any type of extracorporeal therapy.

- Access is particularly important in CRRT where catheter performance is tested 24 hours a day.

- The most common catheter now in use is the large-bore, double-lumen catheter.

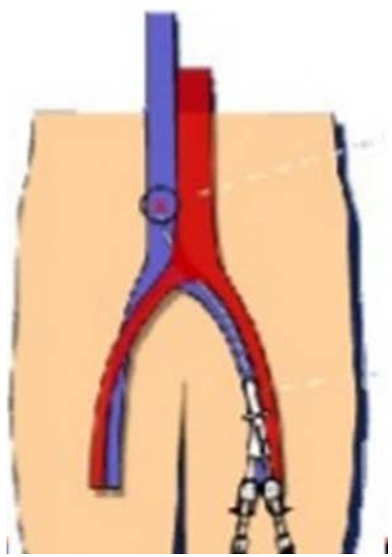
Access Location

Internal Jugular Vein

- Primary site of choice due to lower associated risk of complication and simplicity of catheter insertion.

Femoral Vein

- Patient immobilized, the femoral vein is optimal and constitutes the easiest site for insertion.



Subclavin Vein

- The least preferred site given its higher risk of pneumo/hemothorax and its association with central venous stenosis.

Choosing the right catheter

- The length of the catheter chosen will depend upon the site used.

- Size of the catheter is important in the pediatric population.

- The following are suggested guidelines for the different sites:

  RIJ=15 cm

  LIJ=20 cm

  Femoral=20 cm

ANTICOAGULATION

- In many critically ill patients undergoing CRRT, anticoagulation is typically achieved through the use of low-dose heparin administered into the blood, before the hemofilter.

- The remaining patients may have underlying conditions, which put them at high risk of bleeding, and therefore heparin anticoagulation is not used.

- All types of anticoagulation have risks. It is a constant challenge to find a balance between the risk of filter clotting and the risk of patient bleeding.

- The formation of clots in the blood is primarily the result of platelet activation and subsequent obstruction of coagulation cascade.

- Therefore the majority of anticoagulation therapies are designed to interfere with the coagulation pathway.

- Both the patient and the circuit should be monitored to determine the effect of anticoagulation delivered, keeping in mind that preventing patient bleeding takes priority over preventing filter clotting.

CRRT uses various anticoagulants, the most common of them are heparin and citrate.

HEPARIN

- Heparin is the most frequently used anticoagulant. It is commonly used during the priming of the hemofilters and is infused into the CRRT circuit post blood pump and before the filter.

- All types of heparin carry the risk of heparin-induced thrombocytopenia (HIT) and platelet counts must be monitored.

- If HIT is suspected, heparin must be discontinued immediately.

HEPARIN DELIVERY

Typical low-dose pre-filter heparin

- Approximately 5-10 units/kg/hr
- Delivered into the CRRT circuit post-pump, pre-filter
- Mildly elevates the activated partial thromboplastin time (aPTT)

Typical medium-dose pre-filter heparin

- Approximately 8-10 units/kg/hr
- Delivered into the CRRT circuit post-pump, pre-filter
- Mildly elevates the aPTT

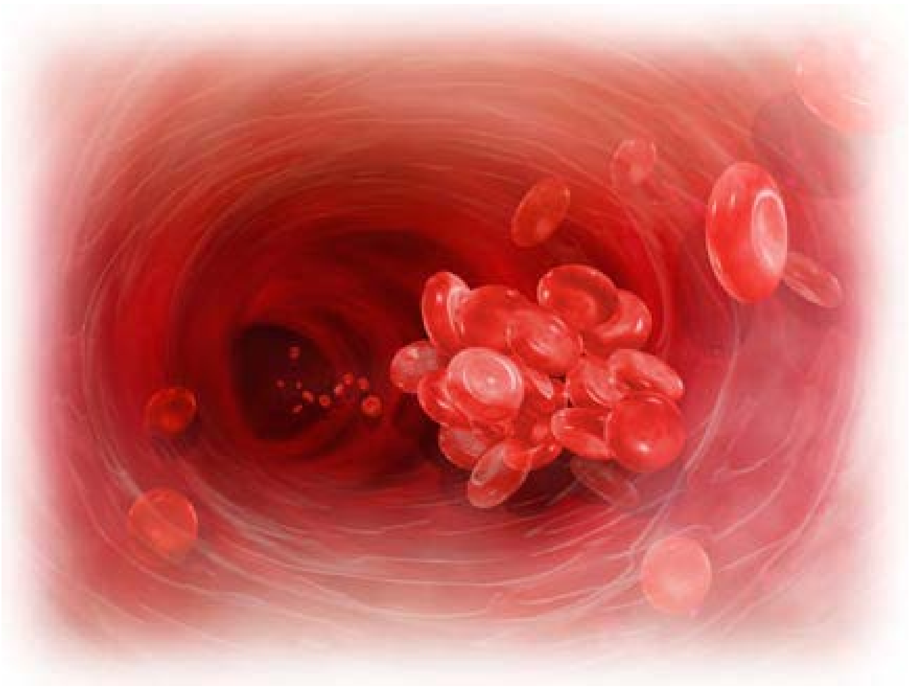
Therapeutic systemic heparin

- Adjusted to achieve required aPTT as prescribed by physician
- Administered via a volumetric infusion pump
- Most commonly used for patients with systemic anticoagulation requirements

Regional heparin - Rarely used

- Heparin is infused pre-filter and protamine infused post-filter to reverse effects of heparin.

- Goal is to anticoagulate the circuit without anticoagulating the patient.



NO ANTICOAGULATION

In some circumstances, risks to the patient complicates the use of any anticoagulant.

These circumstances may include, but are not limited to:

- Active bleeding
- Increased aPTT
- Increased international normalized ratio (INR)
- Liver failure
- Low platelet count

- In patients at high risk of haemorrhage or requiring rapid reversal of anticoagulation, prostaglandin I2 (Prostacyclin) or prostaglandin E2 may be considered.

- Prostaglandins inhibit platelet reactivity and aggregation in a dose dependent manner, an effect that lasts for up to 2 hours after stopping infusion of prostaglandins.

