Cardiorenal Syndrome: What the Clinician Needs to Know

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Contemporary Multi-Disciplinary Cardiovascular Medicine
A Disease-Based Learning Experience for the Practitioner

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Renal Hemodynamics in Heart Failure

- **Glomerular Filtration Rate (GFR)**
  - Normal in early or mild heart failure
  - Reduced as cardiac performance becomes more severely impaired

- **Renal Vascular Resistance**
  - Increased with a concomitant decrease in RBF
  - A consequence of efferent arteriolar constriction

**Renal Blood Flow (RBF)**
- Decreased in proportion to the decrease in cardiac performance

**Filtration Fraction** (ratio of GFR to RBF)
- Usually increased
Effects of Efferent Arteriolar Constriction

Abraham and Schrier, 1991
Angiotensin II Enhances Sodium Chloride Reabsorption in the Proximal Tubule

Liu and Cogan, 1987
Renal Effects of Neurohormonal Activation in Heart Failure

- **Vasoconstrictor Systems**
  - Promote efferent > afferent arteriolar constriction
  - Enhance sodium and water reabsorption in proximal and distal tubules
  - Increase water reabsorption in the collecting duct
  - Co-activate other vasoconstrictor systems

- **Vasodilator Systems**
  - Improve/maintain GFR
  - Promote renal vasodilation
  - Diminish tubular sodium and water reabsorption
  - Inhibit vasoconstrictor systems
The Cardio-Renal Syndrome of Heart Failure

- Increased LV Filling Pressure
- Increased water and Na+ Retention
- Impaired Renal Function
- Decreased Cardiac Output
- Neurohormonal Activation
- Diminished Blood Flow
- Decreased Renal Perfusion

Abraham WT, 2004
Predictive Value Of Moderate-Severe Renal Dysfunction In Chronic Heart Failure

- 1708 HF patients (NYHA III-IV) from Prime II Trial (Ibopamine)
- Multiple regression analysis for variables predicting survival
- GFR was most predictive of survival
- GFR < 60 ml/min associated with 2.1 risk of mortality
- Surpassed LVEF, NYHA class, hypotension concomitant meds, DM, tachycardia
Predictive Value Of Moderate-Severe Renal Dysfunction In Chronic Heart Failure

Girbes et al., 1998

Survival

Days

GFR >60ml/min
GFR <60ml/min

p=0.0001
Predictive Value Of Mild Renal Dysfunction In Chronic Heart Failure

- 6797 HF subjects (NYHA III-IV) from SOLVD Trials
- Multivariate analysis of survival in subjects with baseline serum Cr < 1.5 compared to those with serum Cr 1.5-2.0 (patients with Cr > 2.0 excluded)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cause Mortality</td>
<td>1.41</td>
<td>1.25-1.59</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Pump Failure Death</td>
<td>1.5</td>
<td>1.25-1.8</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Sudden Death</td>
<td>1.28</td>
<td>0.99-1.63</td>
<td>p=0.051</td>
</tr>
</tbody>
</table>
ADHERE Predictors of Mortality in Acutely Decompensated Heart Failure

**SYS BP 115**

Less than

- 2.68%  
  - n=25,122

- 5.49%  
  - n=4,099

Greater than

- 8.98%  
  - n=7,202

- 12.42%  
  - n=1,425

**BUN 43**

- N=33,324

- 2.14%  
  - n=20,834

- 6.41%  
  - n=5,102

**Cr 2.75**

- 15.28%  
  - N=2,048

- 21.94%  
  - n=620

Highest to Lowest Risk Cohort

OR 12.9 (95% CI 10.4-15.9)

Fonarow et al., JAMA 2005
Relationship between heart failure treatment and development of worsening renal function among hospitalized patients

Javed Butler, Dan E. Forman, William T. Abraham, Steven S. Gottlieb, Evan Loh, Barry M. Massie, Christopher M. O’Connor, Michael W. Rich, Lynn W. Stevenson, Yongfei F. Wang, James B. Young, and Harlan M. Krumholz

Am Heart J 2004; 147:331-338
Methods

- A multicenter cohort study of 1004 subjects hospitalized for heart failure demonstrated worsening renal function (defined as an increase in serum creatinine of > 0.3 mg/dl) in approximately 30% of the patients.

- These patients had a 6-fold higher risk of in-hospital mortality and > 3-fold higher risk of prolonged hospitalization.

