Diuretic Resistance and Cardiorenal syndrome

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**Definition of Cardiorenal Syndrome (CRS)**

**NHLBI working group definition (2004)**
The extreme cardio-renal dysregulation whereby therapy to relieve congestive symptoms of heart failure is limited by further decline in renal function.

**ADQI Classification (2009)**
Disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other

**Definition of Cardiorenal Syndrome (CRS)**

Worsening renal failure (WRF) + Persistent congestion (Diuretic resistance)

Increase in creatinine of $\geq 0.3$ mg/dl or 25% increase from baseline

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**Definition & Classification of Cardiorenal Syndrome**

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

| CRS Type 1 (acute cardiorenal syndrome) | Acute worsening of cardiac function (e.g. ADHF or ACS) leads to AKI |
| CRS Type 2 (chronic cardiorenal syndrome) | Chronic cardiac dysfunction leads to progressive and potentially permanent CKD |
| CRS Type 3 (acute renocardiac syndrome) | AKI leads to acute cardiac dysfunction (e.g. acute HF, arrhythmia, or ischemia) |
| CRS Type 4 (chronic renocardiac syndrome) | CKD leads to progressive cardiac dysfunction |
| CRS Type 5 (secondary cardiorenal syndrome) | Systemic conditions (e.g. sepsis or DM) cause simultaneous cardiac & renal dysfunction |

Prevalence and Prognostic Importance of WRF in ADHF

- Prevalence: 23%
- Serum creatinine $\geq 0.3$ mg/dL
- In-hospital mortality:
  - Sensitivity of 65%
  - Specificity of 81%
- 2.3 days increase in LOS
- 67% $\uparrow$ risk of death within 6 months after discharge
- 33% $\uparrow$ risk for readmission

Graph showing patient survival and rise in serum creatinine.

Degree of Worsening Renal Function, Serum Creatinine and Mortality

Graphs showing reference decline and classes I, II, III with reference to estimated decrease in GFR (mL/min/1.73m²).
Cardiorenal syndrome Type 1

- Hemodynamic alterations
- Pharmacological intervention
- Neurohormonal activation
- Biochemical dysregulation

Cardiorenal syndrome: Pathophysiology

Hemodynamic Abnormalities

- Low cardiac output
- Venous congestion
- Increased intraabdominal pressure

Complex Interplay in Cardiorenal syndrome: Hemodynamic Abnormalities

- Pulmonary hypertension
- RV failure
- ↑ Venous Congestion
- ↑ Renal venous pressure
- ↑ Intra-abdominal pressure
- ↑ Renal interstitial pressure
- ↓ Cardiac Output
- ↑ Neurohormonal Activation
- ↑ SNS activity
- ↑ RAAS activity
- ↑ AVP release
- ↓ Peripheral vascular resistance
- ↓ Arterial Underfilling
- ↓ Renal Hemodynamics and Renal Salt/Water Excretion

Tang WH and Mullens W. Heart 2010;96::255-60.

Venous Congestion and Worsening Renal Function in Advanced HF

WRF defined as an increase of serum creatinine ≥0.3 mg/dl during hospitalization

- CVP
- CI
- SBP
- PCWP

Venous Congestion and Worsening Renal Function in AHF

WRF defined as an increase of serum creatinine $\geq 0.3$ mg/dl during hospitalization

Cutoff values for CI = 2.4 l/min/m² and CVP = 8 mm Hg.


Elevated Intraabdominal Pressure and Worsening Renal Function in AHF

Elevated IAP : $\geq$ 8 mm Hg, Prevalence 60% (24/40)

Glomerular Hemodynamic Changes in Heart Failure

\[ \text{GFP} = \text{RPP} - \text{RVP} \]

- GFP = glomerular filtration pressure
- RPP = renal perfusion pressure
- RVP = renal venous pressure

↓ CO/Map
↑ Renal venous congestion
↓ GFP
↓ GFR
↑ PTP
↑ IAP and RIP

GFP = glomerular filtration pressure
RPP = renal perfusion pressure
RVP = renal venous pressure
PTP = proximal tubule pressure
IAP = intraabdominal pressure
RIP = renal interstitial pressure

Glomerular hemodynamics:
Effects of ACEI on Renal Hemodynamics

\[ P_M = \text{Glomerular filtration pressure} \]

- Different arteries
- Different arterioles

WRF after RAAS inhibitor use in Heart Failure

- **Hypothesis:** low-dose dopamine or low-dose nesiritide may enhance decongestion and preserve renal function in patients with acute heart failure and renal dysfunction
- **Low-dose dopamine (2 μg/kg/min) vs. Low-dose nesiritide (0.005 μg/kg/min without bolus) vs placebo on top standard diuretic**
- **Multicenter, double-blind, placebo-controlled clinical trial**
- **360 hospitalized patients with acute HF and renal dysfunction (eGFR 15-60 mL/min/1.73m²), randomized within 24 hours of admission.
ROSE-AHF Study
Renal Optimization Strategies Evaluation

Co-primary end points:
- 72-hour cumulative urine volume (decongestion end point) and
- Change in serum cystatin C from enrollment to 72 hours (renal function end point).

