Biomarkers, the Kidney and the Heart: Acute Kidney Injury

12th Annual Conference on Biomarkers in Heart Failure and Acute Coronary Syndromes: Diagnosis, Treatment and Devices
San Diego May 13, 2016

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University of California San Diego
The Cardio-Renal Syndrome

Heart–kidney interactions

Cardio-renal

Primary insult

ADHF – CHF

Physiological derangements

AKI – CKD

Renal dysfunction

Therapy

Imaging biomarkers

Prevention

Secondary

Prevention

Imaging biomarkers

Reno-cardiac

Primary insult

AKI – CKD

Physiological derangements

ADHF – CHF

Heart dysfunction

Therapy

Imaging biomarkers

Therapy

Imaging biomarkers

Imaging biomarkers

Therapy

Therapy

Therapy

Therapy

Prevention

Prevention

Prevention
Cardio-Renal Syndrome Type 1

Definition
Acute worsening of heart function leading to kidney injury and/or dysfunction.

Key Features
- Epidemiology is challenging:
  - Associated with heart failure, ACS, AMI
  - Retrospective/secondary analyses
  - Definition of worsening renal function (WRF)
  - Variable observed time-at-risk
Cardio-Renal Syndrome Type 2

**Definition**

Chronic abnormalities in heart function leading to kidney injury or dysfunction.

**Key Features**

- Patients generally develop CKD
- Unclear rate of progression of CKD in patients with established CVD
- Mechanistic link of heart-kidney interaction and synergistic interaction
- Effect of cardio-protective therapies on progression/exacerbation of CKD
Management Issues: CRS Type 1

**Definition**
Acute worsening of heart function leading to kidney injury and/or dysfunction.

**Clinical Need**
- Criteria for WRF
- Differential diagnosis of WRF
  - Reversible hemodynamic change
  - Structural damage
- Contributory factors
  - Primary disorder
  - Therapy for primary disorder
- Severity of renal dysfunction
- Nature and timing of intervention
- Response to intervention
- Prognosis
Management Issues: CRS Type 2

**Definition**
Chronic abnormalities in heart function leading to kidney injury or dysfunction.

**Clinical Need**
- Determine level of CKD
- Determine rate of progression of CKD
- Mechanistic link of heart-kidney interaction and synergistic interaction
- Effect of cardio-protective therapies on progression/exacerbation of CKD
Clinical Need

- Determinants of renal function
- Contributory factors for WRF in heart failure
Determinants of renal function

- Cardiac output
- Renal blood flow
- Autoregulation
Inhomogeneous regional blood supply

- Cortex receives nearly 20% of cardiac output, tissue PO$_2$ 50-60 mmHg
- Medulla receives about 2.5% of cardiac output, tissue PO$_2$ of 10-20 mm Hg
- Medulla - brink of hypoxia

Brezis, M et al, NEJM 1995
Corticomedullary junction: Critical zone of medullary hypoxia - $\downarrow O_2$ delivery and $\uparrow O_2$ consumption
Renal Compensatory Mechanisms

Figure 1. The Three Steps of Fractionation of Cardiac Output to Form Glomerular Filtrate in the Cardiorenal Loop.

Note the three regulatory sites through which mechanisms intrinsic to the kidney are capable of modulating the glomerular filtration rate: fractional renal blood flow (renal blood flow/cardiac output; 1), filtration fraction (glomerular filtration rate/glomerular plasma flow rate; 2), fractional tubular fluid reabsorption (tubular reabsorption/glomerular filtration rate; 3).

Figure 2. Mechanism of Autoregulation.

When an otherwise normal person faces a hypotensive episode, a highly efficient homeostatic mechanism (autoregulation) comes into play to maintain the glomerular filtration rate (GFR). This is accomplished by a marked reduction in afferent arteriolar resistance ($R_A$), by virtue of both myogenic reflex and tubuloglomerular feedback mechanisms, and an increase in efferent arteriolar resistance ($R_E$) in response to locally released angiotensin II. By maintaining the glomerular plasma flow rate (GPF) and glomerular capillary hydraulic pressure ($P_{GC}$), these arteriolar adjustments successfully maintain the GFR.

