The Cardiorenal Syndrome in Heart Failure

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Disclosures

None
Cardiorenal Syndrome (CRS)

A pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ.


Heart-kidney Interactions

- A bidirectional relationship
  - The heart is directly dependent on regulation of salt and water by the kidneys
  - The kidneys are dependent on blood flow and pressure generated by the heart
- The effects can be both acute and chronic
- Mortality is increased in HF patients with a reduced glomerular filtration rate (GFR)
- Acute or chronic systemic disorders can cause both cardiac and renal dysfunction
Types of CRS

Type I (Acute Cardiorenal Syndrome)
Abrupt worsening of cardiac function (e.g. ADHF) leading to acute kidney injury.

Type II (Chronic Cardiorenal Syndrome)
Chronic HF causing progressive CKD

Type III (Acute Renocardiac Syndrome)
Abrupt worsening of renal function (e.g. acute kidney ischemia or glomerulonephritis) causing acute cardiac dysfunction (e.g. HF)

Type IV (Chronic Renocardiac Syndrome)
Chronic kidney disease (e.g. chronic glomerular disease) contributing to cardiac dysfunction and/or increased risk of adverse cardiovascular events.

Type V (Secondary Cardiorenal Syndrome)
Systemic disorders (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction.

Epidemiology of CRS

- 30-60% of HF patients have CKD (eGFR < 60 mL/min/1.73 m²)
- ADHERE: Only 9% of patients had normal GFRCRS often complicates the management of HF:
  - 20-30% of patients had a rise in serum creatinine > 0.3 mg/dL
  - Risk factors include DM, admission creatinine > 1.5 mg/dL, uncontrolled hypertension
- Renal dysfunction is associated with 2-fold increase in mortality
- Type I CRS:
  - The rise in serum creatinine usually occurs within 5 days of admission
  - ADHF, post-MI, post-cardiac surgery
  - Associated with increased LOS, readmissions, and post-discharge mortality
Diagnosis of CRS

- Usually based on the serum creatinine
  - Caution in older, sicker patients
  - Most eGFR equations assume the serum creatinine concentration is stable
- In those with HF and reduced GFR, one must distinguish underlying kidney disease from impaired function related to CRS
  - Proteinuria
  - Active sediment
  - Small kidneys on imaging
  - None of these can rule out intrinsic kidney disease
- BUN/Cr often used, but should not be used to decide regarding diuretics
  - Urine sodium concentration < 25 is more consistent with HF

Pathophysiology of CRS

- **Hemodynamic**
  - ↓ systemic perfusion → ↓renal blood flow (RBF)
  - Impaired intra-renal autoregulation
  - ↑ central venous pressure (CVP) and intraabdominal pressure → ↑renal venous pressure (RVP)
- **Non-hemodynamic**
  - ↑ SNS, RAAS, AVP activation → impaired intra-renal autoregulation
  - ↑ systemic inflammation → cytokine release and intra-renal vasculature endothelial dysfunction
GFR Regulation in HF

- 34 pts with HF, off meds, multiple hemodynamic and neurohormonal parameters assessed
- What accounts for variability in GFR: \( \text{RBF} \ 69\%, \ \text{FF} \ 25\% \)


Organ-specific factors in CRS

- Abdominal pressure ↑
- Renal blood flow ↓
- Renal artery stenosis
- ACEi/ARB
- Congested kidney
- Number of nephrons ↓
- Renal venous pressure ↑

Hemodynamics and CRS Type I

CVP was a better predictor of low GFR on discharge than CO


CRS: Glomerular factors

Nephron-specific factors in CRS


Hemodynamic Profile in CRS Type I

Congestion at Rest

| NO | Warm & Dry |
|------------------|
| \( \downarrow \) RBF |
| Intra-renal microvascular dysregulation |

| YES | Warm & Wet |
|------------------|
| \( \downarrow \) RBF |
| Impaired intra-renal autoregulation |
| Renal v. pressure ↑ |

| NO | Cold & Dry |
|------------------|
| \( \downarrow \) RBF |
| Impaired intra-renal autoregulation |

| YES | Cold & Wet |
|------------------|
| \( \downarrow \) RBF |
| Impaired intra-renal autoregulation |
| Renal v. pressure ↑ |

Non-hemodynamic factors in CRS

- Modulation of RAAS
  - Angiotensin II promotes renal fibrosis, causes SNS activation
- Inflammation/oxidative stress
- Endothelial dysfunction
- Humoral/cellular immunity
- Anemia

Management of CRS

- No therapy has been clearly shown to improve outcomes in CRS
- Careful management of
  - Fluid status
  - CVP
  - Cardiac Output
  - SVR/ BP (renal perfusion)
  - Pre existing renal disease (urine protein)
- Avoid mismatches between these factors
Management of CRS

- Managing volume
  - Diuretics
  - Aquaretics (i.e. vasopressin antagonists)
  - Dopamine
  - Inotropes
  - Ultrafiltration

- Preventing decreases in RBF and FF:
  - Keeping plasma refill rate (PRF) constant
  - Preventing excessive intra-renal vasodilatation/vasoconstriction


Diuretic Strategies in CRS

Diuretic Resistance

“Braking” phenomenon
• Decrease in response to diuretic after the first dose given

