THE CARDIOURETERAL SYNDROME
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Disclosures

• I have no financial disclosures
• I will not discuss off-label drug or device use
• I am not a heart failure specialist
• Some of my slides are taken from presentations given at Cardiology at Cancun 2015 by Dr. Barry Boilson and Dr. Paul McKie
• Cardiology at Cancun 2020
Evil Easter Bunny
Case Report

- 80 yo female with chronic HFpEF (first name is a flower)
- Admitted from CHF Clinic with 7 lb. weight gain and increased SOB after drinking a jar of pickle juice
- Oxygen sat 75% on RA
- Chronic AFib
- Decreased breath sounds at bases and coarse wheezes
- 2+ edema
Case Report

- LVEF 50%-55% with mild LVH and BiAE – AFib present
- Chest X-ray with diffuse patchy infiltrate
- Sodium 133
- Potassium 3.3
- BUN 43/Creat. 1.2 (21/0.8)
Case Report

- Antibiotics and diuretics
- Sodium 124/Potassium 6.3
- BUN 51/Creat. 1.5
- Chest X-ray and edema no better
- Diuretics stopped and normal saline started
- “Dr. Farrar, I feel awful. I can’t breathe.”
Cardiorenal Syndrome
Cardiorenal Syndrome

• A condition in which therapy to relieve congestive symptoms of heart failure is limited by a decline in renal function as manifested by a reduction in GFR
  – www.nhlbi.nih.gov

• A spectrum of acute or chronic disorders of heart and kidney function characterized by mutual deterioration
Cardiorenal Syndrome

- Very common – 30%-60% of patients
- ADHERE – 30% creatinine >2 mg/dl
- 20%-30% increase in creatinine >0.3 mg/dl
- Risk factors
  - Diabetes mellitus
  - Admission creatinine >1.5 mg/dl
  - Uncontrolled hypertension
Cardiorenal Syndrome

Type 1: Acute HF causes AKI

Type 2: Chronic HF causes chronic KI

Type 3: AKI causes acute HF

Type 4: Chronic KI causes chronic HF

Type 5: Chronic systemic disease causing HF and KI

Pathophysiology

• Complex
• Neurohormonal adaptations
• Reduced renal perfusion
• Renal congestion
• Right ventricular dysfunction
Cardiorenal Syndrome

Neurohormonal adaptations

- CHF
- Cardiac Output
- Atrial Pressure
- Venous congestion

SNS activation
- Renal perfusion

Renin

RAAS activation

Aldosterone

Vasopressin

Endothelin-1

Angiotensin II

Salt and water retention

Systemic vasoconstriction
Cardiorenal Syndrome

Neurohormonal adaptations

CHF

SNS activation

↓ Renal perfusion

Renin

RAAS activation

Aldosterone

Vasopressin

Endothelin-1

↓ Cardiac Output

↑ Atrial Pressure

Venous congestion

Salt and water retention

Systemic vasoconstriction
Cardiorenal Syndrome

Reduced renal perfusion

- Normal LV function
- Mild LV dysfunction
- Severe LV dysfunction

Stroke Volume / Cardiac Output vs. LVEDP or wedge pressure
Cardiorenal Syndrome

The diagram illustrates the relationship between Stroke Volume/Cardiac Output and LVEDP or wedge pressure. The graph shows three curves:

- **Normal LV function**
- **Mild LV dysfunction**
- **Severe LV dysfunction**

The point A on the graph represents a specific condition or measurement in the context of cardiorenal syndrome.
Cardiorenal Syndrome

**Diagram:**
- **Normal LV function**
- **Mild LV dysfunction**
- **Severe LV dysfunction**

**Axes:**
- **Stroke Volume / Cardiac Output**
- **LVEDP or wedge pressure**

**Points:**
- A
- B

**Note:**
- The graph illustrates the relationship between stroke volume/cardiac output and LVEDP or wedge pressure, showing different degrees of LV function.
Cardiorenal Syndrome

