Cardiorenal Syndromes: New Insights into Combined Heart and Kidney Failure

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FACC, FACP, FAHA, FCCP, FNKF

History

- 1913: Sir Thomas Lewis gave a clinical lecture on paroxysmal dyspnoea in cardio-renal patients with special reference to “cardiac” and “uremic” asthma.
- 1951: The term cardiorenal syndromes (CRS) was coined by Ledoux.[i]
- 1997 to present: Schrier in multiple papers summarized the impact of salt and water retention combined with neurohormonal activation in the pathogenesis of CRS.[ii][iii][iv]
- 2003: Brammah and colleagues pointed out that treatment of bilateral renal arterial disease could result in improvement of both heart and kidney function.[v]
- 2005: Braam demonstrated in animals that organ dysfunction in one system influences that in the other.[vi]
- 2008: Ronco and colleagues proposed five distinct CRS according to the temporal sequence of organ injury and failure as well as the clinical context.[vii]
- 2008: Acute Dialysis Quality Initiative (ADQI) involving nephrology, critical care, cardiac surgery, and cardiology was convened.[viii]
- 2011: Karger launches “Cardiorenal Medicine” James Sowers, MD, Editor
- 2012: ADQI conducted a second consensus conference to review the spectrum of pathophysiologic mechanisms involved in CRS.[ix]

Outline

- Definitions
- Complex, bidirectional pathogenesis
- Novel diagnostic targets
- Therapy
- Putting it all together
Five Cardiorenal Syndromes

Cardiorenal Syndrome (CRS) General Definition:
A pathophysiologic 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 I (Acute Cardiorenal Syndrome)
Abrupt worsening of cardiac function (acute decompensated congestive heart failure) leading to acute kidney injury.

CRS Type II (Chronic Cardiorenal Syndrome)
Chronic abnormalities in cardiac function (chronic congestive heart failure) causing progressive and permanent chronic kidney disease.

CRS Type III (Acute Renocardiac Syndrome)
Abrupt worsening of renal function (acute kidney ischaemia or tubular injury) causing acute cardiac disorder (new or decompensated heart failure).

CRS Type IV (Chronic Renocardiac Syndrome)
Chronic kidney disease (diabetic nephropathy) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events.

CRS Type V (Secondary Cardiorenal Syndrome)
Systemic condition (e.g. sepsis) causing both cardiac and renal dysfunction.

Recognition of Cardiorenal Syndrome

Definition of Acute Kidney Injury (KDIGO Guidelines 2012)

2.1.6. AKI is defined as any of the following (Not Guided)
- Increase in SCr by ≥ 0.3 mg/dl or ≥ 26.4 μmol/l within 48 hours or
- Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or
- Urine volume < 0.5 ml/kg/h for 6 hours.

2.1.7. AKI is staged for severity according to the following criteria (Table 2). (Not Guided)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine</th>
<th>Time output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5-2.9 times baseline&lt;br&gt;≥ 0.3 mg/dl&lt;br&gt;≥ 26.4 μmol/l</td>
<td>&lt;0.5 ml/kg/h for 4-12 hours</td>
</tr>
<tr>
<td>2</td>
<td>3-6 times baseline&lt;br&gt;≥ 2.0 mg/dl&lt;br&gt;≥ 176.8 μmol/l</td>
<td>&lt;0.5 ml/kg/h for 4-12 hours</td>
</tr>
<tr>
<td>3</td>
<td>7 or more times baseline&lt;br&gt;≥ 3.0 mg/dl&lt;br&gt;≥ 264 μmol/l</td>
<td>&lt;0.5 ml/kg/h for 24 hours&lt;br&gt;Urea for 4-12 hours</td>
</tr>
</tbody>
</table>
Risk of Worsening Renal Function (WRF) by Number of Risk Factors

- No. of Risk Factors
  - N=1,681, WRF, defined as a rise in serum creatinine of >0.3 mg/dl (26.5 µmol/l).

