CRRT
(Continuous Renal Replacement Therapy)

www.cardiconcept.com
continuous renal replacement therapy (cRRT)

- Evolved as a treatment for the hemodynamically unstable patient unable to undergo standard intermittent hemodialysis (IHD).
Physiologic Principles

• Diffusivity of solute and solvent
• Permeability of membrane
• Surface area
• Concentration gradient
• Membrane characteristic: pore size, thickness etc.

Diffusion and/or Convection
Diffusion VS Convection

\[ J_x = DTA \frac{dx}{dx} \]

Solute flux (function of concentration gradient)

\[ J_f = K_f \times \text{TMP} \]

Convection flux (Pressure gradient between two side)

Temperature

Surface area

Diffusivity coefficient

Membrane permeability coefficient

Transmembrane pressure

Oncotic pressure

Blood hydrostatic pressure

Ultrafiltrate side hydrostatic pressure
Molecular weight

- Better with Diffusion
- Better with Sieving / Convection
Diffusion

Convection w/o diffusion
(move all molecule equally)

Diffusion w/o convection
causes initially separated molecules to move together.

Forced diffusion
Forced act differently on different molecular type
Adsorption

- Usually time dependent
- Membrane is changed q 72 hrs
- Molecular adherance to the surface of membrane
- E.g. cytokines
Ultrafiltration

- Fluid removal
  - Convection removal of solute across semipermeable membrane
  - **Positive** pressure on blood side
  - **Negative** pressure on collection side
  - Fluid loss may be replaced before (predilution mode) or after (post dilution mode)
Sieving coefficients

- ratio of the solute concentrations
  - hemofiltrate to the plasma

- function of membrane thickness, pore size, and electrostatic charge

  more efficient in middle-molecular-weight compound clearance

  less for smaller solutes.


## Modality of CRRT

<table>
<thead>
<tr>
<th>Feature</th>
<th>SCUF</th>
<th>CVVH</th>
<th>CVVHD</th>
<th>CVVHDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of clearance</td>
<td>Convection</td>
<td>Convection</td>
<td>Diffusion</td>
<td>Convection and diffusion</td>
</tr>
<tr>
<td>Middle molecular size clearance</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Replacement fluid</td>
<td>None</td>
<td>Present</td>
<td>None</td>
<td>Present</td>
</tr>
<tr>
<td>Dialysate</td>
<td>None</td>
<td>None</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Effluent composition</td>
<td>Ultrafiltrate</td>
<td>Ultrafiltrate</td>
<td>Dialysate + ultrafiltrate</td>
<td>Dialysate + ultrafiltrate</td>
</tr>
</tbody>
</table>

**CVVH**
- continuous venovenous hemofiltration

**CVVHD**
- continuous venovenous hemodialysis

**CVVHDF**
- continuous venovenous hemodiafiltration

**SCUF**
- slow continuous ultrafiltration.
SCUF
(Slow continuous ultrafiltrate)

- No dialysis

- Ultrafiltrate only

- Volume overload or Heart failure
Schematic representation of different renal replacement modalities

CVVHD
Dialysis only (no ultrafiltrate)

CVVH
Ultrafiltrate + Hemofiltration (no dialysis)

CVVHDF
Dialysis + Ultrafiltrate + Hemofiltration
Indications

- Metabolic acidosis: Refractory to medical treatment
- Electrolyte abnormalities: Refractory to medical treatment
- Volume overload: Refractory to diuretics
- Uremia and its complication

Box 18.1 Nonrenal Indications for Continuous Renal Replacement Therapy (cRRT)
- Lactic acidosis - with ongoing production
- Crush injury - Myoglobin removal
- Tumor lysis syndrome
- Temperature control
- Massive volume overload
- High ammonia
- Removal of toxins with high intracellular concentrations (e.g., Li+)
- Maintenance of cerebral perfusion pressure (CPP) (suggested by some evidence)
Commonly used forms of extracorporeal renal replacement therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Definition</th>
<th>Use</th>
<th>Specific Techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrafiltration</td>
<td>Plasma water removal, usually &lt;5 L/d</td>
<td>Fluid overload, High delivery in CRF, AKI, CHF, Azotemia, Acid-base disturbance, Electrolyte balance, Volume control</td>
<td>SCUF, CVVUF, IUF</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Diffusion-based process using dialysate and semipermeable membrane</td>
<td>Cytokine removal, ARDS, AKI, CHF, MOF</td>
<td>CVVHD, IHD, SLED</td>
</tr>
<tr>
<td>Hemofiltration</td>
<td>Convection-based process using plasma water exchange methods across semipermeable membrane</td>
<td>Azotemia, Acid-base disturbance, Electrolyte balance, Volume control</td>
<td>CVVH, IH</td>
</tr>
<tr>
<td>Hemodiafiltration</td>
<td>Combining diffusion and convection (10-L exchanges) for small and middle molecular loss</td>
<td>Cytokine removal, ARDS, AKI, CHF, MOF</td>
<td>CVVHDF, IHDF</td>
</tr>
</tbody>
</table>

