Defining and Managing the Cardiorenal Syndrome in Acute Decompensated Heart Failure

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Professor of Medicine
UCSF
DISCLOSURES

Consulting fees:
Merck-Novacardia
Novartis
Bristol Myers Squibb
Medtronic
Scios/Johnson and Johnson
Daiichi

Payments for DSMB Service
Amgen, Biotronik, DCRI, Lonestar Heart,
Novartis, Zensum, Cephalon
The Cardio-Renal Interactions in Acute and Chronic Heart Failure

- **↓ Cardiac performance**
- **Vasoconstriction and cytokine activation**
- **Neurohormonal Activation**
- **Increased water & Na+ retention**
- **Impaired Renal Function**

- **↓ Cardiac output**
- **Congestion and elevated CVP**
- **Neurohormonal activation & inflammation**
- **↓ Renal perfusion & renal hypoxia**

Schematic developed in NHLBI workshop
Early Inability to Excrete Volume Load

Effect of Na⁺ Load in “Mild” Heart Failure

Normal controls

NYHA I – II (mean LVEF 0.34)

2 liters normal saline infused over 2 hours

## Incidence of Worsening Renal Function in ADHF

<table>
<thead>
<tr>
<th>Definition of WRF</th>
<th>% WRF</th>
<th>Baseline elevated Cr</th>
<th>HTN</th>
<th>Volume overload</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑Cr mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ahkter 2004 (VMAC)</td>
<td>&gt;0.5</td>
<td>25</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Cowie 2006 (POSH)</td>
<td>&gt;0.3</td>
<td>33</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Forman 2004</td>
<td>&gt;0.3</td>
<td>27</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Gottlieb 2002</td>
<td>&gt;0.3</td>
<td>39</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Krumholz 2000</td>
<td>&gt;0.3</td>
<td>28</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

Other predictors: age, female sex, diabetes, CKD
The “Cardiorenal Syndrome”
New Insights into Pathophysiology

- Diuretics
- Hemodynamic abnormalities
- Congestion
- Intrarenal autoregulation (Adenosine)
- Neurohormonal/SNS interactions
- Ultrafiltration
Relationship of Diuretic Dose to $\Delta$ SCr in the ESCAPE Trial

Hasselblad EJHF 2007
PA Catheter Monitoring Does not Prevent Worse Outcomes in Patients with Renal Dysfunction

Table 3  Impact of PAC on 6-Month Outcomes In Patients Stratified by Baseline Renal Function

<table>
<thead>
<tr>
<th>End Point</th>
<th>Subgroup (eGFR, ml/min)</th>
<th>HR for PAC Versus CLIN</th>
<th>95% CI</th>
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<td>0.92-2.30</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>≥60</td>
<td>0.88</td>
<td>0.54-1.44</td>
<td>0.61</td>
</tr>
<tr>
<td>Death or rehospitalization</td>
<td>&lt;60</td>
<td>1.17</td>
<td>0.90-1.52</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>≥60</td>
<td>0.92</td>
<td>0.71-1.20</td>
<td>0.55</td>
</tr>
</tbody>
</table>

The p value for the interaction between eGFR and treatment was not significant for both death (p = 0.18) and death or rehospitalization (p = 0.26). Abbreviations as in Tables 1 and 2.

Nohria A, et al. JACC 2006; 58;268-74.4
Pathophysiology?

- Underlying CKD (hypertension, diabetes)
- Drug effect or toxicity (diuretics ?, RAAS blockers)
- Low CO, hypotension, renal artery stenosis (rare!)
- Volume overload/venous congestion
- Dysfunctional compensatory mechanisms (adenosine mediated proximal Na reabsorption, tubuloglomerular feedback)
- Abnormal renal and CNS sympathetic regulation
Are Diuretics the Cause of Cardiorenal Syndrome?

- **Theory:** “Overdiuresis” $\rightarrow \downarrow \text{PCWP} \rightarrow \downarrow \text{CO} \rightarrow \downarrow \text{GFR} \rightarrow \uparrow \text{SCr}

- **But…** WRF occurs early in volume overloaded patients, often before iv diuretics have been administered

- WRF often occurs in diuretic refractory patients

- Most hemodynamic data refute this explanation
  - CO often increases with Rx ($\downarrow$ MR, PAP, TR, RAP)

- Volume redistributes rapidly in HF (except ascites)
Relation of Diuretic Dose to Survival

1,354 Patients With Advanced Systolic Heart Failure

Do diuretics have an adverse effect on outcomes?

