WORKSHOP: THE CARDIORENAL SYNDROME

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Heart failure

Heart failure is a growing epidemic

- Heart failure is on the rise in Canada.
- 600,000 Canadians are living with heart failure.
- 50,000 Canadians are diagnosed each year with heart failure.
- 1 in 2 Canadians has been touched by heart failure.
- Heart failure costs more than $2.8 billion per year.

Heart failure costs everyone

- Heart failure patients have long and frequent hospital stays.
- There is no cure for heart failure.
- Heart failure patients are complex, often managing other conditions.
- Heart failure patients experience shortness of breath, exhaustion, and swelling.
- Heart failure caregivers are often overwhelmed and stressed.
The cardio-renal syndrome

Summary

The cardiorenal syndrome has recently been defined as “disorders of the heart and kidney whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other.” The syndrome is extremely common and independently associated with poor clinical outcomes. However, no pharmacological therapy has been shown to improve its outcomes. Unfortunately, the mechanisms that initiate the development of renal dysfunction in heart failure are still debated.

The cardio-renal syndrome
What are the types of cardio-renal syndromes?
The cardio-renal syndrome

In types 1 and 2 CRS, worsening of HF in acute (type 1) or chronic HF (type 2) leads to worsening kidney function.

In types 3 and 4 (termed acute and chronic renocardiac syndromes, respectively), AKI or CKD leads to worsening HF.

In type 5 CRS, systemic conditions cause simultaneous dysfunction of the heart and kidney.
Cardio-renal syndrome: prevalence

Prevalence of Type 1
25-45% patients with HF

Prevalence of Type 2
32-50% patients with HF
What are risk factors for cardio-renal syndrome?
The cardio-renal syndrome: risk factors

Risk Factors
- Age
- Race or ethnic group
- Genetic factors
- Hypertension
- Diabetes mellitus
- Metabolic syndrome

Disease Modifiers
- Severity of acute kidney injury
- Stage of chronic kidney disease
- No. of episodes
- Duration of acute kidney injury
- Proteinuria

Chronic Kidney Disease

Acute Kidney Injury

Outcomes
- Cardiovascular events
- Kidney events
- ESRD
- Disability
- Diminished quality of life
- Death
The cardio-renal syndrome: risk factors

Risk factors for WRF in acute HF syndromes

Chronic kidney disease
  Reduced baseline GFR
  Increased serum creatinine level
  Increased serum cystatin C level
Diuretic resistance
  Higher loop diuretic doses
Congestion
  Increased central venous pressure or right atrial pressure
  Pulmonary edema

Not LVEF

Increased HF severity
  Increased New York Heart Association class
  Increased number of HF exacerbations
Hypotension
  Hyponatremia
  Atrial fibrillation
Risk factors for renal disease
  Older age
  Hypertension
  Diabetes mellitus
Magnitude of blood pressure reduction
  Use of vasodilators
  Increased admission blood pressure
Does the cardiorenal syndrome affect prognosis?
Cardio-renal syndrome: prognosis

- Both types 1 and 2 CRS independently associated with increased mortality and morbidity in ADHF and chronic HF
- In ADHERE registry, in-hospital mortality increased from 1.9% for patients with normal renal function to 7.6% for patients with severe renal dysfunction
- Any increase in serum creatinine during treatment of ADHF is associated with worse prognosis
- An increase in creatinine of 0.3 mg/dl has highest sensitivity and specificity
Cardiac-renal syndrome: pathophysiology

- Complicated!!!
  - Hemodynamic consequences of reduced CO with low renal perfusion and activation of the sympathetic and RAAS probably play the most prominent role in initiating renal dysfunction, salt and water retention, and venous congestion.
  - Venous congestion in turn, further worsens renal function through several mechanisms.
  - Anemia, a common comorbidity in HF, can also worsen renal function.
  - Drugs, such as blockers of RAAS or NSAIDS used for the management of comorbidities, may contribute to worsening renal function.
  - Primary renal parenchymal disease related to longstanding diabetes and hypertension, common comorbidities in HF, may also worsen renal function.
- Theory: “a threat to the arterial BP” and not “underfilling of the arterial tree” is the stimulus for the retention of salt and water by the kidney.