- **IUF** (Intermittent (frequency))
- **CVVUF** (Continuous (frequency))
- **IHDF** (Intermittent)
- **Ultrafiltrate (technique)**
- **Venovenous (access site)**
- **Hemodiafiltration**
Principle of ultrafiltration

Intermittent forms of pump-driven UF are more efficient.

- $Q_b =$ blood flow rate
- $Q_f =$ ultrafiltrate rate (Slow) 100-400 ml/hr
- $K_{uf} =$ UF coefficient
- Increasing viscosity (clot)
- Negative pressure (pump : volume driven system)
Principle of hemofiltration

- fluid may be needed to replace that which is lost.

- before UF (predilutional hemofiltration)

- after fluid has been removed by the filter (postdilutional hemofiltration).
Comparison of Pre- and Postdilution Techniques for Continuous Venovenous Hemodiafiltration/Hemofiltration

<table>
<thead>
<tr>
<th>Feature</th>
<th>Predilution</th>
<th>Postdilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance</td>
<td>Less clearance per ml</td>
<td>High small solute clearance per ml</td>
</tr>
<tr>
<td>Efficiency</td>
<td>Reduce efficiency by 10-15% and reduced filtration fraction</td>
<td></td>
</tr>
<tr>
<td>Ultrafiltration rate limitation</td>
<td>Ultrafiltration rate not limited</td>
<td>Ultrafiltrate limited by BP and hemoconcentration</td>
</tr>
<tr>
<td>Blood viscosity</td>
<td>Low viscosity of blood</td>
<td>High viscosity of the blood and increased risk of clotting</td>
</tr>
</tbody>
</table>

The system should be kept below a filtration fraction of **15% in postdilution** and **30% in predilution** hemofiltration for efficient operation and a lower risk of clotting.
Principles of hemodialysis

Blood flow rate: 100-300 ml

Dialysate flow rate: 15-30 ml

Counter current to maximize gradient
Molecular weight

Membrane dependent (Clearance ขึ้นกิย membrane)

Flow dependent (clearance ขึ้นกับ flow)
High-flux VS Low-flux

Low-flux membrane

High flux membrane ➔ High molecular weight

Low flux membrane ➔ Low molecular weight
## CRRT VS Intermittent therapy

Clinical Considerations in Continuous versus Intermittent Renal Support in the Intensive Care Unit

<table>
<thead>
<tr>
<th>Condition/Feature</th>
<th>Intermittent</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamic instability</td>
<td>No/yes</td>
<td>Yes</td>
</tr>
<tr>
<td>High fluid requirements</td>
<td>No/yes</td>
<td>Yes</td>
</tr>
<tr>
<td>High potassium generation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>High catabolism</td>
<td>Yes</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>Yes</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Global cardiac dysfunction</td>
<td>No/yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Septic shock</td>
<td>No/yes</td>
<td>Yes</td>
</tr>
<tr>
<td>APACHE II score &gt;25</td>
<td>No/yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## IHD VS SLED VS cRRT

<table>
<thead>
<tr>
<th>Feature</th>
<th>IHD</th>
<th>SLED</th>
<th>cRRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting</td>
<td>Hemodynamically stable</td>
<td>Hemodynamically unstable</td>
<td>Hemodynamically unstable</td>
</tr>
<tr>
<td>Advantages</td>
<td>Rapid removal of low-molecular-weight substances and toxins</td>
<td>Hemodynamic stability</td>
<td>Increased intracranial pressure</td>
</tr>
<tr>
<td></td>
<td>Time when not receiving treatment may be used for diagnostic or therapeutic procedures</td>
<td>Time when not receiving treatment may be used for diagnostic or therapeutic procedures</td>
<td>Easy control of fluid balance</td>
</tr>
<tr>
<td></td>
<td>Reduced anticoagulation exposure</td>
<td>Decreased anticoagulation requirements</td>
<td>Hemodynamic stability</td>
</tr>
<tr>
<td></td>
<td>Low cost</td>
<td>Slower clearance of toxins</td>
<td>Continuous removal of toxins</td>
</tr>
<tr>
<td></td>
<td>Hypotension with rapid fluid removal</td>
<td>Technically complex</td>
<td>Slower clearance of toxins</td>
</tr>
<tr>
<td></td>
<td>Dialysis disequilibrium with risk of cerebral edema</td>
<td></td>
<td>May require anticoagulation</td>
</tr>
<tr>
<td></td>
<td>Technically complex</td>
<td></td>
<td>Patient Immobilization</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypothermia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increased costs</td>
</tr>
</tbody>
</table>