Renal autoregulation of RBF and GFR. If MAP is in the range of ~80 to 180 mm Hg, fluctuations in blood pressure have only marginal effects on RBF and GFR. This is an intrinsic mechanism and can be modulated or overridden.
Determinants of renal function

- Renal perfusion
  - Cardiac output
  - Renal blood flow
  - Autoregulation

- GFR
  - Structural integrity
  - Pressure gradients
  - Autoregulation
AKI Pathophysiology

Pressure gradients are needed for GFR

Table 1 | Reasons for decreased glomerular ultrafiltration in patients with acute kidney injury

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Physiological effect</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low systemic blood pressure</td>
<td>Low glomerular hydrostatic pressure</td>
<td>Decreased glomerular filtration</td>
</tr>
<tr>
<td>Afferent arteriole vasoconstriction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efferent arteriole vasodilatation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal interstitial edema</td>
<td>High intracapsular pressure</td>
<td>Decreased glomerular filtration</td>
</tr>
<tr>
<td>Extrinsic compression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubular obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure of downstream tubular reabsorption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low renal plasma flow</td>
<td>Rapid rise in oncotic pressure</td>
<td>Decreased glomerular filtration</td>
</tr>
</tbody>
</table>

Figure 1 | Normal glomerular hemodynamics. Table 1 shows abnormalities that lead to a loss of ultrafiltration pressure in patients with acute kidney injury. Only relatively small pressure changes are required to abolish ultrafiltration.

Pathophysiology of AKI

RENAL EFFECTS OF CRITICAL ILLNESS

A

<table>
<thead>
<tr>
<th>Afferent arteriole</th>
<th>Glomerular capillary</th>
<th>Efferent arteriole</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{GC}$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>Afferent arteriole</th>
<th>Glomerular capillary</th>
<th>Efferent arteriole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P_{GC}$</td>
<td>$RBF$</td>
</tr>
<tr>
<td>$\uparrow$ Afferent-arteriolar resistance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C

<table>
<thead>
<tr>
<th>Afferent arteriole</th>
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<tbody>
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<tr>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

D

<table>
<thead>
<tr>
<th>Afferent arteriole</th>
<th>Glomerular capillary</th>
<th>Efferent arteriole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P_{GC}$</td>
<td>$RBF$</td>
</tr>
<tr>
<td>$\uparrow$ Afferent-arteriolar resistance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Murray P Eds: Intensive Care Nephrology
Tubuloglomerular Feedback

Changes in the delivery of NaCl to the macula densa region of the thick ascending limb of the loop of Henle cause changes in the afferent arteriolar caliber. The response is mediated by adenosine or possibly ATP, and modulated by other locally produced agents, such as angiotensin II and nitric oxide.

Increased macula densa NaCl delivery results in afferent arteriolar constriction, thereby reducing GFR.

Summary of effects mediated by adenosine A1 and A2 receptors on the afferent arteriole. In normal conditions, the A1 receptor mediated constriction predominates and vasoconstriction of the afferent arterioles is seen.
Normal GFR

Renal Reserve (Recruitable Nephrons)

Baseline GFR depends on many factors, including diet and fluid intake. Each person has the capability to increase GFR in response to different stimuli. The difference between maximum GFR (Max GFR) and baseline GFR describes the renal functional reserve. When renal mass is lost, Max GFR declines in an almost linear function. RFR is still present any time the baseline GFR is lower than the Max GFR at a given value for functioning renal mass.
Serum Creatinine and GFR Relationships

GFR, glomerular filtration rate; SCr, serum creatinine
Determinants of renal function

Renal perfusion
- Cardiac output
- Renal blood flow
- Autoregulation
- Microcirculation

GFR
- Structural integrity
- Pressure gradients
- Autoregulation

Tubular function
- Tubular reabsorption
- Water balance
- Acid excretion
- Divalent ions
- Hormones
Majority of renal $QO_2$ is driven by Na reabsorption which is determined by GFR.

Tubular transport is among the principal determinants of intrarenal oxygenation.