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CHF: Worsened Renal Function in Hospital
- 27% of 1,004 pts had worsened renal function (>0.3mg/dl)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of CHF</td>
<td>1.3 (1.01-1.7)</td>
<td>0-10%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.4 (1.1-1.6)</td>
<td>453%</td>
</tr>
<tr>
<td>SBP&gt;160</td>
<td>1.4 (1.1-1.7)</td>
<td>453%</td>
</tr>
<tr>
<td>1.5&lt;creat&lt;2.5</td>
<td>2.1 (1.6-2.8)</td>
<td>453%</td>
</tr>
<tr>
<td>Creat ≥ 2.5</td>
<td>3.5 (2.5-4.6)</td>
<td>453%</td>
</tr>
</tbody>
</table>

Score = 0 – 10% risk
Score = 4 – 53% risk

52% of WRF develops by day 3 and results in:
- 7X increase in risk of death
- 3X increase in length of stay
- 2X increase in complications
- No relation to hypotension or hypovolemia

Krumholz. JACC 2004;43:81
Cardio-Renal Syndrome Pathophysiology

Pathophysiology of the Cardiorenal Syndromes: Executive Summary from the Eleventh Consensus Conference of the Acute Dialysis Quality Initiative (ADQI)


for the Acute Dialysis Quality Initiative (ADQI) Consensus Group

High Central Venous Pressure and Cardiorenal Syndrome

Cardio-Renal Syndrome Pathophysiology

Venous Congestion and Glomerular Filtration
~30% of in-hospital AKI results in permanent loss in eGFR (~5% ESRD)
~70% must have had tubular recovery or compensation by the remaining nephrons

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History of Urine in Western Medicine

- Ancient Babylonian and Sumerian physicians first inscribed their evaluations of urine into clay tablets as early as 4,000 B.C.

Figure: People showing for a diagnosis of their urine to the physician Constantine the African.
Blood and Urine Biomarkers of Acute Kidney Injury


Urinary Biomarkers of AKI and Mortality 3 Years after Cardiac Surgery

Predicted AKI Detection
Multimarker Panel Approach

<table>
<thead>
<tr>
<th>Diagnostic value of biomarker</th>
<th>Single</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liangos et al., Biomarkers 2008</td>
<td>0.50-0.66</td>
<td>0.78</td>
</tr>
<tr>
<td>Han et al., Clin JASN 2009</td>
<td>0.59-0.68</td>
<td>0.80-0.84</td>
</tr>
<tr>
<td>Kashani K et al, Crit Care 2013</td>
<td>0.76-0.79</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Inducers of G1 cell cycle arrest (Urine TIMP-2, IGFBP7)

Adapted Courtesy Herget-Rosenthal 2010

FDA News Release

FDA allows marketing of the first test to assess risk of developing acute kidney injury

For Immediate Release September 3, 2014

Release

Today the U.S. Food and Drug Administration allowed marketing of the nephroCheck test, a first-of-its-kind laboratory test to help determine if certain critically ill hospitalized patients are at risk of developing moderate to severe acute kidney injury (AKI) in the 12 hours following the administration of the test. Early knowledge that a patient is likely to develop AKI may prompt closer patient monitoring and help prevent permanent kidney damage or death.
NephroCheck® Test System: (TIMP-2 × IGFBP-7 Product in Spot Urine): Sapphire Study

The Astute Medical NephroCheck® Test System has received 510(k) clearance through FDA’s de novo classification process. On 9/5/14, FDA stated, “Current laboratory tests can only assess whether a patient may already have AKI; often, the patient has progressed to moderate to severe AKI before the test results confirm the clinical diagnosis. NephroCheck detects the presence of insulin-like growth-factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases (TIMP-2) in the urine, which are associated with acute kidney injury. Within 20 minutes, the test provides a score based on the amount of the proteins present that correlates to the patient’s risk of developing AKI within 12 hours of the test being performed. No other tests currently on the market are FDA-approved or cleared to assess the risk of developing AKI in at-risk patients.”

Baseline Samples and Prediction of AKI

Urinary [TIMP-2]•[IGFBP7] Discriminates Patients With AKI From Those Without AKI (Topaz Study)

Bihorac et al, AJRCCM 2014
Neutrophil Gelatinase-Associated Lipocalin (NGAL) — a specific biomarker of acute kidney injury

NGAL is an endogenous bacteriostatic protein by reducing available catalytic iron

Goetz et al. Mol Cell 2002

ACLS

Siderophore

E. coli

bacterial growth curves

Cumulative

bacterial growth curves

Without NGAL

with NGAL

Goetz et al. Mol Cell 2002

Oxidative Stress Reactions

Fonte: iron = Fe⁺; Ferrum = ßeta; Fe²⁺; hydrogen peroxide = H₂O₂; Hydroxyl radical = •OH; Hydroxylation = •OH; oxygen = O₂; superoxide anion = O₂⁻.
NGAL for the Diagnosis of AKI in the Emergency Department