OR

Does this association reflect higher diuretic requirements in sicker patients?

We Need a Randomized Controlled Trial of Diuretics in ADHF Heart Failure!


Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Diuretic Optimization Strategies Evaluation in AHF (DOSE)

Aims

- To evaluate the safety and efficacy of two initial strategies of furosemide Rx in patients with ADHF
  - Dosing
    - Low intensification (1 x oral dose)
    - High intensification (2.5 x oral dose)
  - Route of administration:
    - Q12 hours bolus
    - Continuous infusion

### DOSE: Secondary Endpoints: Q12 vs. Continuous

<table>
<thead>
<tr>
<th></th>
<th>Q12</th>
<th>Continuous</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea VAS AUC at 72 hrs</td>
<td>4456</td>
<td>4699</td>
<td>0.36</td>
</tr>
<tr>
<td>% free from congestion at 72 hrs</td>
<td>14%</td>
<td>15%</td>
<td>0.78</td>
</tr>
<tr>
<td>Change in weight at 72 hrs</td>
<td>-6.8 lbs</td>
<td>-8.1 lbs</td>
<td>0.20</td>
</tr>
<tr>
<td>Net volume loss at 72 hrs</td>
<td>4237 mL</td>
<td>4249 mL</td>
<td>0.89</td>
</tr>
<tr>
<td>Change in NTproBNP at 72 hrs</td>
<td>-1326</td>
<td>-1773</td>
<td>0.44</td>
</tr>
<tr>
<td>% treatment failure</td>
<td>38%</td>
<td>39%</td>
<td>0.88</td>
</tr>
<tr>
<td>% with Cr increase &gt;0.3 mg/dL</td>
<td>17%</td>
<td>19%</td>
<td>0.64</td>
</tr>
<tr>
<td>Length of stay, days (median)</td>
<td>5</td>
<td>5</td>
<td>0.97</td>
</tr>
</tbody>
</table>

*No significant differences observed between continuous infusion and bolus administration*

## DOSE: Secondary Endpoints

<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 hours</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>-6.1 lbs</td>
<td>-8.7 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>0.001</td>
</tr>
<tr>
<td>Change in NTproBNP at 72 hrs (pg/mL)</td>
<td>-1194</td>
<td>-1882</td>
<td>0.06</td>
</tr>
<tr>
<td>% Treatment failure</td>
<td>37%</td>
<td>40%</td>
<td>0.56</td>
</tr>
<tr>
<td>% with Cr increase &gt; 0.3 mg/dL</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>

DOSE: Proportion with Worsening Renal Function*: Low vs. High

*Based on local lab creatinine values

DOSE: 60 Day Endpoint
Death, Rehospitalization, or ED Visit

HR for High vs. Low = 0.83
95% CI 0.60, 1.16, p = 0.28

Prevalence of Worsening Renal Function in Relation to Hemodynamics

Figure 1: Distribution of CVP and Curvilinear Relationship Between CVP and eGFR in the Study Population

Adjusted for age, sex, and cardiac index. The curvilinear model had the following individual polynomial components for the relationship between CVP and eGFR: First order: \( Y = -\frac{25.8 \cdot (CVP + 1)}{10} \) (Wald 28.2, \( p < 0.0001 \)) and second order: \( Y = \frac{35.7 \cdot (CVP + 1)^{0.5}}{10} \) (Wald 17.4, \( p < 0.0001 \)). CVP = central venous pressure, eGFR = estimated glomerular filtration rate.

Damman, JACC 2009
Impact of Venous Congestion on Glomerular Net Filtration Pressure

An illustration of the afferent and efferent pressures at a glomerular capillary in a patient with normal hemodynamics and a patient with increased right atrial (RA) pressure and venous congestion. $P_{BC}$ = hydrostatic pressure in Bowman’s capsule; $P_{GC}$ = glomerular capillary hydrostatic pressure; $\pi_{GC}$ = oncotnic pressure in glomerular capillaries.