Increasing metabolic cost of Na transport along the nephron

*Cohen JJ et al, 1981
Traditional Urinary Biomarkers in the Assessment of Hospital-Acquired AKI

Mark A. Perazella and Steven G. Coca

<table>
<thead>
<tr>
<th>Table 1. Limitations of fractional excretion of sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenarios with FeNa &lt; 1%</td>
</tr>
<tr>
<td>normal kidney function with low or moderate</td>
</tr>
<tr>
<td>salt intake</td>
</tr>
<tr>
<td>acute GN</td>
</tr>
<tr>
<td>early AIN</td>
</tr>
<tr>
<td>acute urinary obstruction</td>
</tr>
<tr>
<td>transplant rejection</td>
</tr>
<tr>
<td>FeNa &lt; 1% despite ATN</td>
</tr>
<tr>
<td>AKI with liver failure or CHF</td>
</tr>
<tr>
<td>sepsis-associated AKI</td>
</tr>
<tr>
<td>radiocontrast nephropathy</td>
</tr>
<tr>
<td>nonoliguric ATN</td>
</tr>
<tr>
<td>myoglobinuric ATN</td>
</tr>
<tr>
<td>hemoglobinuric ATN</td>
</tr>
<tr>
<td>Scenarios with FeNa &gt; 2%</td>
</tr>
<tr>
<td>normal kidney function with high salt intake</td>
</tr>
<tr>
<td>or IV saline</td>
</tr>
<tr>
<td>late urinary obstruction</td>
</tr>
<tr>
<td>late AIN</td>
</tr>
<tr>
<td>glucosuria</td>
</tr>
<tr>
<td>bicarbonaturia</td>
</tr>
<tr>
<td>FeNa &gt; 2% despite prerenal AKI</td>
</tr>
<tr>
<td>use of diuretics</td>
</tr>
<tr>
<td>CKD</td>
</tr>
<tr>
<td>FeNa after IVF therapy</td>
</tr>
<tr>
<td>glucosuria</td>
</tr>
<tr>
<td>bicarbonaturia</td>
</tr>
<tr>
<td>salt-wasting disorders</td>
</tr>
</tbody>
</table>

FeNa, fractional excretion of sodium; AIN, acute interstitial nephritis; ATN, acute tubular necrosis; CHF, congestive heart failure; IV, intravenous; IVF, intravenous fluid.
Clinical Need

- Determinants of renal function
- Contributory factors for WRF in heart failure
Clinical Need: Risk Assessment

**At risk for heart failure**

**Stage A**
At high risk of heart failure but without structural heart disease or symptoms of disease

**Stage B**
Structural heart disease but without signs or symptoms of heart failure

**Stage C**
Structural heart disease with previous or current symptoms of heart failure

**Stage D**
Refractory heart failure requiring specialised interventions

**Heart failure**

**Development of symptoms of heart failure**

**Stage D**
Refractory symptoms of heart failure at rest

**Stage C**
Known structural heart disease and shortness of breath and fatigue, reduced exercise tolerance

**Stage B**
- Known structural heart disease
- Asymptomatic left-ventricular hypertrophy and low ejection fraction
- Asymptomatic valvular disease

**Stage A**
- Hypertension
- Atherosclerotic disease
- Diabetes
- Obesity
- Metabolic syndrome
- Patients: Using cardiotoxins
- With family history of cardiomyopathy

**Stage D**
- Pronounced symptoms at rest despite best medical treatment
- Those who are recurrently admitted or cannot be safely discharged from hospital without specialised interventions
Clinical Need: Risk Assessment
Predictors of WRF during decompensated heart failure

Clinical
- Older age
- Comorbid conditions (diabetes mellitus, uncontrolled hypertension, anaemia)
- Drugs:
  - Anti-inflammatory drugs
  - Diuretics (thiazides, loop diuretics)
  - Angiotensin converting enzyme inhibitor/angiotensin II receptor blocker
  - Aldosterone receptor antagonists

Cardiac
- History of heart failure/impaired left ventricular ejection fraction
- Prior myocardial infarction
- New York Heart Association functional class
- Elevated cardiac troponin

Renal
- Baseline renal dysfunction (elevated blood urea nitrogen/creatinine or cystatin C)
## Correlates of Worsening Renal Function (WRF)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>1.41</td>
<td>(1.12-1.77)</td>
<td>.003</td>
</tr>
<tr>
<td>HTN</td>
<td>1.64</td>
<td>(1.12-2.40)</td>
<td>.003</td>
</tr>
<tr>
<td>Rales&gt;Bases</td>
<td>1.28</td>
<td>(1.02-1.61)</td>
<td>.03</td>
</tr>
<tr>
<td>HR &gt;100 bpm</td>
<td>1.34</td>
<td>(1.06-1.68)</td>
<td>.01</td>
</tr>
<tr>
<td>SCr ≥1.5 mg/dL</td>
<td>1.77</td>
<td>(1.42-2.22)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SBP &gt;200 mm Hg</td>
<td>1.63</td>
<td>(1.13-2.35)</td>
<td>.009</td>
</tr>
</tbody>
</table>

N=1,681, WRF, defined as a rise in serum creatinine of >0.3 mg/dl (26.5 µmol/l).

