Continuous Renal Replacement Therapy

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Definition of Terms

- SCUF - Slow Continuous Ultrafiltration
- CAVH - Continuous Arteriovenous Hemofiltration
- CAVH-D - Continuous Arteriovenous Hemofiltration with Dialysis
- CVVH - Continuous Venovenous Hemofiltration
- CVVH-D - Continuous Venovenous Hemofiltration with Dialysis
- SLED – Sustained Low-Efficiency Dialysis

Indications for Renal Replacement Therapy

- Remove excess fluid because of fluid overload
- Clinical need to administer fluid to someone who is oliguric
  - Nutrition solution
  - Antibiotics
  - Vasoactive substances
  - Blood products
  - Other parenteral medications

Advantages of Continuous Renal Replacement Therapy

- Hemodynamic stability
  - Avoid hypotension complicating hemodialysis
  - Avoid swings in intravascular volume
- Easy to regulate fluid volume
  - Volume removal is continuous
  - Adjust fluid removal rate on an hourly basis
- Customize replacement solutions
- Lack of need of specialized support staff

Advantages of SLED

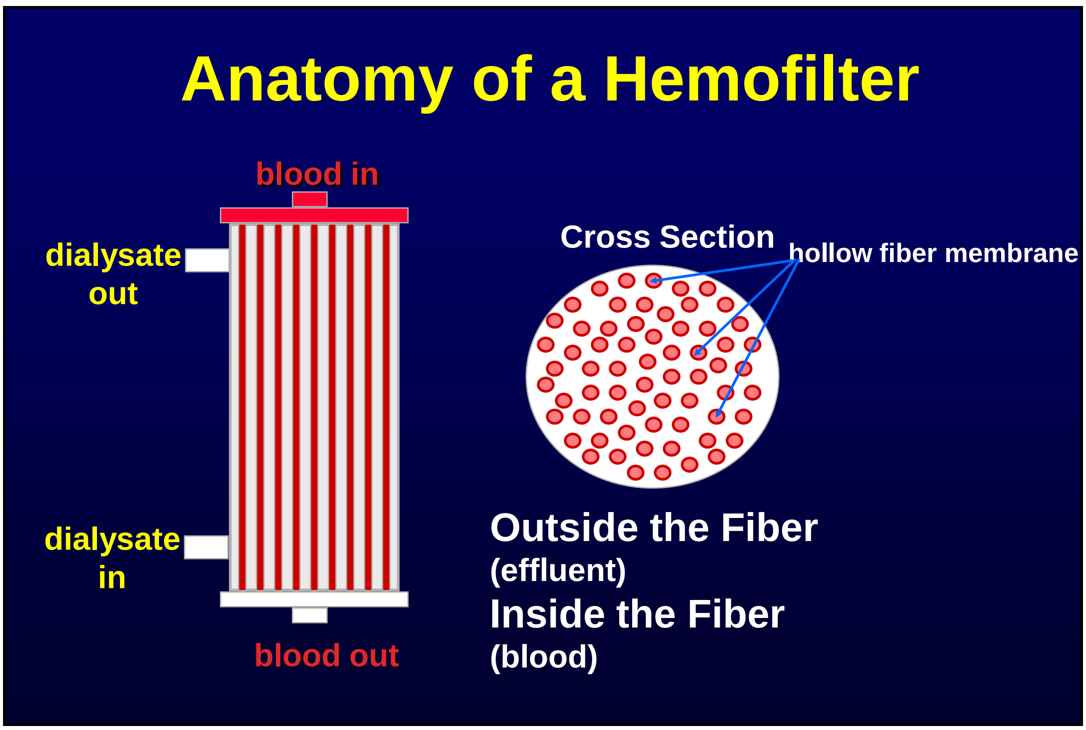
- Hemodynamic stability
  - Avoid hypotension complicating hemodialysis
  - Avoid swings in intravascular volume
- High solute clearance
- Flexible scheduling
- Lack of need for expensive CRRT machines
- Lack of need for custom replacement solutions
- Lack of need of specialized support staff

Disadvantages of Continuous Renal Replacement Therapy

- Lack of rapid fluid and solute removal
  - GFR equivalent of 5 - 20 ml/min
  - Limited role in overdose setting
    - SLED – Developing role
- Filter clotting
  - Take down the entire system

