Cardio-Renal Syndrome: What the *Kidneys* Want

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Financial Disclosure

I have no conflicts of interest to disclose
Learning Objectives

• Describe the key factors that impair renal function in cardiorenal syndrome, including arterial underfilling and venous congestion

• Compare and contrast options for diuretic therapy in cardiorenal syndrome based on principles of pharmacology and renal physiology
 Challenges to guideline-directed therapy in cardio-renal syndrome:

• Moderate to severe CKD patients often excluded from trials
• Long-term renal outcomes not well studied
• Difficult to measure renal function in non-steady-states
“No BP, No PP”
Dual hemodynamic pathways for acute cardiorenal syndrome

Andrew A. House CJASN 2013;8:1808-1815

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Results in a pre-renal state

Arterial underfilling
- Decreased cardiac output
- Decreased effective circulating volume
- Decreased RBF, RPF
- Activation of RAAS, SNS
- Inflammatory pathways

Results in "nephrosarca"

Venous congestion and venous hypertension, raised IAP
- Decreased AV perfusion gradient
- Kidney interstitial edema
- Activation of RAAS, SNS
- Inflammatory pathways

Venous congestion
“Effective Blood Volume”

- 85% of blood circulates on the low-pressure, venous side
- 15% circulates in the high-pressure, arterial circulation
- Increases in “total blood volume”, therefore, may primarily be due to *expansion of the venous compartment*, and still be associated with an *underfilling of the arterial circulation*
What is “nephrosarca”?

Increased interstitial pressure in the renal parenchyma that leads to tubular collapse and increased hydrostatic pressures within the proximal tubules and Bowman’s space, leading to a reduction in net glomerular capillary ultrafiltration pressure and glomerular filtration rate.
Renal Effects of Increased IAP

Seminal Study in 1947 by Bradley and Bradley using external compression to raise IAP < 20 mmHg

- Elevation in renal parenchymal pressure (Nephrosarca)
- Elevation in renal vein pressure
- Fall in renal plasma flow (variable effect due to CO)
- Variable effect of ureteral compression

Fall in GFR

J Clin Invest 1947; 26:1010-1022
Congestive renal failure: the pathophysiology and treatment of renal venous hypertension

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GFR = \( K_f(P_c - P_b) - \pi_c \)
Vignette

• 55 year old man with HFrEF (LVEF 35%) and CKD (Cr 1.4 mg/dl) admitted with 30 lbs of weight gain and typical HF symptoms.
• Home meds: Sacubitril/valsartan low dose, Carvedilol mid-dose, Furosemide 40 mg BID
• Exam: BP 130/80, HR 80, JVP 15 cm, Pitting edema
• Labs: proBNP 8500, Cr 1.4 mg/dl
• Initial management: IV lasix 40 mg BID, Continued home medication
• Hospital day 2: Stable vitals, No weight change, Cr 1.7 mg/dl
Questions

- Should the diuretics be changed?
- Should the Entresto be held?
- What are the goals of diuresis?
Should the diuretics be changed?

Change to a different loop?

Higher Dose Bolus?

Drip?
Loop Diuretics

“High-Ceiling” Diuretics
Not all loop diuretics are the same…

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ORAL BIOAVAILABILITY</th>
<th>ELIMINATION HALF-LIFE (HOURS)</th>
<th>ROUTE OF ELIMINATION</th>
<th>DURATION OF ACTION (HOURS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop Diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>85%</td>
<td>1.25</td>
<td>65% R and 35% M</td>
<td>5 for oral 1 for IV</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>100%</td>
<td>1</td>
<td>65% R and 35% M</td>
<td>7 for oral 2 for IV</td>
</tr>
<tr>
<td>Furosemide</td>
<td>60%</td>
<td>2</td>
<td>60% R and 40% M</td>
<td>7 for oral 2 for IV</td>
</tr>
<tr>
<td>Torsemide</td>
<td>80%</td>
<td>3.5</td>
<td>30% R and 70% M</td>
<td>7 for oral 7 for IV</td>
</tr>
</tbody>
</table>

Furosemide dosing po:IV is 2:1; all other loop diuretics po:IV is 1:1
Loop Diuretics

“BRAKING PHENOMENON”

magnitude of natriuresis of a diuretic declines over time
Na+ in Proximal tubule 60%