Risk of Worsening Renal Function (WRF) by Number of Risk Factors

N=1,681, WRF, defined as a rise in serum creatinine of >0.3 mg/dl (26.5 µmol/l).

### Impact of Worsening Renal Function (WRF) on Clinical Outcomes and Resource Consumption

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>%</th>
<th>WRF Absent</th>
<th>WRF Present</th>
<th>Adj. Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hosp. mortality</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>2.72 (1.6-4.6)</td>
</tr>
<tr>
<td>30-d mortality</td>
<td>7</td>
<td>6</td>
<td>10</td>
<td>1.87 (1.2-2.8)</td>
</tr>
<tr>
<td>30-d readmission (all-cause)</td>
<td>18</td>
<td>17</td>
<td>20</td>
<td>1.29 (1.0-1.7)</td>
</tr>
<tr>
<td>30-d readmission (HF)</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>1.17 (0.8-1.8)</td>
</tr>
<tr>
<td>6-m mortality</td>
<td>21</td>
<td>19</td>
<td>25</td>
<td>1.56 (1.2-2.0)</td>
</tr>
<tr>
<td>6-m readmission (all-cause)</td>
<td>47</td>
<td>46</td>
<td>50</td>
<td>1.16 (0.9-1.4)</td>
</tr>
<tr>
<td>6-m readmission (HF)</td>
<td>23</td>
<td>22</td>
<td>25</td>
<td>1.07 (0.8-1.4)</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>7.5±4.7</td>
<td>6.9±3.9</td>
<td>9.1±6.0</td>
<td>2.28 (0.25)</td>
</tr>
<tr>
<td>Hosp. Cost ($)</td>
<td>6,823±5,175</td>
<td>6,327±4,874</td>
<td>8,085±5,665</td>
<td>1,758±287.2</td>
</tr>
</tbody>
</table>


N=1,681, WRF, defined as a rise in serum creatinine of >0.3 mg/dl (26.5 µmol/l).
Clinical Need: Contributory Factors for WRF

- **Patient Factors**
  - Impaired renal compensatory mechanisms
    - Underlying level of renal function
    - RAAS inhibition
    - Other agents
Figure 2. Intrarenal Mechanisms for Autoregulation of the Glomerular Filtration Rate under Decreased Perfusion Pressure and Reduction of the Glomerular Filtration Rate by Drugs.

Panel A shows normal conditions and a normal glomerular filtration rate (GFR). Panel B shows reduced perfusion pressure within the autoregulatory range. Normal glomerular capillary pressure is maintained by afferent vasodilatation and efferent vasoconstriction. Panel C shows reduced perfusion pressure with a nonsteroidal antiinflammatory drug (NSAID). Loss of vasodilatory prostaglandins increases afferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease. Panel D shows reduced perfusion pressure with an angiotensin-converting–enzyme inhibitor (ACEI) or an angiotensin-receptor blocker (ARB). Loss of angiotensin II action reduces efferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease.
Clinical Need: Contributory Factors for WRF

- Patient Factors
  - Impaired renal compensatory mechanisms
  - Venous hypertension
Effects of increased CVP on renal blood flow and GFR

Firth et al, Lancet 1988
Relationship between CV parameters and renal function

**Objective**
To determine whether venous congestion, rather than impairment of cardiac output, is primarily associated with the development of worsening renal function in patients with advanced decompensated heart failure.

**Methods**
Observational prospective study
145 consecutive patients admitted with acute decompensated CHF treated with intensive medical therapy guided by PAC were studied. Worsening renal function defined as an increase of serum creatinine ≥0.3 mg/dl during hospitalization.