- Normal LV function
- Mild LV dysfunction
- Severe LV dysfunction

Stroke Volume / Cardiac Output vs. LVEDP or wedge pressure
Cardiorenal Syndrome

Mild LV dysfunction

Normal LV function
Mild LV dysfunction
Severe LV dysfunction

Stroke Volume / Cardiac Output

LVEDP or wedge pressure
Cardiorenal Syndrome

Mild LV dysfunction - compensation

- Normal LV function
- Mild LV dysfunction
- Severe LV dysfunction

Stroke Volume / Cardiac Output vs. LVEDP or wedge pressure
Cardiorenal Syndrome

Severe LV Dysfunction

- Normal LV function
- Mild LV dysfunction
- Severe LV dysfunction

Stroke Volume / Cardiac Output vs. LVEDP or wedge pressure

A

D
Cardiorenal Syndrome

Severe LV Dysfunction - Decompensation

Stroke Volume / Cardiac Output vs. LVEDP or wedge pressure

- Normal LV function
- Mild LV dysfunction
- Severe LV dysfunction

A, D, E markers indicate different stages of dysfunction.
Cardiorenal Syndrome

Severe decompensated HF - Diuresis

Stroke Volume / Cardiac Output

LVEDP or wedge pressure

Normal LV function
Mild LV dysfunction
Severe LV dysfunction
Cardiorenal Syndrome

Severe decompensated HF - Diuresis

Message

Do not be afraid to diurese!!
Cardiorenal Syndrome

Renal Congestion

IVC

Renal vein
Cardiorenal Syndrome

Renal Congestion

Increased intra-abdominal pressure
Cardiorenal Syndrome

Renal Congestion

Increased central venous pressure

IVC

Renal vein
Cardiorenal Syndrome

Renal Congestion

Increased central venous pressure

Reduced GFR

Renal vein

IVC

TR!!
Cardiorenal Syndrome

Renal Congestion

Diuretic therapy

improved GFR

IVC

Renal vein
Cardiorenal Syndrome

Right Ventricular Dysfunction

- Increased central venous pressure
- *Reverse Bernheim phenomenon*

Haddad et al. *Circ* 2008; 117: 1717-1731
Cardiorenal Syndrome

Right Ventricular Dysfunction

Reverse Bernheim phenomenon

Increased pericardial constraint

Dilated RV

LV

D-shaped Left Ventricle

Haddad et al. Circ 2008; 117: 1717-1731
Clinical Importance

• First-line therapy should be diuretics/volume removal
  – Diuretic resistance is common

• CVP is a major driver and predictor

• Cardiac index is secondary
Clinical Evidence

• **ESCAPE**: No correlation between cardiac index and either the baseline GFR or worsening renal function
  – Nohria et al. JACC 2008;51(13):1268

• **CVP is a major predictor of worsening renal function, independent of systemic BP, PCWP, cardiac index and estimated GFR**
  – Mullens et al. JACC 2009;53(7):589
Congested Patient Treatment

- **Diuretics are first-line treatment**
  - Elevated BUN/creatinine ratio should not deter diuretics, if congestion is present
  - ESCAPE and EVEREST
- **Negative effect on renal function with aggressive diuresis, but survival improved**
  - Testani et al. Circ 2010;122:265
Congested Patient Treatment

• ACC/AHA Heart Failure Guidelines
  – Eliminate clinical evidence of fluid retention, such as elevated JVP and peripheral edema
  – Goal of diuretic therapy is to eliminate fluid retention even if this leads to mild to moderate reductions in blood pressure or renal function
• Yancy et al. Circ 2013;128:1310
Therapeutic Paracentesis

- Rapid symptom improvement
- Decompress kidneys and renal veins
- Increase diuretic responsiveness
- Relatively low risk
- No routine replacement of albumin
Therapeutic Paracentesis

![Graph showing baseline serum creatinine levels for different intra-abdominal pressures.](image)