Cardio-renal syndrome: pathophysiology

- Cardiac output
- Neurohormonal activation
- Sodium excretion, venous congestion

Cardiac-renal syndrome: pathophysiology

Average percent change from normal in a number of parameters in patients with severe untreated low-output DCM. LV systolic function was severely depressed, with approximately 50% decrease in the CO.

The SVR increased by a factor of two, but the arterial BP remains within the normal range.

There was variable increase in several circulating neurohormones, including norepinephrine, plasma renin activity, aldosterone, and atrial natriuretic peptide.

The levels of arginine vasopressin were normal but inappropriately high relative to the low serum sodium seen in these patients.

The renal blood flow (RBF) and GFR were decreased.

A significant increase in total body water, blood volume, extracellular volume, and total body exchangeable sodium.

![Graph showing hemodynamic, renal function, plasma hormones, and body fluid compartment data expressed as percent of normal in a group of patients with untreated congestive heart failure. Data are from reference 27. AVP, arginine vasopressin.](Clin J Am Soc Nephrol 8: 1800-1807, 2013.)
Cardiac-renal syndrome: pathophysiology

Compensatory mechanisms seen in low-output HF seem to be designed to preserve arterial BP which is maintained partly by an increase in SVR and partly by an expansion of the blood volume. Unfortunately, it occurs at the expense of renal function.
AVP: increases the amount of solute-free water reabsorbed back into the circulation and constricts arterioles, which increases PVR and raises arterial BP.

Figure 3. Diagram showing the sequence of events that leads to salt and water retention by the kidney and development of renal dysfunction. Notice that, in both low and high cardiac output heart failure, the common stimulus seems to be a threat to the arterial BP. The direct effects of these mechanisms are shown by solid blue lines, and mechanisms that may help to improve renal function are indicated by the dotted blue lines and red symbol. The role of increased venous pressure in worsening renal function is shown in red lines. Modified from reference 32, with permission.
Theory: -1) an increase in renal venous pressure decreases the arteriovenous pressure gradient across the kidney and reduces the already compromised RBF, causing GFR to decrease - 2) intratubular pressure is one of the important driving forces for glomerular filtration so any increase in intratubular pressure is likely to oppose filtration, reduce net ultrafiltration pressure, and decrease the GFR.
Cardio-renal syndrome: clinical signs

<table>
<thead>
<tr>
<th>Table 2. Summary of Diagnostic Accuracy of History and Physical Findings for the Presence of Volume Overload in ED Patients Presenting With Dyspnea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
</tr>
<tr>
<td>Orthopnea</td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Dyspnea on exertion</td>
</tr>
<tr>
<td>Fatigue and weight gain</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Third heart sound</td>
</tr>
<tr>
<td>Abdominal jugular reflux</td>
</tr>
<tr>
<td>Jugular venous distention</td>
</tr>
<tr>
<td>Rales</td>
</tr>
<tr>
<td>Any murmur</td>
</tr>
<tr>
<td>Lower extremity edema</td>
</tr>
<tr>
<td>SBP &lt; 100 mm Hg</td>
</tr>
<tr>
<td>Fourth heart sound</td>
</tr>
<tr>
<td>SBP &gt; 150 mmHg</td>
</tr>
<tr>
<td>Wheezing</td>
</tr>
<tr>
<td>Ascites</td>
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</tbody>
</table>

Abbreviations: LR, likelihood ratio; SBP, systolic BP.
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Cardio-renal syndrome: HF patient presentation
Cardio-renal syndromes: biomarkers