N = 635

- 33% of NGAL > 130 µg/g required dialysis

Urine NGAL, µg/g

Serum Creatinine, mg/dL

N = 635

Meta-Analysis:
Accuracy of NGAL in AKI

- Meta-analysis of 19 diagnostic studies (2538 patients)
- NGAL was a valuable and early predictor of AKI, both overall and across a diverse range of clinical settings
- The cutoff NGAL value for optimum sensitivity and specificity across all settings was >100 ng/mL
- A more consistent cutoff value of >150 ng/mL was identified when using standardized platforms

<table>
<thead>
<tr>
<th>Setting</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC-ROC</th>
<th>Diagnostic Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI across settings</td>
<td>0.815</td>
<td>0.815</td>
<td>0.815</td>
<td>18.5</td>
</tr>
<tr>
<td>AKI after cardiac surgery</td>
<td>0.77S</td>
<td>0.775</td>
<td>0.775</td>
<td>13.1</td>
</tr>
<tr>
<td>AKI in critically ill patients</td>
<td>0.738</td>
<td>0.738</td>
<td>0.738</td>
<td>10.0</td>
</tr>
<tr>
<td>AKI after contrast infusion</td>
<td>0.894</td>
<td>0.894</td>
<td>0.894</td>
<td>92.0</td>
</tr>
<tr>
<td>AKI prediction using serum NGAL</td>
<td>0.775</td>
<td>0.775</td>
<td>0.775</td>
<td>17.9</td>
</tr>
<tr>
<td>AKI prediction using urine NGAL</td>
<td>0.837</td>
<td>0.837</td>
<td>0.837</td>
<td>18.6</td>
</tr>
</tbody>
</table>

New Spectrum of AKI based on Combination of Functional and Damage Biomarkers

Based on NGAL

<table>
<thead>
<tr>
<th>NO DAMAGE</th>
<th>DAMAGE PRESENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No functional changes or damage</td>
<td>Damage without loss of function</td>
</tr>
<tr>
<td>Loss of function without damage</td>
<td>Damage with loss of function</td>
</tr>
</tbody>
</table>

New Criteria for AKI Diagnosis and Staging Using Biomarkers

Based on Serum Creatinine

<table>
<thead>
<tr>
<th>NO FUNCTIONAL CHANGE</th>
<th>FUNCTIONAL CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO DAMAGE</td>
<td>DAMAGE</td>
</tr>
</tbody>
</table>

Pharmacologic Therapy and CRT for HF

- Post-MI LV Dysfunction
- Mild HF
- Moderate HF
- Severe HF

- AIRE/SAVE (ramipril/captopril)
- SOLVD Treatment (enalapril)
- CONSENSUS (enalapril)

- CAPRICORN (carvedilol)
- CHARM (candesartan)
- EPHESUS (spironolactone)

- US Carvedilol/MERIT (candesartan/metoprolol)
- COPERNICUS (carvedilol)

- EFHF (candesartan/valsartan)
- A-HeFT (spironolactone)
- Long-acting nitrates/hydralazine
Treatment Patterns and Mortality in Advanced HF

**Table:**

<table>
<thead>
<tr>
<th>Group</th>
<th>Diuretic dose</th>
<th>ACE inhibitor dose</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>Low</td>
<td>240</td>
</tr>
<tr>
<td>B</td>
<td>High</td>
<td>High</td>
<td>160</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>Low</td>
<td>526</td>
</tr>
<tr>
<td>D</td>
<td>Low</td>
<td>High</td>
<td>224</td>
</tr>
</tbody>
</table>

Chi-square = 33.83
P = .0001

Months from Randomization

**Graph:**


Risk of Developing Renal Insufficiency on ACEI Therapy: Results From SOLVD

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Enalapril RR (95% CI)</th>
<th>Placebo RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 yrs)</td>
<td>1.42 (1.32-1.52)</td>
<td>1.18 (1.12-1.23)</td>
</tr>
<tr>
<td>Baseline EF (per 5% increment)</td>
<td>0.93 (0.91-0.96)</td>
<td>0.93 (0.91-0.96)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1.69 (1.70-2.08)</td>
<td>1.35 (1.08-1.64)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.33 (1.13-1.53)</td>
<td>1.96 (1.57-2.44)</td>
</tr>
<tr>
<td>Blockers</td>
<td>0.70 (0.57-0.85)</td>
<td>0.70 (0.57-0.85)</td>
</tr>
</tbody>
</table>

EF, ejection fraction; SOLVD, Studies of Left Ventricular Dysfunction.