**Rapid removal of substances and toxins (small molecular weight better)**

**Hemodynamic stability**
SLED
(Sustain low-efficiency dialysis)

- Low blood flow 200 ml/min
- Dialysate flow 100-300 ml/min
- Diffusive clearance predominate
Continuous Hemodialysis Versus Continuous Hemofiltration

• **Depend on**
  – Patient’s primary diagnosis
  – rate of catabolism
  – mean arterial pressure with resultant blood flow rates
  – UF rates required or desired
  – access choice
  – Circuit variations, anticoagulation

• Some data suggest an improved outcome with the use of hemofiltration in some patients with multiple organ failure.

• If one desires a high rate of removal in a short time, then an intermittent therapy should be employed.
Algorithm for the choice of modality in continuous renal replacement therapy (cRRT).
Prescription variable

• **Dose**
  
  – how much of a measure of the quantity of a representative marker solute is removed from a patient.

  – **Urea** is chosen as an easily measured surrogate for low-molecular-weight products of metabolism.

  – The current recommendation for a minimum dose of RRT supports the delivery of at least 20 mL/kg per hr of CVVH, CVVHD, CVVHDF (usually 25-30 mL/kg/hr)
Prescription variable

• Prescribed Versus Delivered Dose

• prescription of dialysis should exceed that which is calculated to be adequate
Access site

• Typically VV (Venovenous) or may be AV (fistula)

Internal jugular vein, Subclavian vein, Femoral vein access

Femoral access: at least 20 cm length from hub site (due to decrease risk of recirculation)

Use of the subclavian vein also includes the long-term risk of subclavian venous stenosis (Should be avoid)

If a patient is to require an AV fistula in the future for end-stage renal disease, subclavian stenosis will delay maturation of the AV fistula.
Tubing for blood transport increases exposure of blood to nonbiologic surfaces, which cools the blood and increases the risk of clotting. May create turbulence flow of blood.
Membrane containing thousands of narrow capillary fibers (blood compartment bath in dialysate)

Material

1) Cellulose (cuprophan)
2) Substitute cellulose
3) Cellulose synthetic material (Hemophan)
4) Synthetic material (polysulfone, polyacrylonitrile)
Fluids

• Exaggerate loss of Chloride and Bicarbonate (Gibbs Donnan effect)

• Calcium and Magnesium should be monitored closely

• Base buffer: Bicarbonate Lactate or Citrate
  – Citrate ➔ anticoagulant
  – Acetate ➔ Vasodilatation, myocardial depression, increase oxygen consumption ➔ Should be avoid
  – Lactate ➔ Conversion to bicarbonate by liver.
Gibbs Donnan effect

Non-diffusible ion in one side

Accumulation of diffusible ion in the other side e.g. Cl
Anticoagulation

• Circuit clotting is the most frequent cause of therapy interruption in cRRT.

• Blood loss due to clotting in the system

**Box 18.4 Current Strategies to Prevent Continuous Renal Replacement Therapy Circuit Clotting**

- Heparin
  - Standard, prefiltter
  - Regional
  - Low dose, prefiltter
  - Systemic
- Low-molecular-weight heparin
- Citrate
- No anticoagulation
  - Saline solution flushes
  - No intervention
- Prostacyclin
- Hirudin
- Heparin bonding
- Serine protease inhibitors

Preferred: (according to the survey)

Continuous renal replacement therapy: A worldwide practice survey

*Intensive Care Medicine*

• September 2007, Volume 33, Issue 9, pp 1563–1570

The Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators

Shigehiko Uchino, Rinaldo Bellomo, Hiroshi Morimitsu, Stanislao Morgera, Miet Schetz, Ian Tan, Catherine Bouman, Ettiene Macedo, Noel Gibney, Ashta Tolwani, Heleen Gudemans-van Straaten, Claudio Ronco, John A. Kellum
The disadvantages of no anticoagulation

- increased UF
- the risk of dialyzer fiber rupture
- extra nursing workload.