**Impact of ↑CVP on glomerular hemodynamics**

![Diagram of glomerular capillary and forces governing filtration](image)

<table>
<thead>
<tr>
<th>Forces</th>
<th>Normal</th>
<th>RA pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Favoring Filtration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerular-capillary</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>hydrostatic pressure, $P_{GC}$</td>
<td>58</td>
<td>63</td>
</tr>
<tr>
<td>2. Opposing Filtration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Hydrostatic pressure in</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Bowman’s capsule, $P_{BC}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Oncotic pressure in</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>glomerular capillaries, $\pi_{GC}$</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Net filtration pressure</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>(1-2)</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Filtration pressure</td>
<td>14 mmHg</td>
<td>4 mmHg</td>
</tr>
</tbody>
</table>

**Editorial Comment**

**The Cardiorenal Syndrome**

Do We Need a Change of Strategy or a Change of Tactics?*

Mariell Jessup, MD, FACC,†
Maria Rosa Costanzo, MD, FACC‡
Philadelphia, Pennsylvania; and Lombard, Illinois
Peripheral venous congestion causes inflammation, neurohormonal, and endothelial cell activation

30 mmHg above baseline value

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (B) (0 min)</th>
<th>Control arm (C) (75 min)</th>
<th>Test arm (T) (75 min)</th>
<th>P-value (T vs. C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 (pg/mL)</td>
<td>1.37 ± 0.44</td>
<td>1.79 ± 0.53</td>
<td>2.26 ± 0.58</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>1.35 ± 0.08</td>
<td>1.27 ± 0.08</td>
<td>1.35 ± 0.11</td>
<td>0.22</td>
</tr>
<tr>
<td>ET-1 (pg/mL)</td>
<td>1.46 ± 0.19</td>
<td>1.26 ± 0.13</td>
<td>2.43 ± 0.27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All (pg/mL)</td>
<td>27 ± 3</td>
<td>25 ± 3</td>
<td>32 ± 4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VCAM-1 (ng/mL)</td>
<td>557 ± 26</td>
<td>544 ± 24</td>
<td>589 ± 25</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ICAM-1 (ng/mL)</td>
<td>158 ± 9</td>
<td>158 ± 7</td>
<td>167 ± 9</td>
<td>0.06</td>
</tr>
<tr>
<td>vWF:Ag (%)</td>
<td>105 ± 9</td>
<td>100 ± 6</td>
<td>113 ± 9</td>
<td>0.15</td>
</tr>
</tbody>
</table>
Endothelial Glycocalyx determines vascular permeability

Figure 1. Role of the Endothelial Glycocalyx Layer in the Use of Resuscitation Fluids.

The structure and function of the endothelial glycocalyx layer, a web of membrane-bound glycoproteins and proteoglycans on endothelial cells, are key determinants of membrane permeability in various vascular organ systems. Panel A shows a healthy endothelial glycocalyx layer, and Panel B shows a damaged endothelial glycocalyx layer and resultant effect on permeability, including the development of interstitial edema in some patients, particularly those with inflammatory conditions (e.g., sepsis).
Figure 3 Effect of supplementing Krebs–Henseleit perfusate with colloids (2% hydroxyethylstarch HES 200/0.5 or HES 450/0.7; 1.7% human albumin) on the coronary flow rate of isolated guinea pig hearts. Albumin (Alb) lost ~50% of its dilatatory potential if hearts were pre-treated with the enzyme heparinase to degrade the glycocalyx or if co-perfused with the NO-synthase inhibitor nitro-L-arginine. Data taken from Jacob et al.41
Glycocalyx degradation induced by hypervolemia and atrial natriuretic peptide


-50% volume glycocalyx
Glycocalyx degradation induced by hypervolemia and atrial natriuretic peptide

controls

+ ANP

Increase vascular permeability

Lung Injury and Barrier Dysfunction in acute heart failure

Interleukin-6 (pg/ml)

Mean 0.30 pg/ml  Mean 0.22 pg/ml

p = 0.014

TNF-alpha (pg/ml)

Mean 0.89 pg/ml  Mean 0.66 pg/ml

p = 0.018

3-isoprostane (pg/ml)

Acute HF  Chronic HF  Controls

Increase intravascular volume in most patients with ADHF

Miller et al, J Am Coll Cardiol HF 2014;2:298–305

predicted normal total blood volume ranged from +9.5% to +107% on admission

Change in Total Blood Volume (mL), Hospital Admission to Discharge

Patients
ADHF = Inappropriate tubular Na$^+$ reabsorption

- Glomerular filtration: ~180l/day
- 25000 mmol Na$^+$

Inappropriate Na$^+$ reabsorption At the tubular level

- Daily Na$^+$ intake
- Diuresis Na$^+$ <100 mmol
The vicious circle of Na$^+$ retention in heart failure

Inappropriate tubular Na$^+$ reabsorption

- Low RBF
- Increase oncotic pressure in efferent arteriole
- Increase oncotic pressure in peritubular capillaries
- Water and sodium reabsorption in proximal tubules

Verbrugge et al, European Journal of Heart Failure (2014) 16, 133–142
Bonventre & Yang, J Clin Invest. 2011;121(11):4210–4221
The vicious circle of Na+ retention in heart failure (1)

Inappropriate tubular Na+ reabsorption

Filtration fraction 45-45%

Afferent arteriole

Efferent arteriole

1000ml/min

Increase oncotic pressure in efferent arterioles

Filtration fraction 20-25%

Afferent arteriole

Efferent arteriole

500ml/min
The vicious circle of Na+ retention in heart failure
Inappropriate tubular Na+ reabsorption

Low RBF

Increase oncotic pressure in efferent arteriole

Increase oncotic pressure in peritubular capillaries

Water and sodium reabsorption in proximal tubules

Activation of renin angiotensin aldosterone system

Verbrugge et al, European Journal of Heart Failure (2014) 16, 13
Clinical Need: Contributory Factors for WRF

**Patient Factors**
- Impaired renal compensatory mechanisms
- Venous hypertension
- Anemia

**Process of Care**
- Contrast
- Diuretics
- Other agents
- Cardiac surgery
Diuretics

- Acetazolamide (1)
- Osmotic agents (mannitol) (2)
- Loop agents (e.g., furosemide) (3)
- Thiazides (4)
- Aldosterone antagonists (5)

Diagram showing the nephron and the different sites where diuretics act to increase urine production.
Determinants of Diuretic Action

- Dose
- Bioavailability
- Tubular secretory capacity
- Rate of absorption
- Time course of delivery

A

Maximal Response

Efficiency

Threshold

B

Altered dose-response relationship
Braking phenomenon

Sodium Excretion Rate

Loop Diuretic Excretion Rate
Diuretic Therapy Significantly Decreases Glomerular Filtration Rate*

N=16; NYHA II (19%) and III (81%)
Mean baseline CrCl: 108 ± 51 µg/mL.
*GFR estimated using 7-hour CrCl.
NYHA, New York Heart Association; CrCl, creatinine clearance.
Diuretic Strategies in Patients with Acute Decompensated Heart Failure

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- Creatinine Changes

![Bar chart showing changes in creatinine for different diuretic strategies.](chart.png)

- Bolus: Change = 0.05, P = 0.45
- Continuous: Change = 0.07, P = 0.21
- Low Dose: Change = 0.04
- High Dose: Change = 0.08

Figure 3. Kaplan–Meier Curves for the Clinical Composite End Point of Death, Rehospitalization, or Emergency Department Visit.