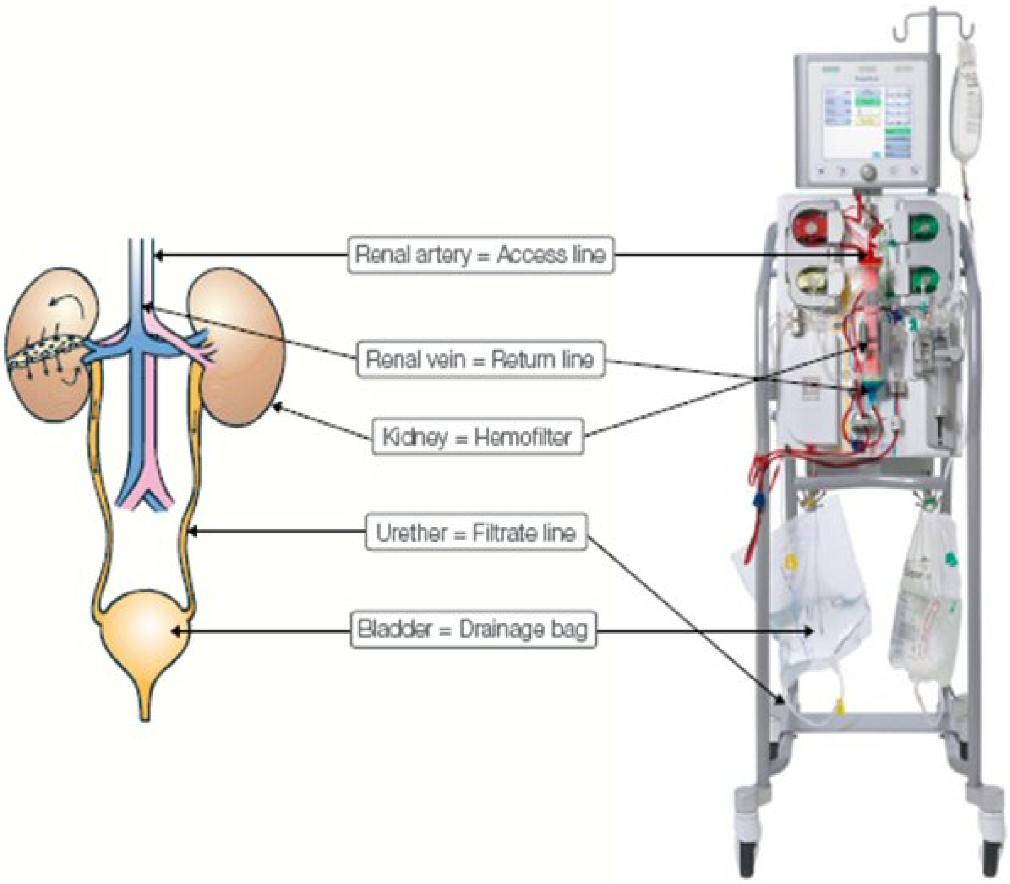
- They act synergistically with heparins and so can be used either alone or in combination with low dose UFH or LMWHs to preserve circuit integrity with a lower risk of bleeding.

The CRRT system

- Machine
- Hemofilter
- Line sets
- Solutions
- Accessories

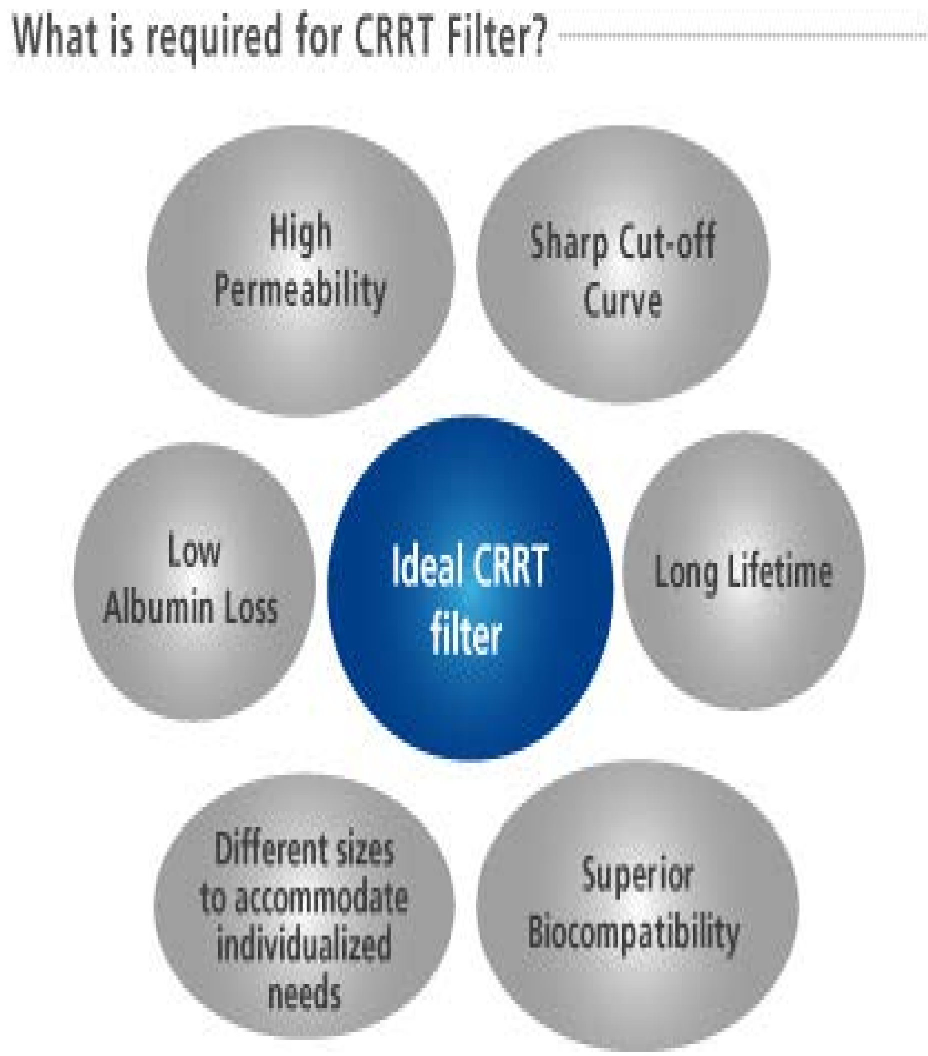
CRRT MACHINE
An instrument designed to deliver CRRT

- It consists of blood and fluid pumps, user-friendly interface, scales and integrated safeguards.