<table>
<thead>
<tr>
<th>Neurohormonal activation biomarkers</th>
<th>Normal</th>
<th>Elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Chronic CRS</td>
<td>Congestive CRS</td>
</tr>
<tr>
<td>Compensated HF with CKD causing low GFR. Treat with standard chronic HF therapy</td>
<td>Congestion leading to reduced GFR. Treat with volume removal alone</td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>Hypovolemic AKI</td>
<td>Refractory CRS</td>
</tr>
<tr>
<td>Volume depletion leading to reduced GFR. Treat with diuretic withdrawal and fluids</td>
<td>Advanced HF causing severe CRS. Treat with volume removal and consider advanced therapies</td>
<td></td>
</tr>
</tbody>
</table>

BNP

Bun/Cr
How does one approach the treatment of cardio-renal syndrome?
Cardio-renal: treatment approach

Low cardiac output:
- Inotropes

Neurohormonal activation:
- RAAS blockers, Beta-blockers, MRA

Decreased excretion of sodium - venous congestion
- Diuretics and ultrafiltration

Cardio-renal syndrome: Diuresis

DOSE trial

No difference in creat at 60 days

N Engl J Med. 2011;364(9):797-805
Cardio-renal syndrome: cause of diuretic resistance

Compensatory distal tubular sodium absorption
Reduced proximal and loop sodium excretion

Inadequate diuretic delivery
Reduced diuretic effect

Cardio-renal syndrome: Ultrafiltration
Cardio-renal syndrome: Ultrafiltration
Cardio-renal syndrome: Ultrafiltration vs diuresis

UNLOAD trial

Intervention
Ultrafiltration (500ml/hr) x 48h vs IV diuretics (2x daily dose)

Population
200 patients with HF

Primary objective
Weight loss at 48hrs
Change in creat at 48hrs

Cardio-renal syndrome: Ultrafiltration vs diuresis

UNLOAD trial

Cardio-renal syndrome: Ultrafiltration vs diuresis

Heart Failure Network

Protocol for the CARdiorenal REScue Study in Acute Decompensated Heart Failure

**CARRESS HF**

<table>
<thead>
<tr>
<th>Current Dose</th>
<th>Suggested Dose</th>
</tr>
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<tbody>
<tr>
<td>loop (/day)</td>
<td>thiazide</td>
</tr>
<tr>
<td>A</td>
<td>+ or -</td>
</tr>
<tr>
<td>B</td>
<td>+ or -</td>
</tr>
<tr>
<td>C</td>
<td>+ or -</td>
</tr>
<tr>
<td>D</td>
<td>+ or -</td>
</tr>
</tbody>
</table>

Car dio-renal syndrome: Ultrafiltration vs diuresis

CARRESS-HF trial

Intervention
Ultrafiltration (200ml/hr) x 48hrs
vs
Diuresis IV

Population
188 patients with CHF and RF

Primary objective
Change in creatinine and weight loss at 96h

Cardio-renal syndrome: Ultrafiltration vs diuresis

CARRESS-HF Trial

A Serum Creatinine

B Body Weight

Hypertonic saline plus i.v. furosemide improve renal safety profile and clinical outcomes in acute decompensated heart failure