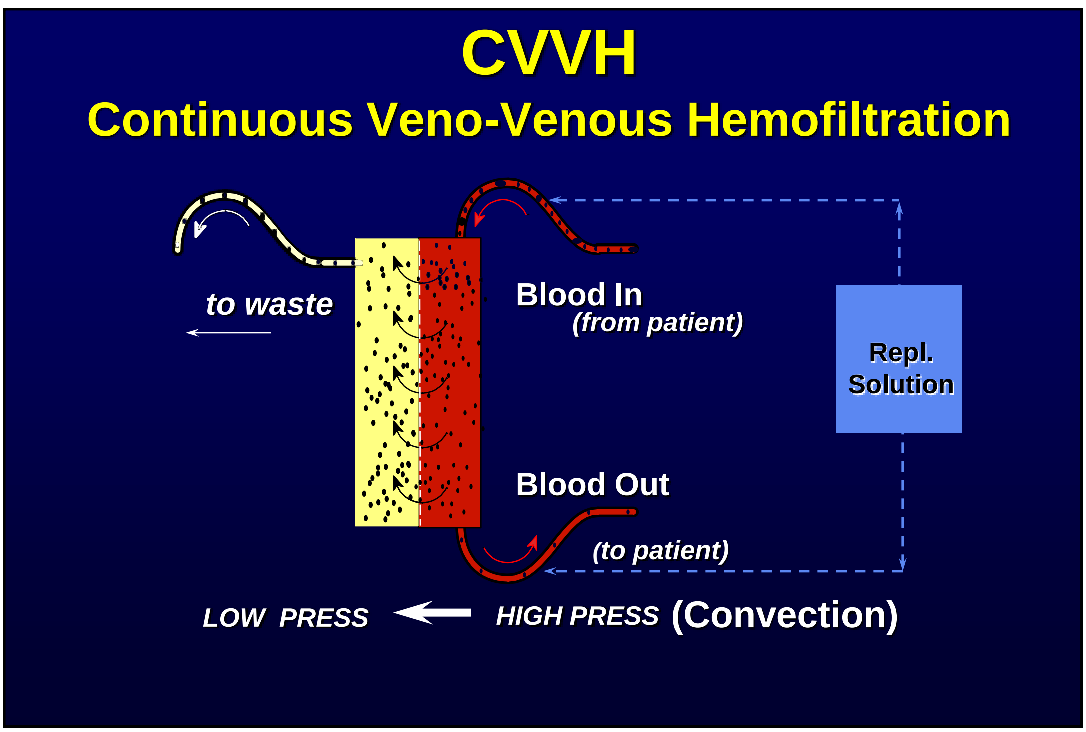
Basic Principles

- Blood passes down one side of a highly permeable membrane
- Water and solute pass across the membrane
  - Solutes up to 20,000 daltons
    - Drugs & electrolytes
- Infuse replacement solution with physiologic concentrations of electrolytes


Anatomy of a Hemofilter
blood in
dialysate out
dialysate in
blood out
Cross Section
hollow fiber membrane
Outside the Fiber
(effluent)
Inside the Fiber
(blood)

Basic Principles

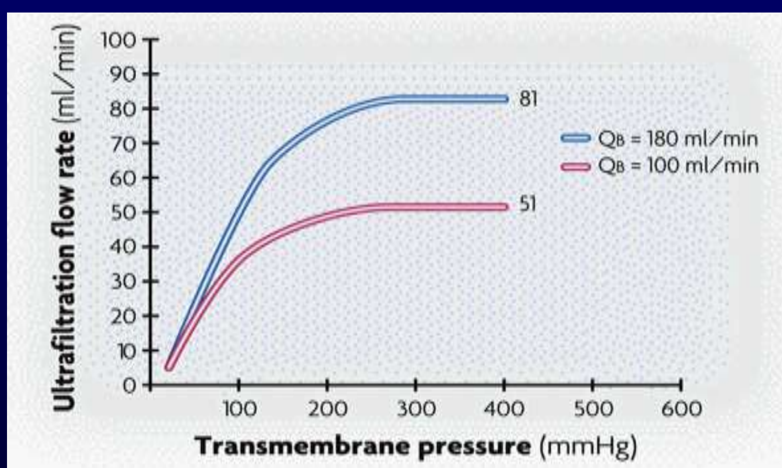
- Hemofiltration
  - Convection based on a pressure gradient
  - 'Transmembrane pressure gradient'
    - Difference between plasma oncotic pressure and hydrostatic pressure
- Dialysis
  - Diffusion based on a concentration gradient