Na+ in Thick-Ascending Limb 25%

Na+ in Distal tubule 10%

Na+ in Cortical Collecting Tubule 5%

Diuretics effects Na+ in LOOP
Proximal tubule 60%

Distal tubule 10%

Cortical Collecting Tubule 5%

Na+ LOOP Diuretics
Proximal tubule: 60%

Distal tubule: 10%

Cortical Collecting Tubule: 5%

Diuretics: Na+ in the LOOP

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Proximal tubule 60%

Distal tubule ~20%

Cortical Collecting Tubule 10%

Na+

LOOP Diuretics
Proximal tubule 60%

Distal tubule ~30%

Cortical Collecting Tubule 10%

Na+

LOOP Diuretics
Proximal tubule 60%

Cortical Collecting Tubule 10%

Na+

Thiazide Diuretics

LOOP Diuretics

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Diuretic Strategies in Patients with Acute Decompensated Heart Failure

G. Michael Felker, M.D., M.H.S., Kerry L. Lee, Ph.D., David A. Bull, M.D., Margaret M. Redfield, M.D., Lynne W. Stevenson, M.D., Steven R. Goldsmith, M.D., Martin M. LeWinter, M.D., Anita Deswal, M.D., M.P.H., Jean L. Rouleau, M.D., Elizabeth O. Ofili, M.D., M.P.H., Kevin J. Anstrom, Ph.D., Adrian F. Hernandez, M.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Abdallah G. Kfoury, M.D., Horng H. Chen, M.B., B.Ch., Michael M. Givertz, M.D., Marc J. Semigran, M.D., Bradley A. Bart, M.D., Alice M. Mascette, M.D., Eugene Braunwald, M.D., and Christopher M. O’Connor, M.D.,
for the NHLBI Heart Failure Clinical Research Network*
“DOSE-HF”

Bolus?

Low-Dose
(home dose)

vs

Drip?

High-Dose
(2.5 times
home dose)
Patients' Global Assessment of Symptoms during the 72-Hour Study-Treatment Period.

Mean Change in Serum Creatinine Level.

<table>
<thead>
<tr>
<th>DOSE-HF Study</th>
<th>Bolus</th>
<th>Drip?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Dose</td>
<td>518 mg</td>
<td>406 mg</td>
</tr>
<tr>
<td>Required Dose Increase</td>
<td>21%</td>
<td>11%</td>
</tr>
</tbody>
</table>
Questions

- Should the diuretics be changed? Yes!
- Should the Entresto be held?
- What are the goals of diuresis?
Afferent Arteriole → GFR → Efferent Arteriole
↓ Effective circulating volume
↓ CO

Efferent Arteriole

GFR
SNS, RAAS cause afferent vasoconstriction

↓ Effective circulating volume

↓ CO

↓ Renal blood flow

↓ Renal plasma flow

GFR

↓ Renal blood flow

↓ Renal plasma flow

Efferent Arteriole
SNS, RAAS cause afferent vasoconstriction

↓ Effective circulating volume
↓ CO
↓ Renal blood flow
↓ Renal plasma flow

Goal is to preserve GFR!!

SNS, RAAS vasoconstriction

efferent >> afferent

Efferent Arteriole
➢ So what happens if we add a RAS blocker?

• ACE-Inhibitors and ARB’s dilate the efferent arteriole
When there is already decreased renal blood flow, RAS blockade will lead to further GFR loss and hemodynamic AKI.
Unfortunately, what the heart and kidney want are not always in agreement....
Strategies

➢ Improve forward flow to the kidney - ?inotropes?

➢ Maintain GFR
  • Hold RAS blockers in the acute setting when creatinine not in steady-state
  • We need BP to make PP

➢ Decongest - get rid of **SALT and Water** – (aquareesis alone not shown to be effective)

➢ Avoid agents that vasoconstrict the afferent arteriole (e.g. contrast, NSAIDs)
Questions

• Should the diuretics be changed?  Yes!
• Should the Entresto be held?  Yes!
• What are the goals of diuresis?  Depends on the patient!
Summary

- AKI in cardiorenal syndrome is due to a combination of arterial underfilling and venous congestion.
- Long-term renal outcomes in Stage IV and V CKD in cardiorenal syndrome are poorly studied.
- Preferential strategy for decongestion may be high-dose infusions of loop diuretics over bolus administration.
- A 2L net negative fluid balance per day may be a “safer” target than just UOP.
Thank You!!

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