A meta-analysis of the literature

<table>
<thead>
<tr>
<th>Studies</th>
<th>Deaths from all causes among pts treated with HSS plus i.v. fur (total of pts treated with HSS plus i.v. fur)</th>
<th>Deaths from all causes among controls (total of controls)</th>
<th>Relative risk (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paterna(^2) (2000)</td>
<td>6 (30)</td>
<td>11 (30)</td>
<td>0.55 (0.23, 1.28)</td>
<td>7.98%</td>
</tr>
<tr>
<td>Licata(^4) (2003)</td>
<td>24 (53)</td>
<td>47 (54)</td>
<td>0.52 (0.38, 0.71)</td>
<td>34.88%</td>
</tr>
<tr>
<td>Paterna(^22) (2005)</td>
<td>0 (48)</td>
<td>3 (46)</td>
<td>0.14 (0.01, 2.58)</td>
<td>0.75%</td>
</tr>
<tr>
<td>Paterna(^24) (2011)</td>
<td>114 (881)</td>
<td>212 (890)</td>
<td>0.54 (0.44, 0.67)</td>
<td>49.28%</td>
</tr>
<tr>
<td>Issa(^25) (2013)</td>
<td>10 (20)</td>
<td>4 (12)</td>
<td>1.5 (0.6, 3.74)</td>
<td>7.12%</td>
</tr>
<tr>
<td>Overall</td>
<td>154 (1,032)</td>
<td>277 (1,032)</td>
<td>0.57 (0.44, 0.74)</td>
<td>100%</td>
</tr>
</tbody>
</table>

Favors HSS plus i.v. furosemide  Favors i.v. furosemide alone
Effect of Renal Function on Prognosis in Chronic Heart Failure

Adrián Ignacio Löffler, MD\textsuperscript{a,*}, Thomas P. Cappola, MD, ScM\textsuperscript{b}, James Fang, MD\textsuperscript{c}, Scott J. Hetzel, MS\textsuperscript{a}, Andrew Kadlec, BA\textsuperscript{a}, Brad Astor, PhD, MPH\textsuperscript{a}, and Nancy K. Sweitzer, MD, PhD\textsuperscript{a}

Renal dysfunction (RD) is associated with increased mortality in heart failure (HF). The aim of this study was to identify whether worsened or improved renal function during mid-term follow-up is associated with worsened outcomes in patients with chronic HF. A total of 892 participants from a multicenter cohort study of chronic HF were followed over 3.1 ± 1.9 years of enrollment. Worsened and improved renal functions were tested with multivariate models as independent predictors of HF hospitalization and mortality. Although 12\% of subjects experienced a ≥25\% decrease in estimated glomerular filtration rate (eGFR), 17\% experienced a ≥25\% increase in eGFR, and there was stability of kidney function observed in the cohort as a whole. The quartile with the worst RD at any point in time had increased risk of HF hospitalization and mortality. Worsened eGFR was associated with HF outcomes in the unadjusted (hazard ratio = 1.71, 95\% confidence interval 1.04 to 2.81, \( p = 0.035 \)), but not the adjusted analysis. Improvement in eGFR was not associated with outcome (\( p = 0.453 \)). In chronic HF, the severity of RD predicts risk of poor outcome better than changes in renal function during mid-term follow-up. This suggests that in patients with appropriately treated chronic HF, worsening renal function in itself does not yield useful prognostic information and may not reflect poor outcome. © 2015 Elsevier Inc. All rights reserved. (Am J Cardiol 2015;115:62–68)
Baseline renal function

Figure 1. The relation between baseline renal function, expressed as eGFR (mL/min/1.73 m²) or creatinine (mg/dl) and the HR for death or HF hospitalization. The risk of the outcome rises markedly in the group with the most impaired renal function at baseline. * = p < 0.001.
Improved renal function

- Improved renal function not associated with improved long-term outcome
- Improvement in renal function accompanying HF therapy may result in improved volume status but does not appear to alter disease trajectory
Cardio-renal syndrome Summary

• Focus simultaneously on heart and kidney and on hemodynamics and congestion
• Reduce and control risk factors
• Optimize medications which improve prognosis and have disease modifying effects in HF
• No real data to support the treatment management of CHF patients with concomitant renal dysfunction (patients excluded from CHF trials) as such there is underprescribing of ACE inhibitors, aldosterone antagonists, ARBs denying patients the survival benefits of these medications
• Under-treatment of CHF patients with concomitant chronic kidney dysfunction can have negative consequences
Cardio-renal syndrome: summary

- Common in patients with HF
- Complicated pathophysiology
- Poor prognosis
- Treatment is challenging