- The hemoconcentration induced by high UF volumes in CVVH and CVVHDF promotes clotting but may be minimized by predilutional fluid replacement.
**Unfractionated Heparin**

- Inactivate factor IIa and Xa
- Bolus 2000 - 5000 IU of heparin
  - Continuous with 5-20 IU/kg/hr
  - aPTT 34-45 seconds (1.5-2.0 X)
- Circuit patency 20-40 hours

---

**Advantage**
- Widely available
- Effective
- Monitoring (aPTT)
- Reversed with protamine
- Inexpensive
- Short halflife

**Disadvantage**
- Systemic bleeding
- Unpredictable kinetics
- aPTT not being a reliable predictor for bleeding
- Heparin resistance due to low antithrombin levels
- Heparin-induced thrombocytopenia (HIT).
HIT

• Day 5-12 after heparin administration
• Thrombosis and Thrombocytopenia
• Rx → Direct thrombin inhibitor: recombinant hirudin (lepirudin), danaparoid, and argatroban
Regional citrate anticoagulation

chelating free calcium in the extracorporeal circuit and prevents the activation of calcium-dependent procoagulants.
Citrate

- The anticoagulant effect of citrate is measured by ionized calcium levels.
- Normal blood citrate = 0.05 mmol/L
- Plasma half-life 5 minutes (metabolized by liver, renal and muscle cells)
- Mx citrate toxicity ➔ decreasing the citrate infusion rate, decreasing the blood pump speed, and increasing the dialysate flow rate.

**Advantage**
- Avoid bleeding complication
- Acid-base buffer
- Not cause thrombocytopenia

**Disadvantage**
- Metabolic alkalosis
- Citrate toxicity
- Metabolic acidosis in liver disease
- Hypoperfusion
- Hypernatremia (4% Sodium citrate)
- Hypocalcemia
preferred over trisodium citrate for routine regional citrate anticoagulation because it is less hypertonic and commercially prepare.

anticoagulant citrate dextrose solution, form A) containing 3% combined trisodium citrate (2.2 g/ 100 mL), citric acid (0.73 g/ 100 mL), and dextrose (2.45 g/ 100 mL
### UHF vs LMWH vs Citrate

<table>
<thead>
<tr>
<th>Feature</th>
<th>None</th>
<th>Heparin (Unfractionated)</th>
<th>Low-Molecular-Weight Heparin</th>
<th>Citrate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>Reduced risk of bleeding</td>
<td>Widely available</td>
<td>Reduced risk of HIT</td>
<td>Strict regional anticoagulation—reduced risk of bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Commonly used</td>
<td>Predictable kinetics</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short half-life</td>
<td>(weight-based dosing)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Available reversal agent</td>
<td>Monitoring not required</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitoring accomplished with routine tests (aPTT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Risk of blood loss and clotting of system</td>
<td>Low cost</td>
<td>Risk of accumulation in kidney failure</td>
<td>Overdose may be fatal</td>
</tr>
<tr>
<td></td>
<td>Risk of blood loss and clotting of system</td>
<td>Narrow therapeutic index—risk of bleeding</td>
<td>If monitoring required, then a nonroutine test is necessary (anti-factor Xa)</td>
<td>Citrate may accumulate in patients with hepatic dysfunction and shock, which may result in metabolic acidosis and hypocalcemia</td>
</tr>
<tr>
<td></td>
<td>Risk of blood loss and clotting of system</td>
<td>Heparin resistance</td>
<td>Incomplete reversal by protamine</td>
<td>Metabolic complications (acidosis, alkalosis, hypernatremia, hypocalcemia, hypercalcemia)</td>
</tr>
<tr>
<td></td>
<td>Risk of blood loss and clotting of system</td>
<td>HIT</td>
<td>May be more expensive than unfractionated heparin</td>
<td>Increased complexity requires a strict protocol</td>
</tr>
</tbody>
</table>
Therapeutic Consideration
Patient selection

• **Timing of Initiation**
  – The use of the traditional biomarkers such as creatinine may delay the initiation of RRT.
    • we will never know whether those who received dialysis would have recovered renal function if they had not received the therapy.

• **Discontinuation**
  – Dialysis is discontinued when the signs of renal recovery are apparent.
    • increased urine output
    • the decrease in biomarkers
    • improvement in the patient's clinical status.
Renal Recovery

- cRRT
  - Decrease serum creatinine from baseline (w/o change in prescription)
  - Urine creatinine and urine sodium
Pharmacokinetics During Continuous Renal Replacement Therapy

• Depending on
  – membrane pore size.
  – Plasma protein binding (only free form)
  – Volume of distribution (smaller)
  – Impact of membrane adsorption of the drugs

• A drug with low protein binding, a low volume of distribution, and low clearance by alternative pathways is one that would be cleared significantly by cRRT.
  e.g. Vancomycin and aminoglycosides