HEMOFILTER - artificial kidney requirement of any CRRT system

- The hemofilter contains a semi-permeable membrane in a hollow fiber design where the blood flows.
- Dialysate flows on the outside of the fibers.
- Solute and fluid removal will be determined by the type of membrane and the surface area.
- Hemofilters are usually synthetic.



SUBSTITUTION SOLUTION

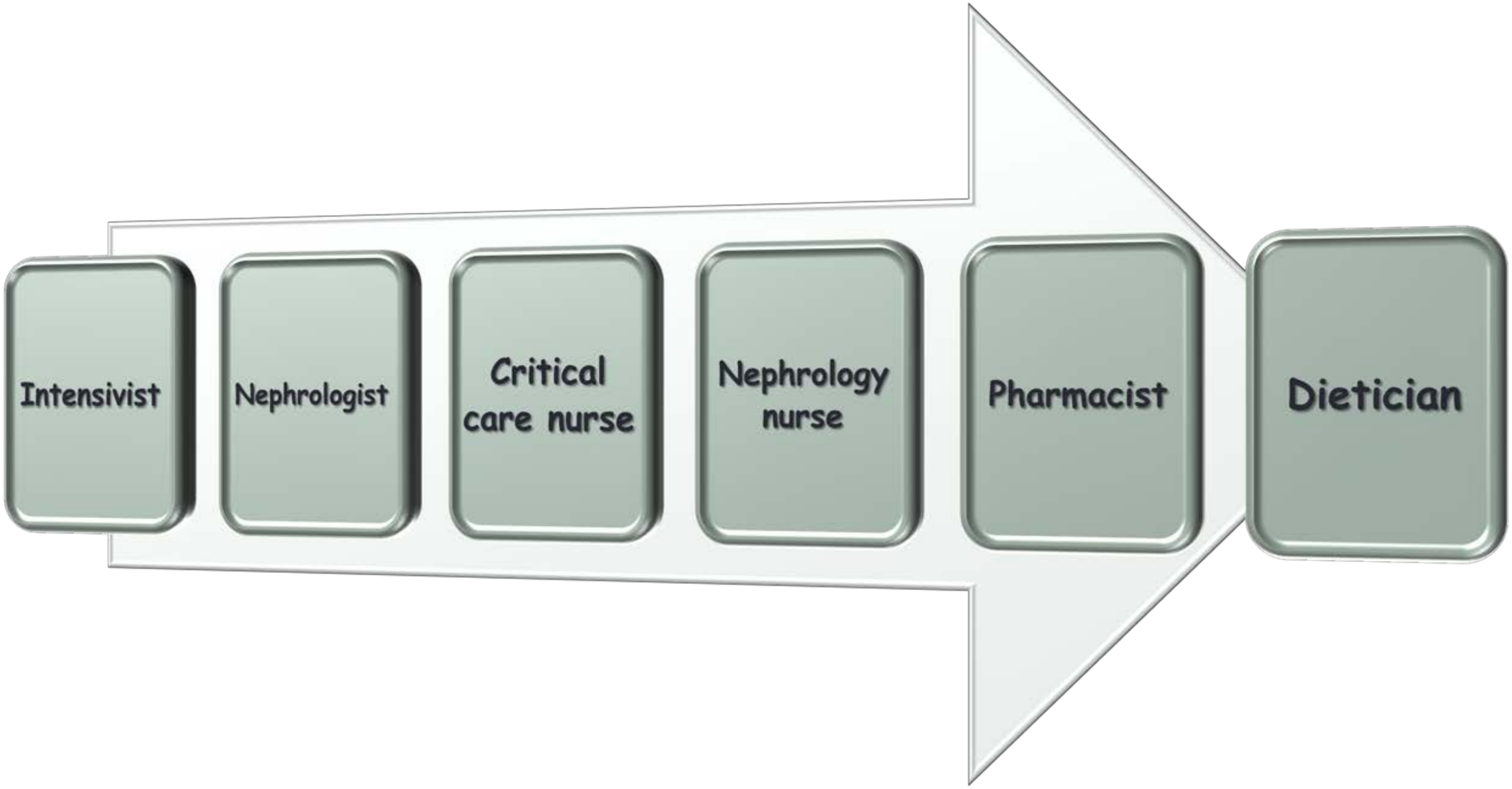
- Primary function: removal of solutes via convection (small, medium, large).
- Does not affect the patient's intravascular volume.
- Must be physiological from an electrolyte standpoint and sterile.
- Infused into the patient's blood pre-dilution, post-dilution or both.
- Substitution solution allows convective clearance.
- The volume of substitution solutions infused is automatically removed by the machine.
- Sometimes referred to as 'replacement fluid'.

DIALYSATE SOLUTION

- Primary function: removal of solutes via diffusion (small).
- Does not affect the patient's intravascular volume.
- Must be physiological and should be sterile.
- Dialysate solution allows diffusive clearance.
- Infused into the external dialysate port of the hemofilter counter-current to the blood flow.
- The volume of dialysate solutions infused is automatically removed by the machine.
- Buffers include lactate and bicarbonate.
- Formulation is usually calcium-free when used with citrate anticoagulation.

TEAM

The addition of CRRT to the critically ill patient's care requires the expertise, cooperation and focus of a cross-functional team, which may include:



Complications

Vascular access

- Vascular spasm (initial BFR too high).
- Movement of catheter against vessel wall.
- Improper length of hemodialysis catheter inserted.

Fluid volume deficit

- Excessive fluid removal without appropriate fluid replenishment.