CVVH
Continuous Veno-Venous Hemofiltration
to waste
Blood In
(from patient)
Repl.
Solution
Blood Out
(to patient)
LOW PRESS
HIGH PRESS
(Convection)

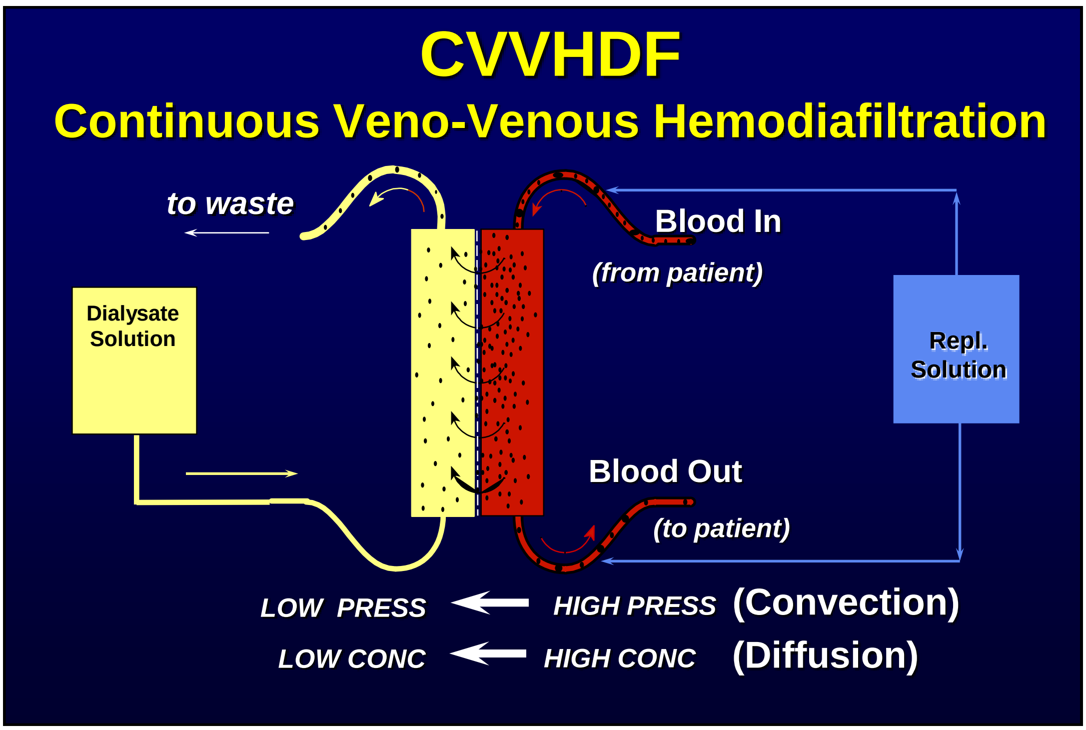
CVVH
Continuous VV Hemofiltration

- Primary therapeutic goal:
  - – Convective solute removal
  - – Management of intravascular volume
- Blood Flow rate = 10 - 180 ml/min
- UF rate ranges 6 - 50 L/24 h (> 500 ml/h)
- Requires replacement solution to drive convection
- No dialysate

CVVH Performance



Continuous venovenous hemofiltration
“In vitro” ultrafiltration with blood (post-dilution)
(values ± 15%) (Bovine blood at 37° C, Hct 32%, Cp 60g/l)


CVVHDF
Continuous Veno-Venous Hemodiafiltration
to waste
Blood In
(from patient)
Dialysate Solution
Repl. Solution
Blood Out
(to patient)
LOW PRESS
HIGH PRESS
(Convection)
LOW CONC
HIGH CONC
(Diffusion)

CVVHDF
Continuous VV Hemodiafiltration

- Primary therapeutic goal:
  - Solute removal by diffusion and convection
  - Management of intravascular volume
- Blood Flow rate = 10 - 180ml/min
- Combines CVVH and CVVHD therapies
- UF rate ranges 12 - 24 L/24h (> 500 ml/h)
- Dialysate Flow rate = 15 - 45 ml/min (~1 - 3 L/h)
- Uses both dialysate (1 L/h) and replacement fluid (500 ml/h)

SLED
Sustained Low-Efficiency Dialysis

- Primary therapeutic goal:
  - Solute removal by diffusion
  - Management of intravascular volume
- Blood Flow rate = 100-300 ml/min
- Dialysate Flow rate = 100-300 ml/min

Pharmacokinetics of Continuous Renal Replacement Therapy

Basic Principles

- Extracorporeal clearance (Cl_{EC}) is usually considered clinically significant only if its contribution to total body clearance exceeds 25 - 30%

$$Fr_{EC} = Cl_{EC} / \ Cl_{EC} + Cl_{R} + Cl_{NR}$$

- Not relevant for drugs with high non-renal clearance
- Only drug not bound to plasma proteins can be removed by extracorporeal procedures

Determinants of Drug Removal by CRRT

• Drug	Same as hemodialysis but increased MW range
• Membrane	Permeability, Size Sieving Coefficient
• Renal replacement technique	Convection ± diffusion Cl Flow rates Blood, Dialysate, UF Duration

Sieving Coefficient (S)

- The capacity of a drug to pass through the hemofilter membrane

$$S = C_{uf} / C_p$$

C_{uf} = drug concentration in the ultrafiltrate

C_p = drug concentration in the plasma

S = 1 Solute freely passes through the filter

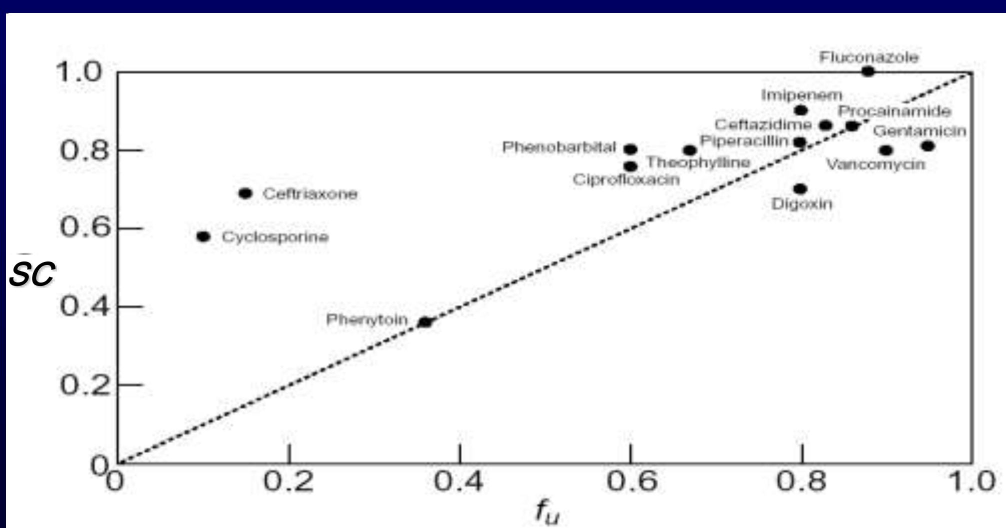
S = 0 Solute does not pass through the filter

$$CL_{HF} = Q_f \times S$$

Determinants of Sieving Coefficient

- Protein binding
  - Only unbound drug passes through the filter
    - Protein binding changes in critical illness
- Drug membrane interactions
  - Not clinically relevant
- Adsorption of proteins and blood products onto filter
  - Related to filter age
  - Decreased efficiency of filter

Relationship Between Free Fraction (*fu*) and Sieving Coefficient (*SC*)



Dialysate Saturation (S_d)

- Countercurrent dialysate flow (10 - 30 ml/min) is always less than blood flow (100 - 200 ml/min)
- Allows complete equilibrium between blood serum and dialysate
- Dialysate leaving filter will be 100% saturated with easily diffusible solutes
- Diffusive clearance will equal dialysate flow

Dialysate Saturation (S_d)

$$S_d = C_d / C_p$$

C_d = drug concentration in the dialysate

C_p = drug concentration in the plasma

- Decreasing dialysate saturation
  - Increasing molecular weight
    - Decreases speed of diffusion
  - Increasing dialysate flow rate
    - Decreases time available for diffusion

$$Cl_{HD} = Q_d \times S_d$$

CVVHDF Clearance

Continuous venovenous hemofiltration - post dilution

QB = 150 ml/min - QD = 2000 ml/h (in vitro saline)

Extracorporeal Clearance

- Hemofiltration clearance ($Cl_{HF} = Q_f$ x S)
  - Q_f = Ultrafiltration rate
  - S = Seiving coefficient
- Hemodialysis clearance ($Cl_{HD} = Q_d$ x S_d)
  - Q_d = Dialysate flow rate
  - S_d = Dialysate saturation
- Hemodialfiltration clearance

$$Cl_{HDF} = (Q_f \times S) + (Q_d \times S_d)$$

Case History

- AP 36yo HM s/p BMT for aplastic anemia
- Admitted to ICU for management of acute renal failure
- CVVH-D initiated for management of uremia
- ICU course complicated by pulmonary failure failure requiring mechanical ventilation, liver failure secondary to GVHD and VOD, and sepsis

Case History
Antibiotic Management on CRRT

- Gentamicin 180 mg IV q24h
- Vancomycin 1 g IV q24h
- Dialysis rate 1000 ml/hour
  - 12 hour post gentamicin levels: 3 - 4 mg/L
  - 12 hour post vancomycin levels: 20 - 23 mg/L
- Dialysis rate increased to 1200 ml/hour
  - 12 hour post gentamicin levels: < 0.4 mg/L
  - 12 hour post vancomycin levels: < 4 mg/L

Dosage Adjustments in CRRT/SLED

- Will the drug be removed?
  - Pharmacokinetic parameters
    - Protein binding < 70 - 80%
      - Normal values may not apply to critically ill patients
    - Volume of distribution < 1 L/kg
    - Renal clearance > 35%
- How often do I dose the drug?
  - Hemofiltration: ‘GFR’ 10 - 20 ml/min
  - Hemofiltration with dialysis: ‘GFR’ 20 - 50 ml/min
  - SLED: ‘GFR” 10 – 50 ml/min

Dosage Adjustments in CRRT/SLED

- Loading doses
  - Do not need to be adjusted
  - Loading dose depends solely on volume of distribution
- Maintenance doses
  - Standard reference tables
  - Base on measured loses or blood levels
  - Calculate maintenance dose multiplication factor (MDMF)

Supplemental Dose Based on Measured Plasma Level

$$Dose_{Suppl} = \left(C_{target} - C_{measured}\right) V_d$$

Adjusted Dose Based on Clearance Estimates

$$MDMF = \frac{CL_{EC} + CL_{R} + CL_{NR}}{CL_{R} + CL_{NR}}$$

COMPARISON OF DRUG REMOVAL BY INTERMITTENT HD AND CRRT

DRUG	$CL_R + CL_{NR}$ (mL/min)	*MDMF*	
		INTERMITTENT HEMODIALYSIS	CONTINUOUS RENAL REPLACEMENT
CEFTAZIDIME	11.2	1.6	2.2
CEFTRIAZONE	7.0	1.0	3.4
CIPROFLOXACIN	188	1.0	2.4
THEOPHYLLINE	57.4	1.1	1.4
VANCOMYCIN	6	3.9	4.9

COMPARISON OF DRUG REMOVAL BY SLED AND CRRT

DRUG	$CL_R + CL_{NR}$ (mL/min)	*MDMF* SLED	CONTINUOUS RENAL REPLACEMENT
LINEZOLID	76	1.1	1.4
LEVOFLOXACIN	37	1.4	1.6
MEROPENEM	21	1.6	1.8
VANCOMYCIN	6	2.9	4.8