Table 2. Co-primary End Points: Effect of Low-Dose Dopamine vs. Placebo or Low-Dose Nesiritide vs. Placebo on Cumulative Urine Volume During 72 Hours and Change in Cystatin C Level From Baseline to 72 Hours

<table>
<thead>
<tr>
<th>Mean (95% CI)</th>
<th>Placebo (n = 119)</th>
<th>Dopamine (n = 122)</th>
<th>Treatment Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative urine volume from randomization to 72 h, mL</td>
<td>8296 (7762 to 8830)</td>
<td>8524 (7917 to 9131)</td>
<td>229 (-714 to 1117)</td>
<td>.59</td>
</tr>
<tr>
<td>Change in cystatin C level from randomization to 72 h, mg/L</td>
<td>0.11 (0.06 to 0.16)</td>
<td>0.12 (0.06 to 0.18)</td>
<td>0.01 (~0.06 to 0.10)</td>
<td>.72</td>
</tr>
</tbody>
</table>

Nesiritide strategy

- Placebo (n = 119) | Nesiritide (n = 119)
- Cumulative urine volume from randomization to 72 h, mL | 8296 (7762 to 8830) | 8524 (7914 to 9134) | 279 (~618 to 1176) | .49     |
- Change in cystatin C level from randomization to 72 h, mg/L | 0.11 (0.06 to 0.16) | 0.07 (0.01 to 0.13) | -0.04 (~0.13 to 0.05) | .36     |

ASCEND-HF
Effect of Nesiritide in Patients with Acute Decompensated Heart Failure

- Multicenter, double-blind, placebo-controlled clinical trial
- 7141 patients who were hospitalized with acute heart failure
- Nesiritide vs. Placebo for 24 to 168 hours in addition to standard care.
- Within 24 hours after admission/48 hours after diagnosis of acute HF

ASCEND-HF Study
Acute Study of Clinical Effectiveness of Nesiritide in ADHF
Renal Outcomes

<table>
<thead>
<tr>
<th>Hypotension — no./total no. (%)</th>
<th>930/3498 (26.6)</th>
<th>538/3509 (15.3)</th>
<th>11.3 (9.4 to 13.1)</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>748/3498 (21.4)</td>
<td>436/3509 (12.4)</td>
<td>9.0 (7.2 to 10.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>250/3496 (7.2)</td>
<td>141/3509 (4.0)</td>
<td>3.2 (2.1 to 4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;25% decrease in estimated GFR from study-drug initiation — no./total no. (%)</td>
<td>1032/3289 (31.4)</td>
<td>968/3278 (29.5)</td>
<td>1.06 (0.98 to 1.21)</td>
<td>0.11</td>
</tr>
<tr>
<td>Baseline estimated GFR &lt;60 ml/min/1.73 m²</td>
<td>484/1714 (28.2)</td>
<td>449/1717 (26.2)</td>
<td>1.11 (0.96 to 1.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Baseline estimated GFR ≥60 ml/min/1.73 m²</td>
<td>548/1575 (34.8)</td>
<td>519/1561 (33.2)</td>
<td>1.07 (0.92 to 1.24)</td>
<td>0.36</td>
</tr>
</tbody>
</table>


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Diuretic Strategies in Patients with Acute Decompensated Heart Failure

- Prospective, double-blind, randomized trial
- 308 pts with ADHF Dx within 24 hr, chronic HF, on oral loop diuretic (furosemide 80-240 mg/d, or equivalent) for ≥ 1 mo
- IV bolus vs. IV continuous
- Low-dose strategy (1x) vs. High-dose strategy (2.5x)

Ultrafiltration as a Therapy for Congestion?

- Removes both sodium and free water (isotonic solution)
- Allows for titration of rate of fluid removal to match plasma refill rate
- Allows for reduction in diuretic use
- Remove inflammatory cytokines
**UNLOAD study: Primary endpoint**

**Primary efficacy endpoint:**
Mean weight loss at 48 hr

**Primary safety endpoint:**
Serum creatinine change

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**Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure**

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Lombard and Chicago, Illinois; Detroit, Michigan; Philadelphia, Pennsylvania; Minneapolis and Brooklyn Park, Minnesota; San Francisco and San Diego, California; Boston, Massachusetts; Baltimore, Maryland; and Columbus, Ohio

**Objectives**
This study was designed to compare the safety and efficacy of venous ultrafiltration and standard intravenous diuretic therapy for hypervolemic heart failure (HF) patients.