Complications

Hypotension

- Intravascular volume depletion
- Underlying cardiac dysfunction

Electrolyte imbalances

- High ultrafiltration rates (high clearance)
- Inadequate replenishment of electrolytes by intravenous infusion,
- Inadequate replenishment of bicarbonate loss during CRRT

Complications

Air embolus

- Leaks or faulty connections in tubing
- Line separation

Cardiac arrest

- Hypotension/hypertension
- Hemolysis
- Air embolism
- Circulatory overload
- Arrhythmias

SUMMARY

- In summary, the main goals of CRRT are removal of waste products, restoration of acid/base balance, and correction of fluid and electrolyte abnormalities, while maintaining hemodynamic stability.

- The goal of any continuous renal replacement therapy is to replace, as best as possible, the lost function of the native kidney. While CRRT provides a good option for a patient with ARF, nothing will replace the complete function of a healthy kidney.

ADVANTAGES

- Compared to standard hemodialysis, applied for a short period of time, CRRT provides improved hemodynamic stability (slow, gentle and continuous).
- Provides continuous fluid and electrolyte management (avoidance of rapid fluid and electrolyte shifts).
- May facilitate removal of cytokines and mediators.
- Adapted to the needs of the critically ill.

LIMITATIONS

- Requires a large-bore central vascular catheter.
- Typically requires continuous anticoagulation.
- Requires immobilization of the patient for prolonged periods.

Objectives

When **to start ?**

What **Modality ?**

HOW **can we do it ?**

CRRT vs. IHD (intermittent HD) in Renal Recovery

- Recent studies suggest that CRRT is superior to IHD with respect to recovery of renal function.

- If length of stay (LOS) in ICU can be reduced this will have a major impact on hospital budget.

- Although both CRRT and IHD may employ similar principles of clearance of uraemic toxins, there are important differences in the actual mode of solute removal and delivery of therapy.

Table 1. Trias comparing early and later initiation of renal replacment therapy for patients with acute kidney injury

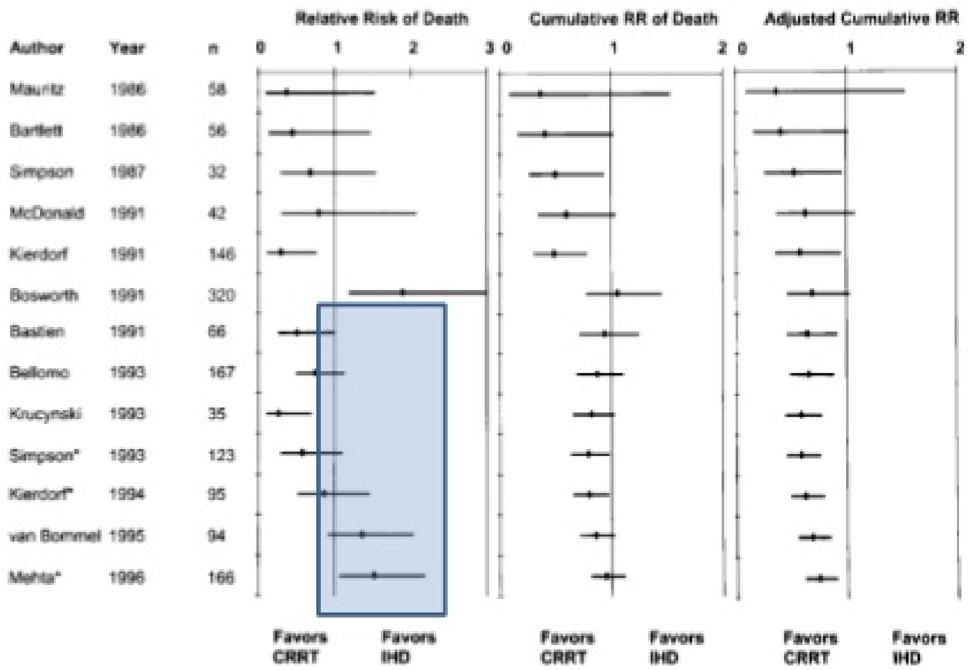
Autor	Year	RRT modality	No-of patients	Earlier	Later	Mortality (early vs.late
Bouman wt al.	2002	CRRT	71	BUN 45	BUN 85	31 vs.25%
Durmaz et al.	2003	HD	44	prophylactic	traditional	4 vs.30%
Sugahara and Suzuki	2004	CRRT	28	UO<30 ml/h	UO<20 ml/h	12 vs.86%
Jamale et al.	2013	HD	248	BUN 71	BUN 101	21 vs.12%
Lim at.al	2015	CRRT	84	Akin 1 or 2	AKIN 3	50 vs.32%

Is CRRT really superior to IHD (IRRT)?

Meta analysis - 2002

Outcome with IRRT vs CRRT (1)

- ***Trial quality low***: many non-randomized
- Therapy ***dosing variable***
- Illness ***severity variable*** or details missing
- ***Small numbers***
- ***Uncontrolled*** technique, membrane
- Definitive trial would require 660 patients in each arm!
- ***Unvalidated instrument*** for sensitivity analysis



> "there is insufficient evidence to establish whether CRRT is associated with improved survival in critically ill patients with ARF when compared with IRRT"

Kellum, J et al. Intensive Care Med 2002; 28: 29-37

Is CRRT really superior to IHD (IRRT)?

Meta analysis - 2002

Outcome with IRRT vs CRRT (2)

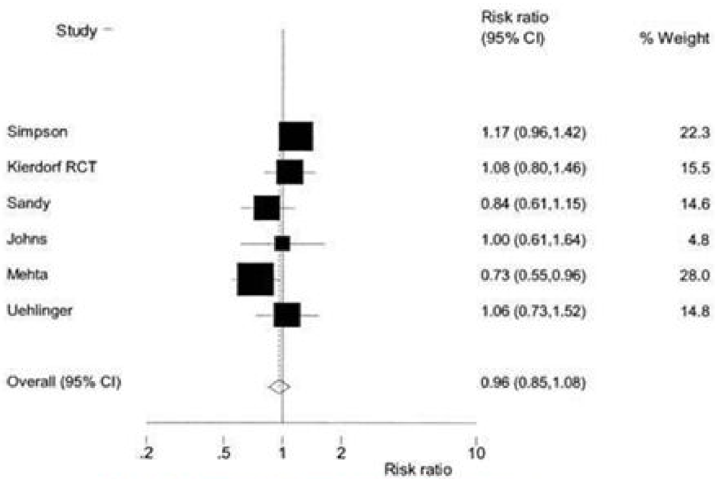


Fig. 2. RR for death for IHD: primary analysis (randomized trials).

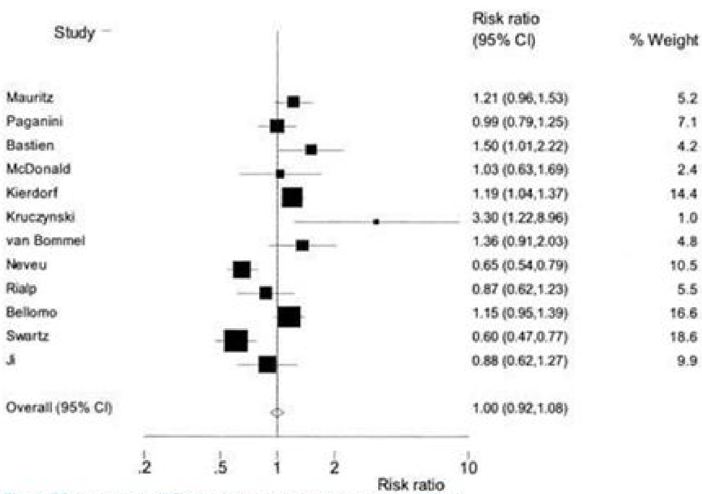


Fig. 3. RR for death for IHD: sensitivity analysis (nonrandomized trials).

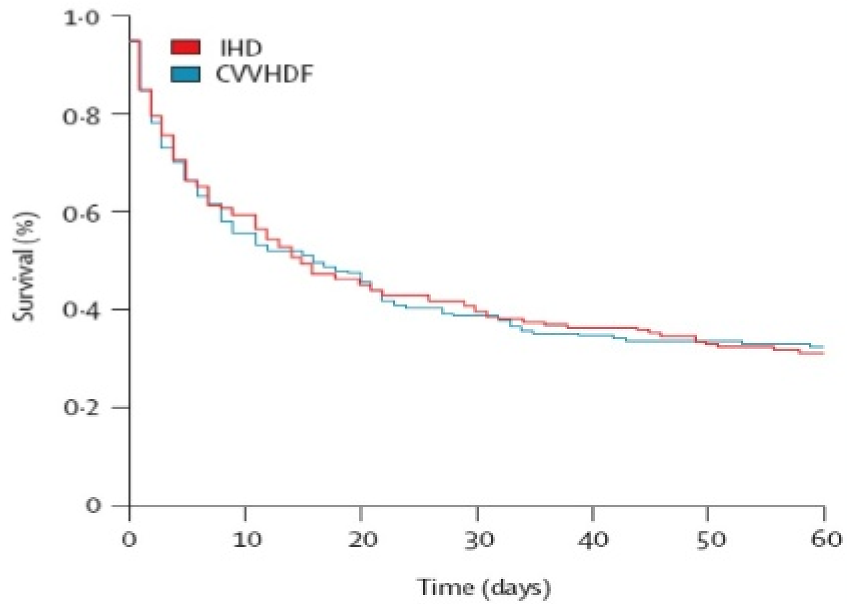
- No mortality difference between therapies
- No renal recovery difference between therapies
- Unselected patient populations
- Majority of studies were ***unpublished***

Tonelli, M *et al.* Am J Kidney Dis 2002; 40: 875-885

Is CRRT really superior to IHD (IRRT)?

Meta analysis - 2002

Outcome with IRRT vs CRRT (3)



Numbers at risk				
IHD	184	85	68	58
CVVHDF	175	83	62	57

Vinsonneau, S *et al*. Lancet 2006; 368: 379-385

Standard/recommendation

1. There is insufficient evidence to recommend CRRT over IHD or vice versa in terms of patient mortality, but data tend to suggest a better renal outcome with CRRT.

2. In particular it appears appropriate to use CRRT in haemodynamically unstable patients and those with fluid balance issues.

3. CRRT also appears to offer particular benefit in patients with/or at risk ofcerebral oedema.

4. IHD is appropriate to use in haemodynamically stable patients during their recovery from a critical illness. Its use will be determined by local organisational factors.

CRRT vs. PD (peritoenal dialysis)

- There are few data comparing peritoneal dialysis (PD) with CRRT.
- A randomised trial in patients with sepsis and AKI was stopped early because of the significant benefit on mortality of CRRT compared to PD.
- Although PD is not usually used in the critically ill, it may have a role in patients with problematic vascular access.

Conclusions

- An increased treatment dose from 20 ml/h/kg to 35 ml/h/kg significantly improved survival.
- A delivery of 45ml/kg/hr did not result in further benefit in terms of survival, but in the septic patient an improvement was observed.
- **It is suggest an early initiation of treatment and a minimum dose delivery of 35 ml/h/kg (ex. 70kg patient = 2450 ml/h) improve patient survival rate.**

Effects of different doses in CVVH on outcome of ARF - *Ronco & Bellomo study. Lancet, 2000.*

CRRT/OUR EXPERIENCE

- WE STARTED IN 2006
- WE HAD ONLY ONE MACHINE
- NOW, WE HAVE THREE WORKING MACHINES

Gender characteristics –10 years

Year	Males	Females
2006	3	0
2007	6	2
2008	12	5
2009	11	6
2010	19	7
2011	26	13
2012	27	19
2013	20	11
2014	15	12
2015	31	21
Total	170	96

