Cardio Renal Syndromes
and
Other Cardio Renal Stuff
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Congestive Heart Failure

- Epidemiology changing from acute management to managing the chronicity of cardiac dysfunction.

- Progressive disease that affects approximately six million Americans, with an incidence of 600,000 new cases each year. Responsible for over 1 million yearly hospitalizations. (1)

- 280,000 deaths annually.

Comorbid Conditions . . .
Associated with a worse prognosis

- Anemia (Hb < 10.0)
- Cirrhosis
- Peripheral Vascular Disease
- Hyponatremia (<135)
Comorbid Conditions ... Associated with a worse prognosis

- Anemia (Hb < 10.0)
- Cirrhosis
- Peripheral Vascular Disease
- Hyponatremia (<135)

- *Renal failure*
ADHERE Registry
Registry of Acute Decompensated Heart Failure (ADHF)

- 105,000 patient registry
- QOC study evaluating variations in CHF treatment

**Best predictors of outcome:**

BUN
Creatinine
Cumulative incidence

- Cardiovascular death
- Unplanned ADHF admission

Stratified by GFR

Hildege, H. L. et al. Circulation 2006;113:671-678
Role of the kidney in congestive heart failure: Relationship of CI to kidney function

RBF, p<.05 with Group A
RVR, p<.01 with Group A

Renal Blood Flow
Renovascular Resistance

A, CI > 2
B, CI > 1.5
C, CI < 1.5

Ljungman, Cody Drugs 1990;39 Suppl 4:10-21
Kidneys play a central role in the volume homeostasis of our body.

Heart, as the pump contributes towards tissue perfusion and oxygenation.

Cross-talk between the kidneys and the heart:
- Control BP.
- Renal sodium and water excretion.
- Arterial perfusion and oxygenation of tissues.
- The extracellular fluid balance, including intravascular volume.
Kidneys play a central role in the volume homeostasis of our body.

Heart, as the pump contributes towards tissue perfusion and oxygenation.

Cross-talk between the kidneys and the heart:
- Low pressure baroreceptor.
- Effector system (venous and atrial receptors).
- High Pressure System (arterial and aortic arch receptors with the Juxta glomerular Apparatus).
DEFINITION

Cardiology Definition

CRS is a clinical presentation that is dominated by pulmonary congestion and edema with worsening renal function

Most Simplistic Description

Associated loss of renal function in the setting of advanced CHF

CRS or RCS?
**DEFINITION**

Cardiorenal syndrome encompasses conditions in which failure of either the heart or the kidney leads to, or accelerates, failure of the other organ.

Condition characterized by the initiation, progression of renal insufficiency secondary to heart failure or both.


Definition

The definition of the cardio-renal syndrome has developed over time.
Definition

- **2004**: The frequent presentation of combined cardiac and renal dysfunction
- **2004**: The presence or development of renal dysfunction in patients with heart failure
- **2006**: Severe cardiorenal syndrome is a pathophysiological condition in which combined cardiac and renal dysfunction amplifies progression of failure of the individual organs
- **2008**: Cardiorenal syndrome is a pathophysiological disorder in which acute or chronic dysfunction of one organ may induce acute or chronic dysfunction in the other
- **2010**: Each dysfunctional organ has the ability to initiate and perpetuate disease in the other organ through common haemodynamic, neurohormonal, and immunological and/or biochemical feedback pathways
Definition

Each dysfunctional organ has the ability to initiate and perpetuate disease in the other organ through common haemodynamic, neurohormonal, and immunological and/or biochemical feedback pathways

Clinical Features of CRS

• Most commonly identified in the setting of hospitalization for ADHF.
• Most patients are volume overloaded with peripheral and pulmonary edema with elevated jugular venous pressure.
  • CVP measurement of more than 6 mm Hg was significantly associated with decreased eGFR (1)
• Some patients may be in severe hypotension and have intravascular volume depletion.
• There is oliguria and worsening kidney function which may be exacerbated with attempts to achieve vigorous diuresis.

Clinical Features of CRS
Clinical Features and Classification of CRS

**CRS type I (acute CRS)** Abrupt worsening of cardiac function leading to acute kidney injury

**CRS type II (chronic CRS)** Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease

**CRS type III (acute renocardiac syndrome)** Abrupt worsening of renal function (e.g. acute kidney ischemia or glomerulonephritis) causing acute cardiac disorders (e.g. heart failure, arrhythmia and ischemia)

**CRS type IV (chronic renocardiac syndrome)** CKD (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy, increased risk of adverse cardiovascular events or all

**CRS type V (secondary CRS) Systemic condition** (e.g. diabetes mellitus and sepsis) causing both cardiac and renal dysfunction
Too wet!!!!