Kaplan–Meier curves are shown for death, rehospitalization, or emergency department visit during the 60-day follow-up period in the group that received boluses every 12 hours as compared with the group that received a continuous infusion (Panel A) and in the group that received a low dose of the diuretic (equivalent to the patients' previous oral dose) as compared with the group that received a high dose (2.5 times the previous oral dose) (Panel B).
### Table 2. Secondary End Points for Each Treatment Comparison.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Bolus Every 12 Hr (N = 156)</th>
<th>Continuous Infusion (N = 152)</th>
<th>P Value</th>
<th>Low Dose (N = 151)</th>
<th>High Dose (N = 157)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC for dyspnea at 72 hr</td>
<td>4456±1468</td>
<td>4699±1573</td>
<td>0.36</td>
<td>4478±1550</td>
<td>4668±1496</td>
<td>0.04</td>
</tr>
<tr>
<td>Freedom from congestion at 72 hr — no./total no. (%)</td>
<td>22/153 (14)</td>
<td>22/144 (15)</td>
<td>0.78</td>
<td>16/143 (11)</td>
<td>28/154 (18)</td>
<td>0.09</td>
</tr>
<tr>
<td>Change in weight at 72 hr — lb</td>
<td>-6.8±7.8</td>
<td>-8.1±10.3</td>
<td>0.20</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>4237±3208</td>
<td>4249±3104</td>
<td>0.89</td>
<td>3575±2635</td>
<td>4899±3479</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in NT-proBNP at 72 hr — pg/ml</td>
<td>-1316±4364</td>
<td>-1773±3828</td>
<td>0.44</td>
<td>-1194±4094</td>
<td>-1882±4105</td>
<td>0.06</td>
</tr>
<tr>
<td>Worsening or persistent heart failure — no./total no. (%)</td>
<td>38/154 (25)</td>
<td>34/145 (23)</td>
<td>0.78</td>
<td>38/145 (26)</td>
<td>34/154 (22)</td>
<td>0.40</td>
</tr>
<tr>
<td>Treatment failure — no./total no. (%) †</td>
<td>59/155 (38)</td>
<td>57/147 (39)</td>
<td>0.88</td>
<td>54/147 (37)</td>
<td>62/155 (40)</td>
<td>0.56</td>
</tr>
<tr>
<td>Increase in creatinine of &gt;0.3 mg/dl within 72 hr — no./total no. (%)</td>
<td>27/155 (17)</td>
<td>28/146 (19)</td>
<td>0.64</td>
<td>20/147 (14)</td>
<td>35/154 (23)</td>
<td>0.04</td>
</tr>
<tr>
<td>Length of stay in hospital — days</td>
<td>5</td>
<td>5</td>
<td>0.97</td>
<td></td>
<td></td>
<td>0.55</td>
</tr>
<tr>
<td>Median</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>3–9</td>
<td>3–8</td>
<td>4–9</td>
<td>3–8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive and out of hospital — days</td>
<td>51</td>
<td>51</td>
<td>0.36</td>
<td></td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>Median</td>
<td>51</td>
<td>51</td>
<td>50</td>
<td>52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. To convert pounds to kilograms, divide by 2.2. AUC denotes area under the curve, and NT-proBNP N-terminal pro-brain natriuretic peptide.
† Treatment failure was defined as the development of any one of the following during the 72 hours after randomization: increase in serum creatinine level of more than 0.3 mg per deciliter (26.5 μmol per liter), worsening or persistent heart failure, clinical evidence of excessive diuresis requiring intervention (e.g., administration of intravenous fluids), or death.
30 patients with chronic systolic heart failure in a presumed euvoletic state and on standard oral furosemide therapy (40 to 80 mg) were examined. At baseline, subjects were withdrawn from their loop diuretics. After 72 h, their furosemide regimen was reinstated, and patients were studied again 3 days later. Serum creatinine, atrial and B-type natriuretic peptide, urinary kidney injury molecule (KIM)-1, urinary N-acetyl-beta-Dglucosaminidase (NAG), and serum as well as urinary neutrophil gelatinase-associated lipocalin (NGAL) were determined at various time points.
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Clinical Need: Therapeutic Interventions

- When the diagnosis is uncertain to define the type and nature of initial therapy
  - CRS 1:
    - whether patient has “pre-renal” state or has suffered structural damage
    - Is the dysfunction due to the underlying disease or to the therapy
  - CRS 2:
    - Is the decline in kidney function chronic and stable or is new injury occurring
    - What will be effect of choice of therapy on kidney function
Clinical Need: Therapeutic Interventions

- When the therapy is in place to define success
  - Has renal function decline resolved
  - Has a new steady state been achieved that is acceptable
  - Is progression occurring
Renal Dysfunction in Heart Failure

Heart Failure

- Adenosine release and tubuloglomerular feedback
- Na$^+$ and H$_2$O retention
- Arterial hypertension
- Anemia
- Inflammation and fibrosis
- Uremic Toxins

Arterial hypertension
- Diabetes mellitus
- Dyslipidemia
- Smoking
- Obesity
- Chronic inflammation

Neurohormonal activation
- Low cardiac output and renal hypoperfusion
- Increased renal venous pressure and vascular resistance
- Inflammation and fibrosis
- AVP release

Renal Dysfunction

It’s Complicated