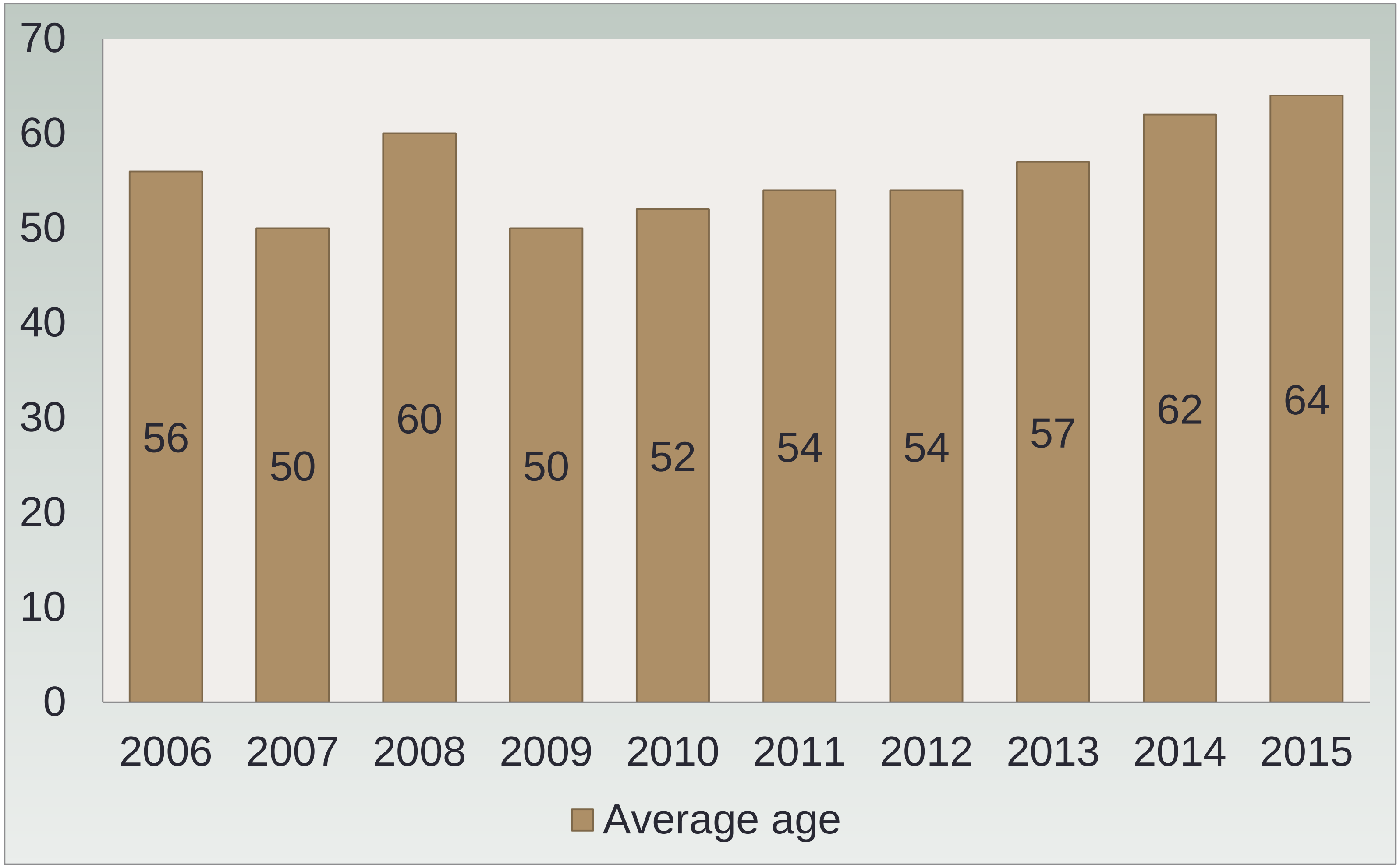
Gender characteristics -10 years

Year	Males	Females
2016	34	30
2017	27	15
2018	27	20
Total	88	65

Average age

Year	Average age
2006	56
2007	50
2008	59,6
2009	50
2010	52
2011	54
2012	53,7
2013	57,26
2014	62,5
2015	64
Total	55,9

Average age


70
60
50
40
30
20
10
0
56
50
60
50
52
54
54
57
62
64
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
Average age

Year	Average age
2016	58,7
2017	63,59
2018	57,53
Total	59,94

Etiology

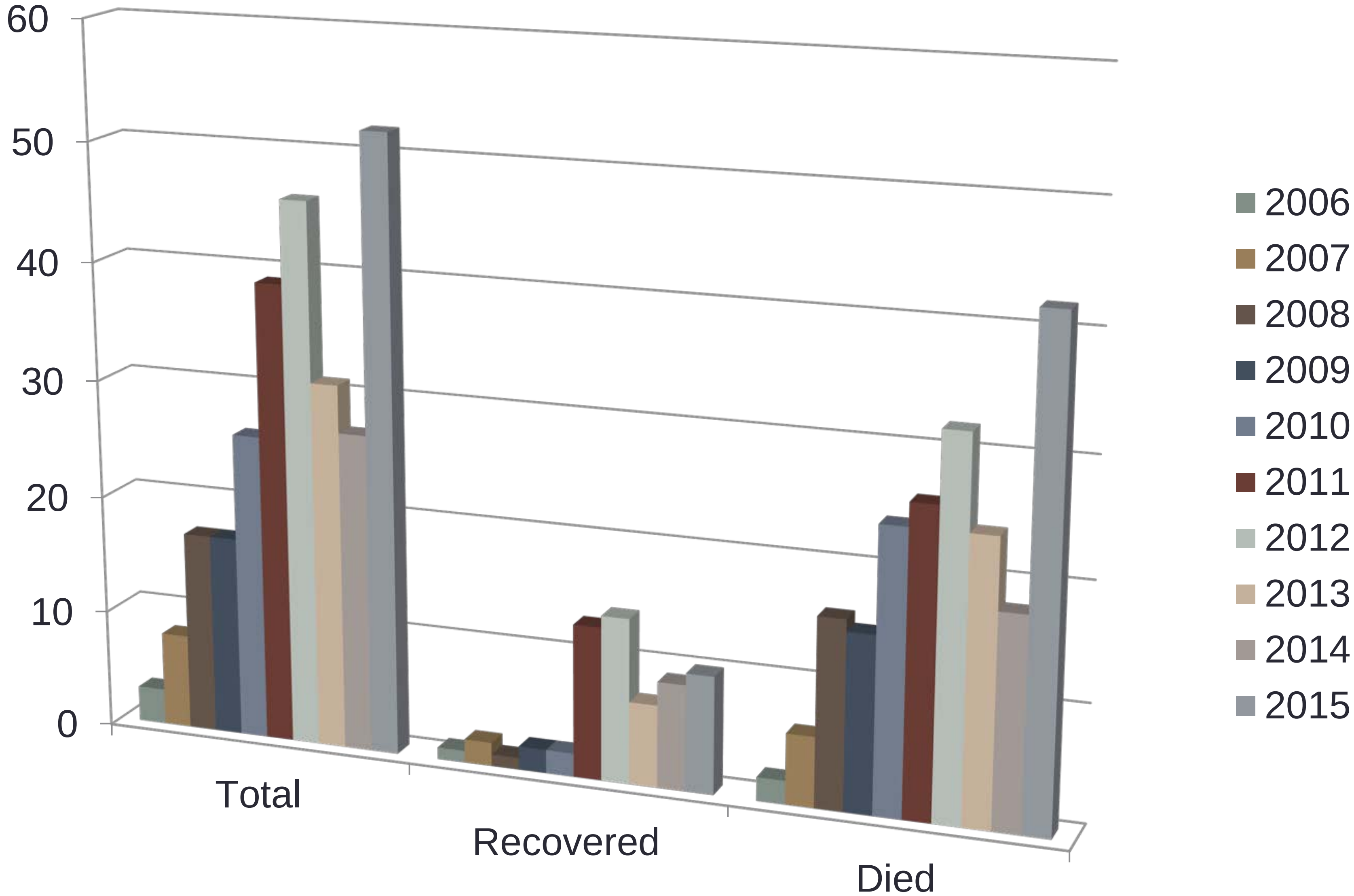
	2009	2011	2014
H1N1	4 (3 died) (1 recovered)	4 (2 died) (2 recoverd)	2 2 ex
CONTRAST NEPHROPATHY		3	2 (all died)