Too Dry!!!!
Pathophysiology

• **Neurohormonal Factors:**
  
  • Sympatetic Nervous System, RAAS, Arginine V.P. System

• **Hemodynamics:**
  
  • Loss of Cardiac Output
  • Transrenal perfusion pressure
  • Intrarenal hemodynamics
Neurohormonal Factors:

![Diagram showing the neurohormonal axis](image)

- Sympathetic Stimulation
- Hypotension
- Decreased Sodium Delivery

Kidney → Renin → Angiotensinogen → AII → ACE

- Cardiac & Vascular Hypertrophy
- Systemic Vasoconstriction
- Increased Blood Volume

- Thirst
- ADH
- Renal Sodium & Fluid Retention

- Adrenal Cortex → Aldosterone

Adenosine
CHF Hemodynamics

Systolic or Diastolic CHF:
Exacerbations -- Symptomatology seen objectively
  Elevated PCWP
  Elevations of INR, Alkaline Phosphatase
  Elevations of Creatinine
CVP and Renal Failure

2,557 patients underwent RHC
Age 59 ± 15 years
57% were men
Renal Function using estimated Glomerular Filtration Rate (eGFR)

Relationship Between CVP and eGFR According to Different Cardiac Index Values

Event-Free Survival According to Tertiles of CVP

Effect of Increased Renal Venous Pressure on Renal Function

- Swine were anesthetized, instrumented, and a unilateral nephrectomy performed.
- In the remaining kidney, the renal vein was constricted in half the animals to obtain a renal venous pressure of 30, while the other animals served as controls.

![Bar graph showing RA Blood flow Index and Aldosterone levels with statistical significance (P < .05) between groups.]

ANEMIA IN CRS

Multifactorial→ Iron deficiency, GI Bleeds (Antiplatelets, anticoagulation), hemodilution, CKD related EPO underproduction and inflammation.

While correcting severe anemia and iron deficiency is worthwhile to achieve Hb levels of around 10g/dL, normalization of Hb has not been found to improve outcomes.

**CRS: Types**

**Type I: Acute Cardiorenal Syndrome:**
Abrupt worsening of cardiac function (e.g., acute cardiogenic shock or ADHF) leading to Acute Kidney Injury (AKI).

**Notes on Pathophysiology**
Altered cardiac and renal hemodynamics.
Diuretic Resistance and WRF

**Type II: Chronic Cardio Renal Syndrome**
Chronic abnormalities in cardiac function (e.g., chronic heart failure) causing progressive and potentially permanent Chronic Kidney Disease (CKD).

**Accelerated renal cell apoptosis and replacement fibrosis**
Type III: Acute Renocardiac Syndrome

Abrupt worsening of renal function (e.g., acute kidney ischemia or glomerulonephritis) causing acute cardiac disorder (e.g., heart failure, arrhythmia, ischemia).

Precipitated by salt and water overload, acute uremic cardiomyocyte dysfunction, and Neurohormonal dysregulation

Type IV: Chronic Renocardiac Syndrome

Heart disease/failure in association and as a result of CKD

Progression of CHF in the setting of CKD. Cardiomyocyte dysfunction and fibrosis, 'CKD Cardiomyopathy'
Type V: Secondary Cardiorenal Syndrome

Systemic conditions (e.g., sepsis) causing both cardiac and renal dysfunction

Microcirculatory dysfunction as a result of acutely abnormal immune cell signalling, catecholamine cellular toxicity and enzymatic activation which result in simultaneous organ injury often extending beyond both heart and kidneys
Cardio-Renal Syndrome
Treatment Goals

• Same goals as ADHF:
  • Removal of Volume
  • Optimizing Hemodynamics
• Complicated by chronic renal failure and acutely worsening renal function
Removal of Volume

Loop Diuretics
Brain Naturetic Peptide
Arginine Vasopressin Antatonism
Adenosine Antagonism
Ultrafiltration

Goal --> Deplete extracellular fluid volume. Balanced refilling interstitium to intravascular compartment.

Reality --> Contraction of circulating volume. --> Activation of neurohormonal response.
Removal of Volume

- Loop Diuretics
- Brain Naturetic Peptide
- Arginine Vasopressin Antagonism
- Adenosine Antagonism
- Ultrafiltration

Diuretic Resistance:

- Inadequate dosing.
- Cellular Hypertrophy
- Bolus vs Continuous Infusion
- Double Diuretic Therapy
- Nutritionally Deficient Patients
Removal of Volume

Loop Diuretics
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The DOSE Trial
Diuretic Optimization Strategies Evaluation

- 308 patients with ADHF
- Low vs High Dose Furosemide
- Continuous vs a12 hour dosing

- Overall no significant difference among all groups
  - Patients symptoms
  - Creatinine
  - High Dose group had a greater diuresis with transient increases in creatinine

Diuretic Resistance

Double Diuretic Therapy or Sequential Nephron Blockade

**Loop + Thiazide**
Chlorothiazide 250 mg vs 500 mg IV / Metolazone 5-10 mg PO
Very Effective -- Weight loss and edema resolution
Double Sodium Excretion
CAUTION: Hyponatremia, Hypotension, Worsening renal function

Chronic use -> cellular hypertrophy -> increased Na reabsorption -> Failure of diuresis

*Figure: Diuretic Sites of Action*

Source: Mendel (1990), Reprinted With Permission.