## Is Worsening Renal Function Due to Low CO?

### Correlation Between Hemodynamics and Renal Function at Admission (ESCAPE)

<table>
<thead>
<tr>
<th></th>
<th>Correlation (p-value)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Creatinine</td>
<td>BUN</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-0.07 (p=0.35)</td>
<td>-0.101 (p=0.16)</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>0.105 (p=0.15)</td>
<td>0.085 (p=0.25)</td>
</tr>
<tr>
<td>PCWP</td>
<td>-0.011 (p=0.90)</td>
<td>0.050 (p=0.58)</td>
</tr>
<tr>
<td>RAP</td>
<td>0.164 (p=0.02)</td>
<td>0.138 P=(0.06)</td>
</tr>
</tbody>
</table>

Nohria et al., J Am Coll Cardiol 2008;51:1268-74
Wet and Cold Kidney (canine model)
Effect of ↑ renal venous pressure

At venous pressures near 19 mmHg
Renal Perfusion flow ↓
Glomerular Filtration ↓
Na⁺ excretion ↓
FeNa ↓

This is a “backwards” model of renal insufficiency, or a congested kidney

Winton J. Physiol. 1931
Many Mechanisms Contribute to the Selective Functions of Adenosine

- Receptor location and expression level
- Diversity of receptors and signaling pathways

- Local extracellular levels of adenosine produced by breakdown of intracellular ATP and ADP in response to increased energy utilization (work)
- Effects on different receptor subtypes act to restore balance between energy supply and demand but may be dysfunctional in pathological states

Renal Effects of Adenosine Mediated by $A_1$ Receptors

1. Enhances reabsorption of Na+ and water in the proximal tubule → counteracts diuresis

2. Activates tubuloglomerular feedback (TGF) → stimulates afferent arteriolar vasoconstriction and renin release → ↓ GFR

3. Enhances distal tubular Na+ reabsorption in TAL and collecting ducts (braking).

These mechanisms protect against renal medullary ischemia in resulting from elevated CVP, but also lead to diuretic resistance.
Interactions Between Adenosine and the Sympathetic Nervous System

Hemodynamic and Afferent Renal Nerve Responses to Intrarenal Adenosine in the Dog.

Intrarenal Adenosine Produces Hypertension by Activating the Sympathetic Nervous System via Renal Nerves in the Dog.
Cardio-Renal Interactions Beyond Cardiac Output

Acute de-congestion from chronic atrial distention

Cardiac hormones respond to distention

SNS connections

Vasodilation

Afferent/effferent

Vasoconstriction
Norepinephrine Spillover to Plasma in CHF Patients: Increased Overall and Cardiorenal SNS Activity

FIGURE 1. Total and regional norepinephrine spillover in patients with congestive heart failure and in control subjects. *p < .02; **p < .002.

## Table 1. Effect of alterations in renal sympathetic nerve activity on renal sodium handling

<table>
<thead>
<tr>
<th></th>
<th>PCT</th>
<th>LH</th>
<th>DCT</th>
<th>CD</th>
<th>U$_{NaV}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNS</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>DNX</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

RNS, low-frequency renal nerve stimulation; DNX, renal denervation; PCT, proximal convoluted tubule; LH, loop of Henle; DCT, distal convoluted tubule; CD, collecting duct; U$_{NaV}$, urinary sodium excretion; ↑, increase; ↓, decrease.
Long-term outcome in relation to renal sympathetic activity in patients with chronic heart failure

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>RR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above median cardiac NA spillover</td>
<td>0.9</td>
<td>0.3–2.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Above median renal NA spillover</td>
<td>4.6</td>
<td>1.5–13.7</td>
<td>0.006</td>
</tr>
<tr>
<td>Above median total body spillover</td>
<td>2.9</td>
<td>1.0–9.0</td>
<td>0.06</td>
</tr>
</tbody>
</table>

P for global test = 0.008; \( \chi^2 = 11.6 \).

Pettersson, Eur Heart J 2005
Renal Sympathetic Afferent Nerves: The Kidney as Origin of Central Sympathetic Drive

- Renal Afferent Nerves
  - Hypertrophy
  - Arrhythmia
  - ↑ Oxygen Consumption
  - Heart Failure

- Vasoconstriction
- Atherosclerosis

- Insulin Resistance

- ↑ Renin Release
- Sodium Retention
- Congestion
- Rightward Shift Pressure-Natriuresis Curve
- ↓ Renal Blood Flow
Renal Nerves as a Therapeutic Target

- Arise from ~ T10-L2
- Follow the renal artery to the kidney
- Primarily lie within the adventitia

Vessel Lumen

Media

Adventitia

1000 µm

Renal Nerves
Renal Sympathetic Nerve Ablation in Resistant Hypertension

Hypothesis: RSN ablation may be an effective intervention for “Cardiorenal Syndrome” or even prevent it.