Long-term tolerance
• Tubular hypertrophy to compensate for salt loss

Post-diuretic NaCl retention
Diuretic malabsorption
• GI edema

Reduced GFR
Aldosterone antagonism


Diuretics increase neurohormonal activation

**Survival and Diuretic Dose in HF**


**Dosing Diuretics: DOSE HF Trial**

### Dosing Diuretics: DOSE HF Trial

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>High</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea VAS AUC at 72 hrs</td>
<td>4478</td>
<td>4668</td>
<td>0.041</td>
</tr>
<tr>
<td>% free from congestion at 72 hrs</td>
<td>11%</td>
<td>18%</td>
<td>0.091</td>
</tr>
<tr>
<td>Change in weight at 72 hrs</td>
<td>-5.3 lbs</td>
<td>-8.2 lbs</td>
<td>0.011</td>
</tr>
<tr>
<td>Net volume loss at 72 hrs</td>
<td>3575 mL</td>
<td>4899 mL</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Treatment failure</td>
<td>37%</td>
<td>40%</td>
<td>0.56</td>
</tr>
<tr>
<td>% with Cr &gt; 0.3 mg/dL at 72 hrs</td>
<td>14%</td>
<td>23%</td>
<td>0.041</td>
</tr>
<tr>
<td>Length of stay, days (median)</td>
<td>6</td>
<td>5</td>
<td>0.55</td>
</tr>
</tbody>
</table>

- High dose better efficacy, more worsening Cr
- No difference bolus vs. drip


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### Tolvaptan

- Inappropriate elevation of arginine vasopressin plays a key role in mediating water retention
- Tolvaptan is a small molecule antagonist of the V2 receptor
- Compared to furosemide:
  - Similar effect on urine output
  - No effect on electrolytes or osmolality
  - Preserves renal blood flow
  - Improves hemodynamics (RAP, PCWP, CI, SVR)
- The EVEREST trial randomized 4133 patients hospitalized for heart failure to tolvaptan vs placebo in addition to standard therapy for HF
  - Overall, a negative trial (no effect on the primary endpoint)

*Udelson JE et al. J Am Coll Cardiol. 2008*
Dyspnea in Hospitalized Patients with Hyponatremia


Tolvaptan in hospitalized patients with hyponatremia

Managing Volume Overload in Heart Failure: Diuretics vs. Vaptans

<table>
<thead>
<tr>
<th></th>
<th>Vaptans</th>
<th>Diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Output</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Serum Sodium</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Serum Potassium</td>
<td>No change</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma Osmolality</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>No change</td>
<td>↓</td>
</tr>
<tr>
<td>BUN/Creatinine</td>
<td>No change</td>
<td>↑</td>
</tr>
<tr>
<td>Renal Blood Flow</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>GFR</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Renal vascular resistance</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Vasopressin level</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Norepinephrine level</td>
<td>No change</td>
<td>↑</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>No change</td>
<td>↑</td>
</tr>
<tr>
<td>Aldosterone level</td>
<td>No change</td>
<td>↑</td>
</tr>
</tbody>
</table>

Dopamine Effects in HF

- Small series found that dopamine can significantly increase GFR in patients with moderate or severe HF
- Increases RBF at doses of 2-10 mcg/kg/min
- Due to dilation of both large and small resistance renal blood vessels
- Also increases cardiac output, but the improvement in RBF was disproportionately higher

Dopamine Effects in HF: DAD HF

Dopamine Effects in HF: ROSE AHF

Chen HH et al. JAMA. 2013; 310: 2533-2543.

Ultrafiltration for ADHF: UNLOAD

- Mechanical strategy for fluid removal
- The UNLOAD trial randomized 20 patients hospitalized for ADHF to usual care vs up front ultrafiltration
  - UF rate/duration at the discretion of the institution
  - Early UF was associated with greater weight reduction compared to IV diuretics, without significant difference in serum creatinine
- No impact on dyspnea
- Early UF reduced:
  - 90-day rehospitalizations
  - ED and unscheduled office visits
  - Days of rehospitalization for HF

Costanzo MR et al, JACC 2007
Ultrafiltration for ADHF: CARRESS

- Examined the efficacy of ultrafiltration in ADHF complicated by worsening renal function
- Randomized 188 patients with ADHF, worsened renal function, and ongoing congestion to stepped pharmacologic therapy vs ultrafiltration
- The primary outcome was the bivariate change from baseline in serum creatinine and body weight at 96 hours

Ultrafiltration in Acute HF: CARESS

A. Serum Creatinine

B. Body Weight

AVOID-HF

- Aim: to determine whether UF prolonged the time to first HF event within 90 days of discharge
  - When fluid removal therapy is adjusted in both arms
- Patients hospitalized for a primary diagnosis of HF were randomized within 24 hours to adjustable UF or adjustable loop diuretics
- Guidelines for UF and diuretics were based on renal function and vital signs
- The study was terminated early unilaterally by the sponsor after enrollment of 224 patients (27.5%) due to slow enrollment

Costanzo MR et al, *JACC HF* in press

AVOID-HF: Time to HF event after discharge

Costanzo MR et al, *JACC HF* in press
Plasma Refill Rate

- **PRR = ECV – U output**
- **Monitor with the serum Hct**
- **Keep Hb/ Htc from rising > 3-5% in 8-12 hrs**

C. Hypovolemia with Continued Diuretic or Vasodilators

- **Plasma Volume Loss**: 100 – 300 mL/hr
- **Diuresis**: 100 – 300 mL/hr
- **Plasma Refill Rate**: <100 mL/hr
- **Extracellular Volume**: 0 L

Conclusions

- **CRS is common and is associated with worse outcomes**
  - Reduced renal perfusion and venous congestion are prominent factors
- **Management requires careful balance between volume status, renal perfusion, and intra-renal hemodynamics**
- **Thoughtful approach to volume management**
  - **Diuretics**: loop (bumetanide) +/- thiazide Consider tolvaptan
  - Use ultrafiltration if massive or refractory volume overload