- A case-control study was based on a total of 382 of these subjects (191 cases of worsening renal function and 191 controls).
Effect of Worsening Renal Function in Hospitalized Heart Failure Patients

- Average length of stay was 7±4 days for cases and 5±3 days for controls (p=0.001)

- Proportion of patients who stayed in the hospital for > 10 days was 14% for cases and 3% for controls (p<0.05)

- Hospital mortality rate was 5.2% for cases and 1.6% for controls (p<0.05)
Predictors of Worsening Renal Function

- Past history of heart failure, diabetes, uncontrolled hypertension, or renal dysfunction

- Use of a calcium channel blocker or higher loop diuretic doses (199±195 mg vs. 143±119 mg, p<0.05)

- The higher doses of loop diuretics were not associated with either increased diuresis or more weight change for the cases

- Treatment with ACE inhibitors, ARBs, or spironolactone was not associated with worsening renal function
The “iatrogenic” Cardio-Renal Syndrome of Heart Failure

Diuretic Therapy

Increased Morbidity And Mortality

Development Of Diuretic Resistance

Impaired Renal Function

Neurohormonal Activation

Diminished Blood Flow

Decreased Renal Perfusion

Abraham WT, 2004
Diuretic Therapy in Heart Failure

- Historically, the only treatment strategy for volume overload status

- Clinical strategies currently involve
  - Accelerating oral and IV dose strategies for recalcitrant edema
  - Simultaneous use of three different diuretics
    - Loop diuretics (volume management)
    - Thiazide diuretics (accelerators)
    - Aldosterone antagonists (neurohormonal blockade)
Diuretic Strategies in ADHF

- Administration of IV loop diuretics is current mainstay of therapy
- Animal studies and limited data in humans suggests better efficacy with continuous versus bolus infusions (concept of maximally effective luminal concentration)
- Recent study suggests little difference in efficacy between low- versus high-dose strategies or continuous versus intermittent administration*
- Synergy may be seen with combined use of loop and thiazide-type diuretics

*Felker et al., NEJM 2011
Diuretic Strategies in ADHF

- Common initial approach to IV loop diuretic:
  - Double oral dose and deliver IV

- Continuous infusion dosing
  - High-dose strategy: 0.6 mg/kg/hr up to 40 mg/hr
  - Low-dose strategy: 5-10 mg/hr
  - IV loop diuretic plus IV or oral thiazide diuretic or oral metolazone
  - IV loop diuretic plus IV nesiritide
  - IV loop diuretic plus IV inotrope
Limitations of Traditional Renal Replacement Therapy in Heart Failure (e.g., Dialysis, CAVHD, CVVHD)

- Cumbersome
  - Requires Nephrologist, Dialysis Technician
  - Requires central venous access
  - In hospitalized HF patients, usually requires ICU bed

- Poorly tolerated
  - Causes hypotension/hemodynamic instability due to shifts in blood volume

- Rarely done
  - Perceived unfavorable risk/benefit relationship
Ultrafiltration Fluid Removal System

- FDA approved
- Uses peripheral venous access (can also use central access)
- Total extracorporeal blood volume 33 mL
- Designed to remove up to 500 ml of fluid per hour with adjustable flow rates of 10-40 mL/min
- Highly automated, computer controlled operation with simple operator interface
Ultrafiltration: Use at OSU

Patient Selection

- Diuretic resistance
  - The state of having an insufficient clinical response to medical (i.e., diuretic) therapy

- “Gross” volume overload
  - > 10-20 pounds of fluid retention
A Proposed Definition of Diuretic Resistance

Volume overload
↓
Furosemide 50 mg IV
↓
Evaluate response in 2-3 hours
↓
If insufficient, furosemide 100 mg IV
↓
Evaluate response in 2-3 hours
↓
If insufficient, furosemide 200 mg IV
↓
Evaluate response in 2-3 hours
↓
If insufficient, patient is diuretic resistant
↓
Hemofiltration?

Sackner-Bernstein JD, et al., J Invasive Cardiol 2003
Ultrafiltration: Use at OSU

General

- Must be performed under the direction of Cardiology or Nephrology service
- Peripheral access may be considered in patients without severe renal failure and when the need for dialysis is not anticipated
- Routine anticoagulation using weight-based heparin protocol or alternative treatment, if contraindication to heparin
Ultrafiltration: Use at OSU Treatment

- **Duration:** Continuously until patient achieves clinical treatment goals of compensated CHF

- **Re-treatment:** If patient relapses, again meeting original selection criteria (volume overloaded and diuretic resistant)

- **Filter Change:** Ultrafiltration filters are to be changed every 72 hours or when therapy can no longer be continued secondary to clotting in the circuit
Ultrafiltration: Use at OSU

Monitoring

- Continuous clinician oversight is needed throughout treatment

- In addition, physician evaluation of patient response and the need to continue therapy is conducted at 24 hours and routinely until the patient meets his/her therapeutic goal
Ultrafiltration: Use at OSU Training

- Registered nurses who attend a two-hour educational in-service and who complete eight hours of precepted clinical use of the Aquadex device are considered competent to use the device.

- Continued competency with ultrafiltration therapy and the Aquadex device will be evaluated annually.