Figure 2: Change in office blood pressure (95% CI) at 1, 3, 6, 9, and 12 months

Krum H et al. Lancet 2009
New Insights into the Pathophysiology of Cardiorenal Syndrome

- Don’t blame it on diuretics!
- Cardiorenal syndrome is usually associated with a congested rather than a low-output state.
- Counterproductive intrarenal autoregulation mediated by adenosine and norepinephrine appears to be involved.
- Cardiorenal-neurohormonal interactions are mechanistically important and promising targets for treatment.
Does PA Catheter Monitoring Reduce the Incidence of WRF?

Correlation between WRF & hemodynamics is poor. Nominally significant only for CVP.

Is Worsening Renal Function Due to Low CO?

Correlation Between Hemodynamics and Renal Function at Admission (ESCAPE)

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Nohria et al., J Am Coll Cardiol 2008;51:1268-74
Physiological Effects of Renal Sympathetic Nerve Stimulation

Fig. 2. Relationship between the frequency of renal nerve stimulation and the magnitude of the response of renin secretion rate (increase), urinary sodium excretion (decrease), and renal blood flow (decrease).

DiBona GF. Am J Physiol 2005
Renal Effects of Adenosine Mediated by $A_1$ Receptors

1. Enhance reabsorption of Na+ and water in the proximal tubule → counteracts diuresis
2. Activates tubuloglomerular feedback (TGF) → stimulates afferent arteriole vasoconstriction and renin release → $\downarrow$ GFR
3. Enhances distal tubular Na+ reabsorption in TAL and collecting ducts (braking).

Inhibiting these mechanisms increases diuretic responsiveness while maintaining kidney function.
PA Catheter Monitoring Does Not Prevent Worse Outcomes in Patients with Renal Dysfunction

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Nohria A, et al. JACC 2006; 58;268-74.4
Adenosine increases Na reabsorption in the proximal tubule (TGF) and possibly in the TAL and CD (braking).

Adenosine stimulates afferent arteriolar constriction and renin release, decreasing GFR.

Mechanism enables improved responsiveness to loop diuretics while maintaining kidney function.
Adenosine A<sub>1</sub> Antagonist

Urine Output vs. GFR

GFR (% change) (1-8 hours)

Placebo

Rolofylline

Rolofylline + Furosemide

Furosemide Alone

Urine Output (mL) (0-8 hrs, Day 1 - Baseline)

Gottlieb et al., Circulation 2002;105:1348
PROTECT Pilot Trial
Change in Serum Creatinine

Mean Change in Serum Creatinine, mg/dL

- Placebo (n = 78)
- 10 mg rolofylline (n = 74)
- 20 mg rolofylline (n = 75)
- 30 mg rolofylline (n = 74)


*Nominal \( P < 0.05 \) for dose-related trend at Day 14
Adenosine and the Kidney: Summary

- Adenosine is a critical modulator of renal physiology and function
- Teleological role appears to be protection against imbalance between work (tubular function) and oxygen supply (blood flow)
- In heart failure, especially with diuretic Rx enhanced salt delivery to tubules, rising extracellular adenosine levels act on cortical AA$_1$ receptors to increase afferent arteriolar vasoconstriction and proximal tubule Na reabsorption (TGF)
- In this situation, an AA$_1$ antagonist maintains GFR and enhances tubular salt excretion
## PROTECT Pilot: 60-Day Outcomes: Death and Rehospitalization

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 78)</th>
<th>Rolofylline 10 mg (n = 74)</th>
<th>Rolofylline 20 mg (n = 75)</th>
<th>Rolofylline 30 mg (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or cardiovascular or renal rehospitalization(^1)</td>
<td>33%</td>
<td>32%</td>
<td>24%</td>
<td>19%</td>
</tr>
<tr>
<td>Death</td>
<td>10%</td>
<td>12%</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Rehospitalization for cardiovascular or renal causes</td>
<td>30%</td>
<td>22%</td>
<td>17%</td>
<td>16%</td>
</tr>
</tbody>
</table>

\(^1\) 30 mg vs. placebo: HR 0.55 (95% CI = 0.28, 1.04)

A Placebo-controlled Randomized study of rolofylline for patients hospitalized with acute heart failure and volume Overload to assess Treatment Effect on Congestion and renal function

• 2,000 patient trial with in-hospital and 60 day endpoints

Time to Death or CV or Renal Rehospitalization - Day 60

Hazard Ratio (95% CI) = 0.98 (0.83, 1.17)
P-value = 0.861

Death: Placebo 9.5% vs rolofylline 8.9%
Re-hospitalization: Placebo 25.6% vs rolofylline 25.7%