JACC 2008 Jan 22;51(3):300-6
Congested Patient Treatment

• Ultrafiltration role
  – Conflicting data

  • UNLOAD and RAPID-CHF
    – Significantly greater rate of fluid loss than diuretic therapy, but no difference in serum creatinine
      » Costanzo et al. JACC 2007;49:675
      » Bart et al. JACC 2005;46:2013
Congested Patient Treatment

• Ultrafiltration role
  – Conflicting data
• CARESS-HF
  – Weight loss was similar in ultrafiltration and stepped pharmacologic therapy groups
  – Ultrafiltration therapy caused an increase in serum creatinine and a higher rate of adverse events
Congested Patient Treatment

• Ultrafiltration may be helpful for fluid removal in acute decompensated heart failure in patients unresponsive to diuretic therapy

• Not first-line therapy
Diuretic Resistance

• **Precipitants**
  – Exogenous fluids/sodium
  – Arrhythmias
  – Anemia
  – Ischemia
  – Infection
  – Drugs
Diuretic Resistance Tools

- High-dose loop diuretics
- Double dose if poor response
- Max dose (FDA) = 600 mg/day
- NHS: 1500 mg/day
- Probably limited benefit over 720 mg/day

[Image of Lasix 500 mg package]
Loop Diuretics

• **Equivalent doses**
  – Furosemide 40 mg
  – Torsemide 20 mg
  – Bumetanide 1 mg

• **Bioavailability**
  – Furosemide 10%-100%
  – Torsemide 80%-100%
  – Bumetanide 80%-100%
  – Ethacrynic acid 100%?
DOSE Study

- IV BID bolus
  - Low dose = 1.0 x outpatient dose
  - High dose = 2.5 x outpatient dose

- High-dose bolus versus low-dose bolus

- Bolus versus continuous infusion

DOSE Study

• No difference between high-dose bolus versus continuous infusion IV loop diuretics
  – Length of stay
  – Renal function
  – NT-proBNP

## DOSE Study

<table>
<thead>
<tr>
<th>Measure</th>
<th>Low Dose</th>
<th>High Dose</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC for dyspnea at 72 hr (higher = better)</td>
<td>4478±1550</td>
<td>4668±1496</td>
<td>0.04</td>
</tr>
<tr>
<td>Change in weight at 72 hr – lb</td>
<td>–6.1±9.5</td>
<td>–8.7±8.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Net fluid loss at 72 hr — mL</td>
<td>3575±2635</td>
<td>4899±3479</td>
<td>0.01</td>
</tr>
<tr>
<td>Change in NT-proBNP at 72 hr</td>
<td>–1194±4094</td>
<td>–1882±4105</td>
<td>0.06</td>
</tr>
<tr>
<td>Increase in creatinine of &gt;0.3 mg/dL within 72 hr — no./total no. (%)</td>
<td>20/147 (14)</td>
<td>35/154 (23)</td>
<td>0.04</td>
</tr>
<tr>
<td>Median stay in hospital – days</td>
<td>6</td>
<td>5</td>
<td>0.55</td>
</tr>
</tbody>
</table>
DOSE Study

Diuretic Resistance Tools

- **Thiazides**
  - Classic teaching: 30-60 minutes prior to loop diuretic?
  - Chlorothiazide (Diuril): 250-1000 mg IV
  - Metolazone (Zaroxolyn): 2.5-10 mg PO
  - Highly variable response
  - Can significantly worsen electrolyte abnormalities
# Diuretic Dosing