Prevention of Type I Cardiorenal Syndrome: Lessons Learned from Clinical Trials and Registries

- Programmatic use of PA catheter (Nohria, JACC 2008)
- Programmatic use of inotropes/indodilators (ACC/AHA Guidelines)
- High-dose loop diuretics (DOSE Trial 2011)
- Beta-blocker withdrawal (Fonarow, JACC 2008)
- ACEI/ARB withdrawal (Shukla, CIRC 2008)
- Digoxin withdrawal (Packer, NEJM 1992)
- Rolipram (PROTECT, ESC 2009)
- Endothelin receptor antagonists (Konzett, JAMA 2007)
- Nesiritide (Yancy, ASCEND HF, 2011, ROSE-HF 2014)
- Ultrafiltration after AKI (Yancy, CAPP2008-2012)

Drug/Strategy Ineffective/Harmful OR Have not identified the ideal patient subset for benefit
**DOSE Trial: Study Design**

- Acute Heart Failure (1 symptom AND 1 sign) ≤24 hours after admission
- 2x2 factorial randomization

- Low Dose (1 x oral) Q12 IV bolus
- Low Dose (1 x oral) Continuous infusion
- High Dose (2.5 x oral) Q12 IV bolus
- High Dose (2.5 x oral) Continuous infusion

- 48 hours
- 72 hours
- Co-primary endpoints
- 60 days
- Clinical endpoints

**Continuous versus Bolus Intermittent Loop Diuretic Infusion in Acutely Decompensated Heart Failure: A Prospective Randomized Trial**

<table>
<thead>
<tr>
<th>Continuous Infusion</th>
<th>Bolus</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury</td>
<td>22%</td>
<td>15%</td>
</tr>
<tr>
<td>NaCl use of hypertonic saline</td>
<td>33%</td>
<td>18%</td>
</tr>
<tr>
<td>Insulin infusion</td>
<td>35%</td>
<td>22%</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>14 ± 5</td>
<td>11 ± 5</td>
</tr>
<tr>
<td>Death or rehospitalization</td>
<td>58%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Manuscript accepted 2014
In theory removes fluid from the blood at the same rate that fluid can be naturally recruited from the tissue.

 transient removal of blood illicits compensatory mechanisms, termed plasma or intravascular reflux. 

 ultrafiltrate is isotonic with plasma,

 removes more sodium than diuretic therapy

 decreases ECF volume more than a comparable volume of diuretic-induced fluid loss without neurohormonal activation

Mean Changes from Baseline Serum Creatinine Levels at Various Time Points in Ultrafiltration/Standard Care Group


Ultrafiltration Arm                 Standard Care Arm

P > 0.05 at all time points

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Ultrafiltration</th>
<th>Standard Care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Median</td>
</tr>
<tr>
<td>8 hrs</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>24 hrs</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>48 hrs</td>
<td>0.04</td>
<td>0.06</td>
</tr>
<tr>
<td>Discharge</td>
<td>0.05</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Trial of UF after AKI has developed
Clinical Actions for Acute Kidney Injury

KDIGO Consensus Guideline for AKI

<table>
<thead>
<tr>
<th>AKI Stage</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>KDIGO 2012</td>
<td>High Risk</td>
<td>High Risk</td>
<td>High Risk</td>
</tr>
<tr>
<td>Actions recommended to start when patients are at high risk</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Novel Therapies in Trials

Acute Decompensated Heart Failure
- Omecamtiv mecarbil
- Serelaxin (RLX030) (recombinant form of human relaxin-2)
- Ularitide (modified natriuretic peptide)
- Caperitide (atrial natriuretic peptide)
- Cinaciguat (activates soluble guanylate cyclase (sGC))
- Istaroxime (stimulates SERCA)

Acute Kidney Injury
- ABT-719 (alpha MSH receptor analogue)
- THR-184 (agonist for renal BMP receptors (ALK2, 3, and BMPR-II))
- AC607 (stem cells)
- BCT197 (anti-inflammatory)
- CMX-2043 (small molecule adduct of lipoic acid)

Selective Cardiac Myosin Activator: Omecamtiv Mecarbil

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Effect of Serelaxin on Cardiac, Renal, and Hepatic Biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) Development Program

Serelaxin IV for up to 48 h, started within 16 h of presentation, with placebo in patients hospitalized for AHF.
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Heart Failure Goals

- Revised Staging System
- Early Recognition and Treatment
- Pharmaceuticals and Devices
- Preserve Renal Function

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