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Placebo (N=677)</th>
<th>Rolofylline (N=1356)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>657</td>
<td>1322</td>
</tr>
<tr>
<td>14</td>
<td>633</td>
<td>1263</td>
</tr>
<tr>
<td>30</td>
<td>566</td>
<td>1134</td>
</tr>
<tr>
<td>55</td>
<td>489</td>
<td>1001</td>
</tr>
<tr>
<td>65</td>
<td>74</td>
<td>158</td>
</tr>
</tbody>
</table>
Effect of Renal Sympathetic Denervation on BP and Na

Fig. 4. Arterial pressure vs. steady-state daily urinary sodium excretion in groups of dorsal rhizotomized (DRX) rats and sham DRX rats. Sham DRX rats (black circles) and DRX rats (white circles) received either a normal NaCl or a high-NaCl diet. [modified and adapted from Kopp UC, Cicha MZ, and Smith LA (30).]
BP Response to RSN Ablation (N=68)

Renal Denervation BP Results

All Treated

mmHg

Systolic  Diastolic

1 month (n=68)  3 months (n=64)  6 months (n=50)  9 months (n=36)  12 months (n=21)

DiBona, AJP 2009
Role of RSNA in Na Balance

Table 5. *Role of RSNA in sodium balance adjustments*

<table>
<thead>
<tr>
<th>Role of RSNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute NaCl loading or chronic high-sodium diet:</td>
</tr>
<tr>
<td>↑ Right atrial pressure, ↓ RSNA.</td>
</tr>
<tr>
<td>Acute furosemide or chronic low-sodium diet:</td>
</tr>
<tr>
<td>↓ Right atrial pressure, ↑ RSNA.</td>
</tr>
</tbody>
</table>

Renal denervated rats, dogs, sheep, and humans with functional denervation due to Shy-Drager syndrome have impaired ability to conserve sodium. Renal denervated rats, monkeys, and dogs have impaired ability to excrete sodium.

Table 6. *Role of RSNA in experimental models of renal sodium retention and edema formation*

<table>
<thead>
<tr>
<th>Role of RSNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased ability to excrete acute sodium loads associated with attenuated inhibition of RSNA; renal denervation improves ability to excrete acute sodium loads.</td>
</tr>
<tr>
<td>In 30-day balance study, 40% cumulative renal sodium retention was dependent on intact renal innervation.</td>
</tr>
<tr>
<td>Losartan treatment (icv or po) decreased basal RSNA and improved aortic and cardiopulmonary baroreflex control of RSNA associated with improved ability to excrete acute and chronic sodium loads.</td>
</tr>
<tr>
<td>icv, Intercerebroventricular; po, oral.</td>
</tr>
</tbody>
</table>
Reflex Stimuli that Affect Renal Function Independent of GFR and RBF

<table>
<thead>
<tr>
<th>Reflex Stimuli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid baroreceptor unloading</td>
</tr>
<tr>
<td>Nonhypotensive hemorrhage</td>
</tr>
<tr>
<td>Somatic afferent stimulation</td>
</tr>
<tr>
<td>Head-up tilt</td>
</tr>
<tr>
<td>Chemoreceptor stimulation: hypoxia, hypercapnia</td>
</tr>
<tr>
<td>C1 spinal cord transection</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
</tr>
<tr>
<td>Positive pressure breathing</td>
</tr>
<tr>
<td>Air jet stress</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate; RBF, renal blood flow.

Table 3. Reflex stimuli that produce natriuresis and decreased renin release in the absence of changes in GFR and RBF and are abolished by DNX

<table>
<thead>
<tr>
<th>Reflex Stimuli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stellate ganglion stimulation</td>
</tr>
<tr>
<td>Left atrial distension</td>
</tr>
<tr>
<td>Head-out water immersion</td>
</tr>
<tr>
<td>Intravascular volume expansion</td>
</tr>
<tr>
<td>Negative pressure breathing</td>
</tr>
</tbody>
</table>
Adenosine and the Kidney: Summary

- Adenosine is a critical modulator of renal physiology and function
- Teleological role appears to be protection against imbalance between work (tubular function) and oxygen supply (blood flow)
- In heart failure, especially with diuretic Rx enhanced salt delivery to tubules, rising extracellular adenosine levels act on cortical AA₁ receptors to increase afferent arteriolar vasoconstriction and proximal tubule Na reabsorption (TGF)
- In this situation, an AA₁ antagonist maintains GFR and enhances tubular salt excretion
Cardiorenal Syndrome: Summary