<table>
<thead>
<tr>
<th>Outpatient furosemide equivalent daily dose</th>
<th>Continuous IV infusion strategy</th>
<th>Twice daily IV bolus dosing strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/day</td>
<td>Initial bolus</td>
<td>hourly rate</td>
</tr>
<tr>
<td>&lt;40</td>
<td>40 mg</td>
<td>2.5 mg/hr</td>
</tr>
<tr>
<td>40 to 80</td>
<td>40 mg</td>
<td>5 mg/hr</td>
</tr>
<tr>
<td>81 to 120</td>
<td>80 mg</td>
<td>7.5 mg/hr</td>
</tr>
<tr>
<td>121 to 160</td>
<td>80 mg</td>
<td>10 mg/hr</td>
</tr>
<tr>
<td>161 to 240†</td>
<td>80 mg</td>
<td>20 mg/hr</td>
</tr>
<tr>
<td>&gt;240†</td>
<td>80 mg</td>
<td>30 mg/hr</td>
</tr>
</tbody>
</table>
# Diuretic Dosing

<table>
<thead>
<tr>
<th>Level</th>
<th>Previous Oral Dose</th>
<th>Furosemide</th>
<th>Infusion Rate</th>
<th>Oral Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤80 mg</td>
<td>40 mg</td>
<td>5 mg/hr</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>81–160 mg</td>
<td>80 mg</td>
<td>10 mg/hr</td>
<td>5 mg daily</td>
</tr>
<tr>
<td>3</td>
<td>161–240 mg</td>
<td>80 mg</td>
<td>20 mg/hr</td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td>4</td>
<td>&gt;240 mg</td>
<td>80 mg</td>
<td>30 mg/hr</td>
<td>5 mg twice daily</td>
</tr>
</tbody>
</table>

N Engl J Med 2017 Nov 16;377(20)
Low Cardiac Output Patients

- Pharmacologic therapy
  - Inotropes
    - Cardiogenic shock
    - Selected ADHF patients but not routinely
      - No survival benefit
Low Cardiac Output Patients

• Pharmacologic therapy
  – Renal dose dopamine?
    • Conflicting data – Insufficient evidence to recommend routine use
      – DAD-HF: Enhanced diuretic effect of dopamine 5 mcg/kg/min combined with low-dose furosemide infusion similar to high-dose infusion
        » Giamouzis et al. J Card Fail 2010;16:922
Low Cardiac Output Patients

• **Pharmacologic therapy**
  – Renal dose dopamine?
    • ROSE: 2 mcg/kg/min combined with furosemide showed no benefit
      » Chen et al. JAMA 2013;310:2533
Low Cardiac Output Patients

- Device therapy
  - LVAD

- INTERMACS registry
  - Improvements in BUN and creatinine among patients with moderate or severe renal dysfunction
  - Improvements in estimated GFR were noted within one month of LVAD implantation
  - Persisted over a two-year follow-up period
    » Kirklin et al. J Heart Lung Transplant 2013;32:1205
Low Cardiac Output Patients

• Device therapy
  – CRT
  • MIRACLE
    – eGFR improved in selected patients with GFR 30-59 ml/min
      » Boerrigter et al. J Card Fail 2008;14:539
Clinical Assessment

**Assessment: Summary**

**Congestion?**
Orthopnea, rales, JVD, ascites, edema, weights, I/O

- **No**
  - Adequate perfusion?
    - Yes
      - Dry and Warm
    - No
      - Dry and Cold

- **Yes**
  - Wet and Warm

Nohria A: Am J Cardiol 2005 [suppl]
Summary

• First-line approach is diuretic therapy if the patient is congested, even if elevated BUN/creatinine ratio

• If diuretic resistant or severe renal dysfunction is present, consider ultrafiltration
Summary

• Don’t forget paracentesis

• Low cardiac output state/cardiogenic shock: Short-term inotropes may be helpful as a bridge to stability for conventional therapy or cardiac replacement therapy
Summary

• These are not patients that the hospitalists should treat without cardiology consultation

• These patients are sick, complex and difficult to manage

• A team approach involving a good nephrologist is recommended
THE PRESENT AND FUTURE

JACC COUNCIL PERSPECTIVES

Contemporary Management of Severe Acute Kidney Injury and Refractory Cardiorenal Syndrome

JACC Council Perspectives

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Thank you!
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