Etiology

	2016	2017	2018
Septic schook	12	15	16
Cardiovascular surgery	20	13	12
H1N1	7 (3 recovered)	-	4 (all died)
Neurological incident	-	6	4

Year	Total	Recovered	Died
2006	3	1	2
2007	8	2	6
2008	17	1	16
2009	17	2	15
2010	26	2	24
2011	39	13	26
2012	46	14	32
2013	31	7	24
2014	27	9	18
2015	52	10	42

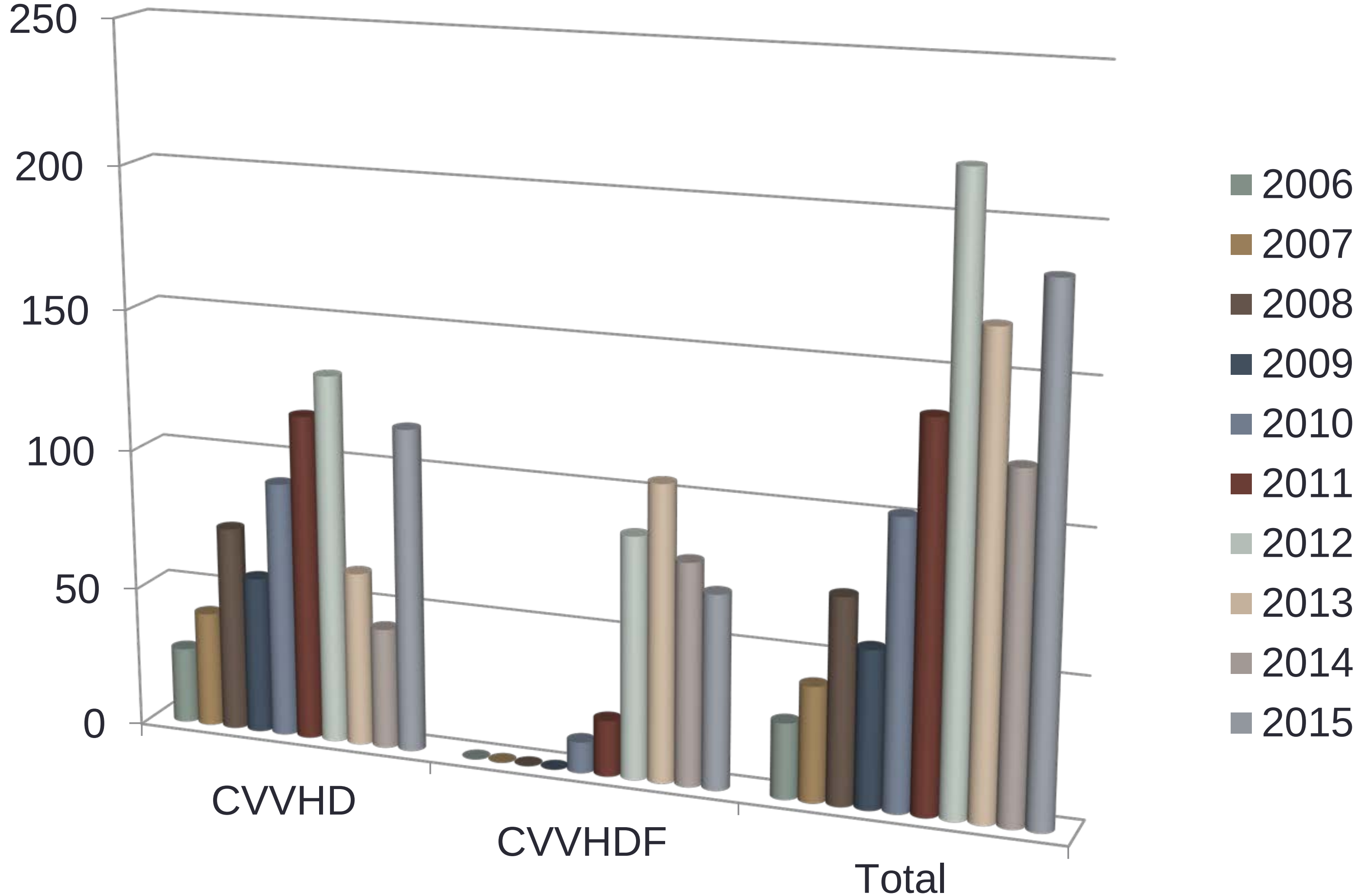
10 years CRRT



Year	Total	Recovered	HBB	Died
2016	64	9	14	41
2017	42	1	6	35
2018	47	7	7	33

CRRT characteristics - 10 years

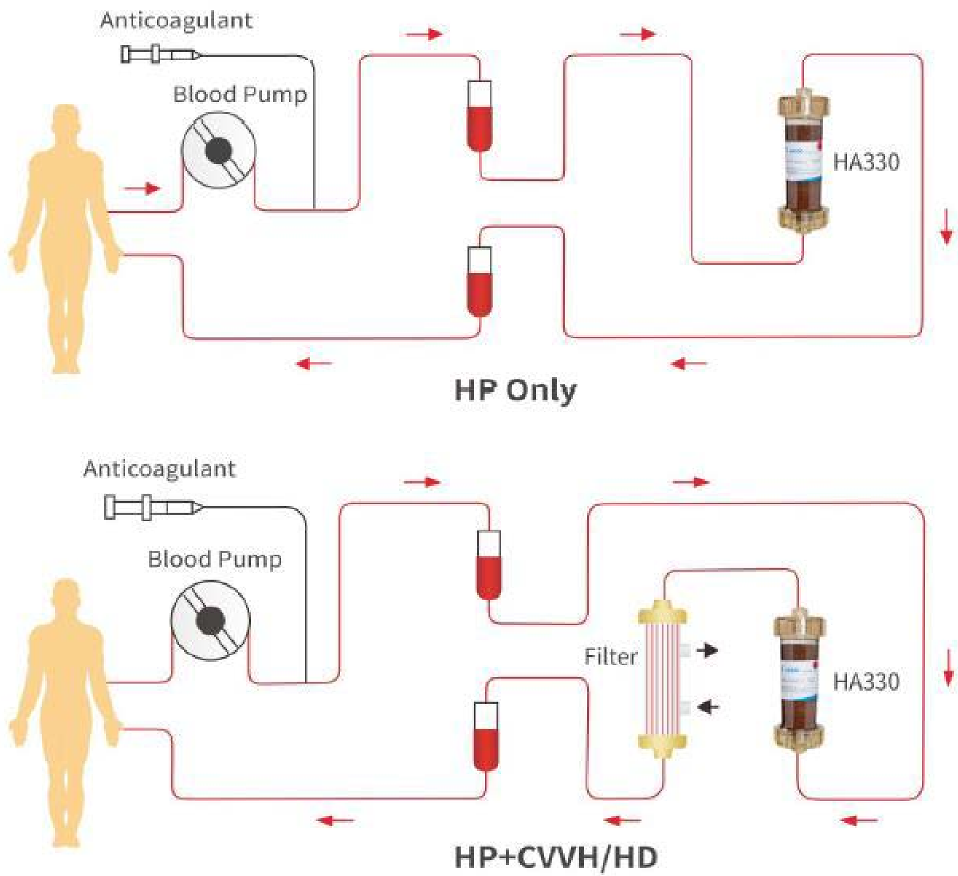
Year	CVVHD+CVVHDF	CVVHD	CVVHDF
2006	27	27 CVVHD	
2007	41	41 CVVHD	