- A common problem in acute and chronic heart failure
- Mechanisms not well understood, but underlying renal disease is usually present
- Systolic dysfunction and low CO are important factors, but cardiorenal dysfunction occurs commonly with preserved EF
- Cardiorenal dysfunction is both a predictor and a mechanism of poor clinical outcomes
- Congestion and volume overload are not just the result of cardiorenal dysfunction but also an important cause
- Diuretics are associated with this syndrome, but probably not a primary cause and should not be withheld
- New therapeutic approaches are eagerly awaited
Minimally Invasive Ultrafiltration
Hemofiltration System
Ultrafiltration versus IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure: A Prospective Randomized Clinical Trial

Principal Findings

- At 48 h after randomization early ultrafiltration compared with IV Diuretics produces:
  - greater weight loss
    \(5.0 \pm 0.68 \text{ Kg vs. } 3.1 \pm 0.75 \text{ Kg; } p= 0.001\)
  - greater fluid loss
    \(4.6 \pm 0.29 \text{ L vs. } 3.3 \pm 0.29 \text{ L; } p= 0.001\)
  - similar changes in sCr
    \(0.12 \pm 0.42 \text{ mg/dL vs. } 0.07 \pm 0.41 \text{ mg/dL; } p=0.356\)

Safety Endpoints: Change in Serum Creatinine

P > 0.05 at all time points

Serum creatinine increased more with ultrafiltration despite lower in-hospital diuretic doses

<table>
<thead>
<tr>
<th>Time</th>
<th>Ultrafiltration arm</th>
<th>Standard care arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 hrs</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>24 hrs</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>48 hrs</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>72 hrs</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Discharge</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>10 days</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>30 days</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>90 days</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

UF: n = 72, 90, 69, 47, 86, 71, 75, 66
SC: n = 84, 91, 75, 52, 90, 75, 67, 62
UNLOAD Primary Endpoint: Weight Loss at 48 Hours

No differences in symptoms, QOL, 6-minute walk, BNP levels

Freedom From Re-hospitalization for Heart Failure

A Randomized, Controlled Trial of the Renal Effects
of Ultrafiltration as Compared to Furosemide in Patients
With Acute Decompensated Heart Failure

HOBART L. ROGERS, PharmD,1 JOANNE MARSHALL, BSN,2 JEREMY BOCK, MD,2 THOMAS C. DOWLING, PharmD, PhD,1
ERIKA FELLER, MD,2 SHAWN ROBINSON, MD,2 AND STEPHEN S. GOTTLIEB, MD2,3

Table 2. Effect of Ultrafiltration and Diuresis on Volume,
Renal Function, and Chemistries

<table>
<thead>
<tr>
<th>Variables</th>
<th>UF</th>
<th>Furosemide</th>
<th>P value, UF vs. furosemide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average urine output (mL)</td>
<td>2286 ± 915</td>
<td>5786 ± 2587</td>
<td>.001</td>
</tr>
<tr>
<td>Δ weight (kg)</td>
<td>−2.2 ± 2.6*</td>
<td>−1.9 ± 2.7*</td>
<td>.85</td>
</tr>
<tr>
<td>Δ GFR (mL/min)</td>
<td>−3.4 ± 7.7</td>
<td>−3.6 ± 11.5</td>
<td>.97</td>
</tr>
<tr>
<td>Δ RPF (mL/min)</td>
<td>27 ± 63</td>
<td>16 ± 45</td>
<td>.68</td>
</tr>
<tr>
<td>Δ FF (%)</td>
<td>−7 ± 13</td>
<td>−4 ± 14</td>
<td>.65</td>
</tr>
<tr>
<td>Δ Na⁺ (mg/dL)</td>
<td>−2 ± 2*</td>
<td>−2. ± 3 *</td>
<td>.52</td>
</tr>
<tr>
<td>Δ K⁺ (mg/dL)</td>
<td>0.1 ± 0.8</td>
<td>−0.1 ± 0.8</td>
<td>.62</td>
</tr>
<tr>
<td>Δ Cr (mg/dL)</td>
<td>−0.01 ± 0.31</td>
<td>0.11 ± 0.15 *</td>
<td>.29</td>
</tr>
</tbody>
</table>

UF, ultrafiltration; GFR, glomerular filtration rate; RPF, renal plasma flow; FF, filtration fraction; Cr, serum creatinine concentration.

*P < .05 compared with baseline.