***Published data do exist to help guide drug dosing during cRRT, but they come from a variety of sources and are often not standardized.
### Complications of Therapy

#### Most common: Electrolyte imbalance

<table>
<thead>
<tr>
<th>Problem</th>
<th>Solutions</th>
</tr>
</thead>
</table>
| ↓ Na⁺     | 1. Change all fluid infusions to 0.9% saline or equivalent.  
           | 2. Increase dialysate sodium (add NaCl).  
           | 3. Ensure adequate sodium delivery in replacement solution. |
| ↓ HCO₃⁻   | 1. Ensure adequate HCO₃⁻ concentration in dialysate/replacement.  
           | 2. With lactate-based solutions, consider change to HCO₃⁻ base (especially in liver failure or shock).  
           | 3. Increase HCO₃⁻ in TPN. |
| ↓ Ca²⁺    | 1. Increase Ca²⁺ in TPN.  
           | 2. Add Ca²⁺ to dialysate/replacement (if HCO₃⁻ base, may need to add elsewhere).  
           | 3. Ensure adequate oral Ca²⁺ intake if appropriate. |
| ↓ PO₄²⁻   | 1. Pay close attention to antacid use (acts as gastrointestinal PO₄²⁻ binder; may need to be stopped).  
           | 2. Increase PO₄²⁻ in TPN. |
| ↓ Mg²⁺    | 1. Increase Mg²⁺ in TPN.  
           | 2. Add Mg²⁺ to dialysate/replacement (if HCO₃⁻ base, may need to add elsewhere). |
| ↑/↓ K⁺    | 1. Avoid repeated bolus therapy if ↓ K⁺.  
           | 3. If ↑ K⁺ uncontrolled, add intermittent therapy.  
           | 4. May need addition or discontinuation of K⁺ binder therapy. |

- Use of hemofiltration
  - the replacement solution determines the final electrolyte outcome.

- lost during continuous hemolonzized calcium, magnesium, and phosphate also are filtration and HD.
Modalities of cRRT.
Techniques available today

CHP, continuous hemoperfusion;
CPF-PE, continuous plasmapheresis– plasma exchange;
CPFA, coupled plasmapheresis–adsorption;
CVVH, continuous venovenous hemofiltration;
CVVHD, continuous venovenous hemodialysis;
CVVHDF, continuous venovenous hemodiafiltration;
CVVHFD, continuous venovenous high-flux dialysis;
D, dialysate;
HVHF, high-volume hemofiltration;
K, clearance;
QB, blood flow;
QD, dialysate flow;
QPF, plasmapheresis flow;
QUF, ultrafiltration flow;
R, replacement;
SCUF, slow continuous ultrafiltration;
SLEDD, sustained low-efficiency daily dialysis;
UF, ultrafiltration;
UFC, ultrafiltration control system.
Nonrenal Application of Continuous Therapies

• Isolated UF for heart failure e.g. UNLOAD trial

• Sieving and adsorption to removal Cytokines in sepsis
  – (e.g. Tumor necrosis factor-alpha, IL-6, IL-8)
  – ➔ underinvestigate
UNLOAD study designs

200 Subjects with volume overload by ≥2 signs of HF
• Edema ≥2+, JVD ≥7 cm, CXR with pulmonary edema or effusion, hepatomegaly or ascites, PND

Na ≤ 2 g/day, restrict fluid ≤ 2L/day, no oral diuretics

Ultrafiltration up to 500cc/hr (determined by physician), no IV diuretics (n = 100)

IV Diuretics as bolus or at infusion; IV doses at least 2x daily po dose for first 48 hrs (n=100)

48 hours follow up

Primary endpoint: weight loss; dyspnea score; safety (labs, hypotension)
Secondary endpoints: BNP at 48 hr, 30 and 90 days; NYHA class; MLWHF questionnaire; diuretic doses after ultrafiltration or diuretics; percentage of rehospitalization for HF (and number of days hospitalized); unscheduled out-patient visits

## UNLOAD

<table>
<thead>
<tr>
<th>End point</th>
<th>Ultrafiltration n = 100</th>
<th>Standard care n = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea scores at 8 hours</td>
<td>5.4</td>
<td>5.2</td>
</tr>
<tr>
<td>(Primary outcome)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Net fluid loss at 48 hours (L)</td>
<td>4.6</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>HF rehospitalization rate at 90</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>days (%)</td>
<td></td>
<td>0.037</td>
</tr>
<tr>
<td>HF rehospitalization days</td>
<td>1.4</td>
<td>3.8</td>
</tr>
<tr>
<td>within 90 days (d/patient)</td>
<td></td>
<td>0.022</td>
</tr>
</tbody>
</table>

Thank you