**Background**
Early ultrafiltration may be an alternative to intravenous diuretics in patients with decompenesated HF and volume overload.

**Methods**
Patients hospitalized for HF with ≥2 signs of hypervolemia were randomized to ultrafiltration or intravenous diuretics. Primary end points were weight loss and diuretics assessment at 48 h after randomization. Secondary endpoints included net fluid loss at 48 h, functional capacity, HF readmissions, and unscheduled visits in 90 days. Safety end points included changes in renal function, electrolytes, and blood pressure.

**Results**
Two hundred patients (63 ± 15 years, 69% men, 71% ejection fraction <40%) were randomized to ultrafiltration or intravenous diuretics. At 48 h, weight (5.0 ± 3.1 kg vs. 3.1 ± 3.5 kg; p = 0.001) and net fluid loss (4.6 vs. 3.3 kg; p = 0.001) were greater in the ultrafiltration group. Demographic scores were similar. Of patients were discharged from hospital. Unadjusted net fluid loss at 48 h was similar between groups (4.6 vs. 3.3 kg; p = 0.001); however, no serum creatinine differences occurred between groups. Nine deaths occurred in the ultrafiltration group, and 3% in the diuretics group

**Conclusions**
In decompenesated HF, ultrafiltration safely produces greater weight loss and fluid less than intravenous diuretics, reduces 90-day resource utilization for HF, and is an effective alternative therapy. (The UNLOAD trial, http://clinicaltrials.gov/ct/show/NCT00124137?term=UNLOAD) (J Am Coll Cardiol 2007;49:875-83) © 2007 by the American College of Cardiology Foundation

CARRESS study: Primary endpoint
Mean changes in creatinine and weight at 96 hours

188 patients with ADHF, WRF (Cr ≥0.3 mg/dL in 12 wks), and persistent congestion
CARRESS study: Changes in Serum Creatinine

![Graph showing changes in serum creatinine over time for pharmacologic therapy and ultrafiltration.](image)


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Positive Effects of Loop Diuretics
- Prostaglandin Synthesis
- Vascular Smooth Muscle Relaxation
- Renal and Pulmonary Vasodilation
- ↓ LV Dilatation
- ↓ Functional MR
- Improved Myocardial Function
- Improved Renal Function
- Negative Sodium, and Water Balance
- Inhibition of the Macula Densa
- ↓ RAAS
- ↓ Distal Sodium Delivery
- ↓ LV Wall Stress and Ischemia
- Hypertrophy of Distal Nephron
- Thiazide Diuretics

Negative Effects of Loop Diuretics
- CHF
- Loop Diuretic
- Secondary Hyperaldosteronism
- Thiazide Diuretics
- Diuretic Resistance

ESCAPE Study: Inpatient Mortality by Diuretic Dose

- Sicker patients get higher doses of diuretics?
  - Older
  - Greater severity of heart failure
  - More chronic kidney disease
- Relationship between diuretic dose and outcomes are confounded by indication

DOSE trial:
Mean Change in Serum Creatinine

Low dose
High dose

DOSE trial:
Death, HF Rehospitalization, ED Visit

A Bolus vs. Continuous Infusion

B Low-Dose vs. High-Dose Strategy


Persistent vs. Transient Worsening Renal Function in AHF

WRF: >0.5 mg/dL increase in serum creatinine above baseline at any time point
Persistent WRF: WRF throughout Day 30
Transient WRF: Creatinine levels subsequently decreased to <0.5 mg/dL above baseline.

**Hemoconcentration is Associated More WRF, but Better Survival – Data from ESCAPE study**

Hemoconcentration defined as top tertile of ≥2 of the change in protein, albumin and Hct

Higher dose of loop diuretic, lost more weight/fluid and greater reduction in filling pressures (p < 0.05)

![Graph showing hemoconcentration and no hemoconcentration](image)

**Confounding issued in AKI definition in CRS**

- Intravascular volume has direct and indirect impact on renal hemodynamics
- Serum creatinine may rise due to azotemia or hemoconcentration
- Decongestive therapy with loop diuretics may obscure AKI urine output criteria
- Change in renal biomarkers may not reflect clinical status in CRS
Other treatment causes of WRF with different prognostic implications

- NSAIDs
- Nephrotoxic ATB
- AKI secondary to contrast or other nephrotoxic agents
- Urinary tract obstruction
- ATN secondary to hypotension/hypovolemia as result of medications or blood loss

Thank you for your kind attention

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