2008	73	73 CVVHD	
2009	56	56 CVVHD	
2010	102	91 CVVHD	11 CVVHDF
2011	136	116 CVVHD	20 CVVHDF
2012	217	131 CVVHD	86 CVVHDF
2013	167	62 CVVHD	105 CVVHDF
2014	122	43 CVVHD	79 CVVHDF
2015	184	115 CVVHD	69 CVVHDF
Total	1125	755 CVVHD	370 CVVHDF


250
200
150
100
50
0
CVVHD
CVVHDF
Total
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015

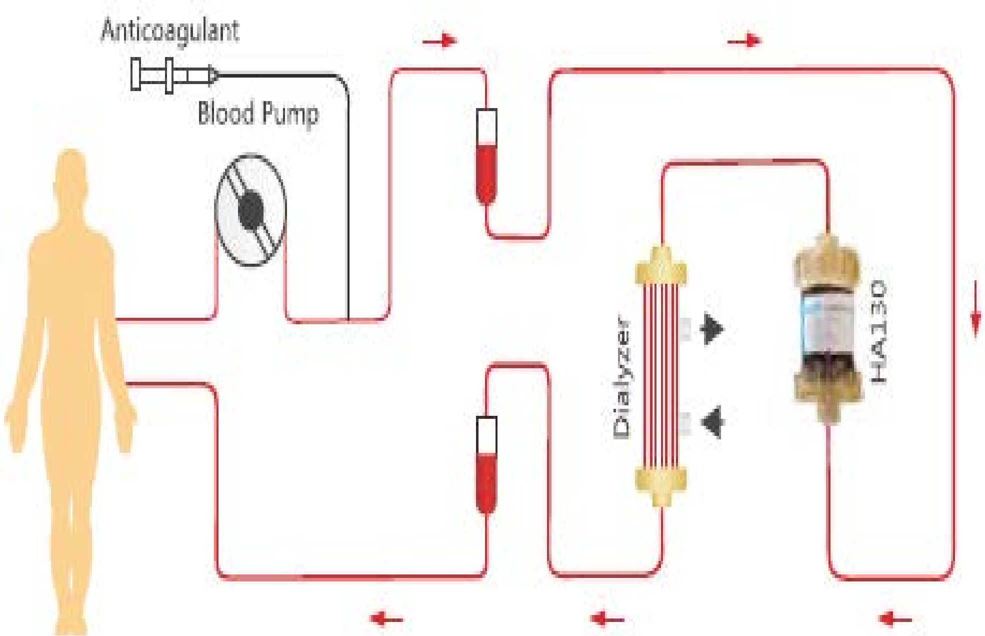
Year	CVVHD+CVVHDF
2016	257
2017	111
2018	119
Total	487

A New Series of Sorbent Devices for Multiple Clinical Purposes

HA330: Various connection with CPB, ECMO, CVVH



HA130:Connection with dialyzer




THANK
YOU!