ACEI play a complex role in renal function in HF

- May improve CO in some patient and hence increase effective renal perfusion
- ACEI may lower BP to the point where effective renal perfusion is impaired
- With chronic renal disease, there is hyperfiltration in the remaining nephrons. ACEI decreases efferent arteriole constriction and hence decreases glomerular capillary pressure which may preserve renal function longterm
- This may result in a 10-20% increase in creatinine, but over the long term renal function is preserved
Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

Bradley A. Bart, M.D., Steven R. Goldsmith, M.D., Kerry L. Lee, Ph.D., Michael M. Givertz, M.D., Christopher M. O'Connor, M.D., David A. Bull, M.D., Margaret M. Redfield, M.D., Anita Deswal, M.D., M.P.H., Jean L. Rouleau, M.D., Martin M. LeWinter, M.D., Elizabeth O. Ofili, M.D., M.P.H., Lynne W. Stevenson, M.D., Marc J. Semigran, M.D., G. Michael Felker, M.D., Horng H. Chen, M.D., Adrian F. Hernandez, M.D., Kevin J. Anstrom, Ph.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Jenny C. Ibarra, R.N., M.S.N., Alice M. Mascette, M.D., Eugene Braunwald, M.D., for the Heart Failure Clinical Research Network

N Engl J Med
Volume 367(24):2296-2304
December 13, 2012
Ultrafiltration is an alternative strategy to diuretic therapy for the treatment of patients with acute decompensated heart failure. 188 patients with DHF were assigned to stepped pharmacologic therapy (94 patients) or ultrafiltration (94 patients).

Ultrafiltration was inferior to pharmacologic therapy with respect to the bivariate end point of the change in the serum creatinine level and body weight 96 hours after enrollment (P=0.003), owing primarily to an increase in the creatinine level in the ultrafiltration group.
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Practical approach to the management of type 1 cardiorenal syndrome

1. Anticipation and prevention

• On admission, assess for the presence of early satiety, anorexia, use of NSAIDs, elevated baseline creatinine, history of orthopnea, and elevated JVP.

• Bioimpedence monitoring if available.¹

• Restrict sodium (and water if hyponatremic).

• Avoid hypotension (MAP <60 mm Hg), contrast agents, and NSAIDs.²

• Avoid urinary retention, constipation, and elevation of head end of the bed >30, which can all raise the intra-abdominal pressure.


Practical approach to the management of type 1 cardiorenal syndrome

2. **Use intravenous route for diuretics.**

   • Continuous infusion has no benefit over bolus dosing.¹
   
   • Start the initial dose at 2–2.5 times the home oral dose.¹
   
   • Escalate the dose until adequate symptom relief is achieved and/or evidence of renal hypoperfusion is present.

   • Avoid single daily dosing.²


Practical approach to the management of type 1 cardiorenal syndrome

3. Judicious use of ACE-I and ARB

- Consider holding ACE-I or ARB temporarily during aggressive diuresis in high-risk patients.¹
- Addition of beta-blockers could be reno-protective when ACE-I is used.¹

4. Overcoming diuretic resistance

- Consider adding thiazides/thiazide-like diuretics or potassium-sparing diuretics.²
- Add mineralocorticoid antagonists such as spironolactone or eplerenone in patients with ejection fraction <35%.

5. Diuretic refractory CHF
Peritoneal dialysis.\textsuperscript{67, 68}
- Peripheral veno-venous ultrafiltration.\textsuperscript{2}

6. Emerging treatment options
- Alternatively spliced BNPs (ASBNP and ASBNP.)\textsuperscript{1}
- Hypertonic saline with furosemide.
- Vasopressin receptor antagonists.
- Sacubitril/valsartan
- Catheter-based renal sympathetic denervation.

\textsuperscript{1}Sanchez JE, [Analysis of the advantages of peritoneal dialysis in the treatment of chronic refractory heart failure]. Nefrologia 2010; 30: 487–489
LCZ696 – sacubitril/valsartan - Entresto

Heart Failure

Angiotensinogen

Renin

Ang II

ACE

Ang II

AT1R

Aldosterone

Sodium Retention
Volume Expansion
VSMC Growth
Vasoconstriction
LV Dysfunction
Myocardial Fibrosis
Myocardial Hypertrophy

LCZ696

Inactive Metabolites

Natriuretic Peptides

Bradykinin

Substance P

Ang I – II

Diuresis
Natriuresis
Vasodilatation
Decreased myocardial remodeling

Vasodilatation

Bugey J, Mentz RJ et al. JCF 2015
Gracias!
Acute cardio-renal syndrome (type 1): acute worsening of heart function leading to kidney injury and/or dysfunction.

Chronic cardio-renal syndrome (type 2): chronic abnormalities in heart function leading to kidney injury or dysfunction.

Acute reno-cardiac syndrome (type 3): acute worsening of kidney function leading to heart injury and/or dysfunction.

Chronic reno-cardiac syndrome (type 4): chronic kidney disease leading to heart injury, disease, and/or dysfunction.

Secondary cardio-renal syndromes (type 5): systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney.