

Cardiorenal Syndrome

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Structural kidney changes with aging

Nephrosclerosis:

- ✓ 2.7 % on 18-29 y/o
- ✓ 73% on 70-77 y/o

Glomerulosclerosis:

- ✓ Up to 1 glomerulus in 25 y/o
- ✓ Up to 6 glomeruli in 75 y/o

Nephron number:

- ✓ 700,000 to 1.8 million per kidney
- ✓ Average nephron loss of about 50/day

Others:

- Decrease kidney size
- Decrease cortical volume
- Increase number of Cysts
- Atherosclerosis or renal arteries

Aging Kidneys

- Since eGFR started to replace serum Cr for evaluation of kidney function more patients in geriatric age are diagnosed with CKD
- About one half of older adults have a GFR of < 60 ml/min/ 1.73 m2
- The increase in CKD diagnosis is due to the misinterpretation of age related changes as manifestations of CKD
- Individuals without proteinuria and with GFR 45-59, the associated mortality is 20% higher for older than 75y and 179% higher for age 18-54y

Functional changes of the kidney with aging

GFR decline with aging:

- 7.5-9.5 ml/min per decade
- 0.6-1 per year
- Currently there is no defined normal GFR range for geriatric population
- Some studies have found that the lower reference limit for measured GFR to be 49 ml/min/1.73 m² among healthy potential donors
- Impaired renal sodium conservation and rapid excretion
- Changes in diluting capacity

Clinical importance of aging kidney

- More advanced disease if a new nephropathy develops (diabetes, vasculitis)
- Increased risk for kidney injuries (contrast, NSAIDs, infections, hypotension)
- Increased risk for toxic accumulation or renally cleared drugs
- Increase risk for hyponatremia and volume overload
- Need more rigorous evaluation prior to kidney donation
- Albuminuria may be a important marker to distinguish normal aging from other causes of CKD

Introduction

- Describes the interaction between heart disease and kidney disease
- Mortality is increased on patients with heart disease who also have abnormal renal function
- Cardiovascular disease is the cause of death in 50% of patients with renal failure
- Systemic disorders can cause both cardiac and renal dysfunction

Introduction

- The prevalence and incidence of HF increases with age
- The prevalence of moderated to severe kidney impairment is approximately 30-60% in patients with heart failure
 - ✓ 80,000 patients (hospitalized and non-hospitalized) with heart failure, 29 % had moderate to severe kidney impairment (ADHERE database)
 - ✓ 100,000 patients hospitalized for heart failure, 20-30% had the diagnosis of CKD (Cr >2) (Acute decompensated heart failure registry database)

1. [Circulation. 2007 Aug;116\(8\):422-30.](#) High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. [Meyerson PJ,](#) [Calkins DC,](#) [Constantino MJ,](#) [Mattur VJ,](#) [Werns JA,](#) [Wessels LC,](#) [Wong GJ.](#) [http://dx.doi.org/10.1161/01.CIR.0000276755.29029.85](#)

2. [Am Coll Cardiol. 2008 May 16;47\(10\):1387-96.](#) Epub 2008 Apr 24. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. [Kovalev V,](#) [Jankinmaa M,](#) [Rissanen AA,](#) [Rissanen AH,](#) [Pohjonenmäki M,](#) [Penttilä M,](#) [Laiho A,](#) [Tuomi T.](#) [http://dx.doi.org/10.1016/j.amcc.2008.02.005](#)

Definition

Acute or chronic dysfunction in one organ induces acute or chronic dysfunction in the other

Condition in which the Therapy to improve congestive heart failure is limited by decline in renal function

(National Heart, Lung and Blood Institute definition of CRS)

Classification

- **Type 1 (acute) Acute HF results in acute kidney injury**
- **Type 2: Chronic Cardiac dysfunction causes CKD**
- Type 3: Abrupt and primary worsening of kidney function causes acute cardiac dysfunction
- Type 4: Primary CKD contributes to cardiac dysfunction
- Type 5: Acute or chronic systemic disorders cause both cardiac and renal dysfunction (sepsis, diabetes, HTN)

1. [Am Coll Cardiol. 2008 Nov 4;52\(19\):1527-39.](#) doi: 10.1016/j.jacc.2008.07.051. **Cardiorenal syndrome.** [Razzaq C,](#) [Mehanna M,](#) [Thomas AG,](#) [Aparicio N,](#) [Bullock B.](#) [http://dx.doi.org/10.1016/j.jacc.2008.07.051](#)

Diagnosis

Impaired kidney function:

- ✓ Serum Cr and BUN concentration vs GFR
- ✓ Normal Aging vs Chronic Kidney disease

Look for other causes of kidney disease:

- ✓ Finding suggestive of underlying kidney disease (proteinuria, active urine sediment, small kidneys)
- ✓ CRS presents with normal UA on patients with normal renal function (obstruction and nephrosclerosis)

Diagnosis

• **kidney disfunction** induced by **Heart failure**

• Impaired kidney function:

- ✓ Interpretation of Serum Cr an BUN concentration vs GFR
- ✓ Normal aging vs Chronic kidney disease

	Functional criteria	Structural criteria
AKI (acute kidney injury)	Increase in SCr by 50% within 7 days, or increase in SCr by 0.3 mg/dL within 2 days, or oliguria	No criteria
CKD (chronic kidney disease)	GFR <60 for >3 mo	Kidney damage for >3 mo
AKD (acute kidney diseases and disorders)	AKI, or GFR <60 for <3 mo, or decrease in GFR by >35% or increase in SCr by >50% for <3 mo	Kidney damage for <3 mo
NKD (no known kidney disease)	GFR >60, stable SCr	No kidney damage

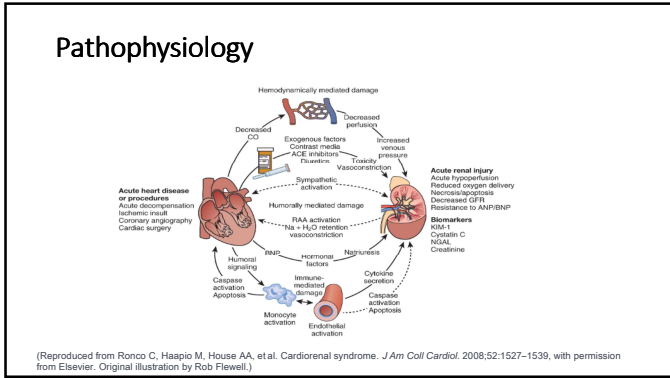
Diagnosis

Impaired kidney function:

- ✓ Interpretation of Serum Cr an BUN concentration vs GFR
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Heart Failure is a cause of prerenal azotemia:

- Elevated BUN/Cr ratio (>20)
- Low urine Na concentration (<25meq/L)



- ### Pathophysiology
- Impaired left ventricular Function:
 - Reduced stroke volume and cardiac output
 - Arterial underfilling
 - Elevated atrial pressure and venous congestions
 - Neurohumoral adaptations
 - Reduced renal perfusion
 - Increased renal venous pressure
 - Right ventricular dilatation and dysfunction

- ### Pathophysiology
- Neurohumoral adaptations:**
- ✓ Activation of Sympathetic Nervous System
 - ✓ Activation of the Renin-Angiotensin-Aldosterone system
 - ✓ Increased Vasopressin (ADH)
 - ✓ Endothelin-1
- Positive effects:
 - ✓ preservation of perfusion to vital organs (brain and heart)
 - ✓ Maintenance of systemic pressure (vasoconstriction, myocardial contractility and heart rate)
 - Negative effects:
 - ✓ Increased cardiac afterload → Reduction of Cardiac output → Reduction of Renal perfusion

Pathophysiology

Reduced renal perfusion:

- Reduction of cardiac index is not the primary driver for renal dysfunction
 - ✓ No correlation between cardiac index and baseline GFR or worsening of renal function(ESCAPE trial)
 - ✓ Hypotension is uncommon in hospitalized patients with decompensated heart failure

Increased renal venous pressure

- Increasing intra-abdominal or Central venous pressure reduces the GFR
- Right ventricular dilatation and dysfunction

Pathophysiology

Right ventricular dilatation and dysfunction

- Elevation in Central venous pressure can lower the GFR
 - ✓ RV dilatation impairs LV filling
 - ✓ Interventricular septal bowing → diminishes LV preload and distensibility → reduces forward flow

Patients with Heart Failure and preserved ejection fraction can also have renal dysfunction.

- Endothelial dysfunction and proinflammatory state mediate Cardiorenal interaction

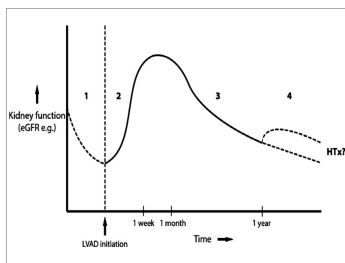
Management

- GFR reduction in heart failure could be a marker of the severity of heart disease.
- No medical therapies have shown to directly improve GFR in HF
- Improving heart failure can produce increase in GFR
- CRS 1&2 have reversible components

Management

- Improvement of cardiac function
- Diuretics
- RAAS antagonists
- Vasodilators
- Inotropic drugs
- Other therapies:
 - ✓ Ultrafiltration
 - ✓ Vasopressin receptors antagonists (Tovaptan)
 - ✓ Adenosine A1 receptor antagonist (Rolofylline)

Improvement of cardiac function



Representation of evolution in renal function over time after LVAD

- Phase 2: perfusion improvement
- Phase 1: cardiorenal physiology
- Phase 3: steady decline in renal function. (usually takes over one year to get to pre-implant levels)
- Phase 4: cardiac transplant vs RRT

Heart Fail Rev. 2015; 20(4): 519-532. Published online 2015 Mar 22. doi: 10.1007/s12345-015-9461-

Diuretics

- Loop diuretics are first line therapy
- Effects of diuretics-induced fluid removal on GFR is variable
- Elevated BUN and Cr should not deter diuretic therapy
- Best outcomes may occur with aggressive fluid removal
- Choice of loop diuretic and dose

The effect of diuretics-induced fluid removal on GFR is variable

Increase in serum creatinine

- Fall in cardiac filling pressure
- Decline in cardiac output
- Reduction in renal perfusion



No change in serum creatinine

- Maintenance of cardiac output

Reduction in serum Cr

- Reduction in intrabdominal and renal venous pressures
- Reduction in right ventricular dilatation
- Improvement of LV filling and function



Diuretic Dose

Best outcomes may occur with aggressive fluid removal

- 336 patients with decompensated heart failure in the SCAPE trial, patients with ***hemoconcentration***:
 - Worse renal function
 - Lower mortality
 - Were treated with higher dose of loop diuretics
 - More and weight fluid loss
 - Greater reduction in intracardiac filling pressures
- 2013 American College of Cardiology/AHA HF guidelines:
 - Diuresis goal: eliminate clinical evidence of fluid overload

Loop diuretics maximal effective dose

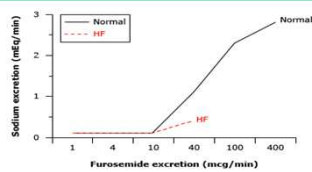
	Equivalent Dose	Moderate CKD	Oliguric AKI
Furosemide PO	40 mg	80-160mg	
Furosemide IV	20 mg	40-80mg	500mg
Torsemide	10 mg	20-50 mg	
Bumetanide	0.5 mg	2-3 mg	

Diuretic Choice

- Patients on loop diuretics still benefit from Na restriction
- Patients with HF have relative resistance to loop diuretics (decreased renal perfusion)
- Side effects:
 - Hypokalemia and hypomagnesemia usually occur in the first 2-3 weeks of therapy
 - There is no evidence of sulfonamide cross-reactivity
 - Ototoxicity is primarily seen at very high doses

Diuretic dose

Dose-response relationship between furosemide and sodium excretion



Relation between the rate of furosemide excretion and the increase in sodium excretion in normals (solid line) and patients with HF (dashed line). A diuresis is not seen until a threshold rate of furosemide excretion is reached. Patients with HF show relative resistance at a given rate of diuretic excretion due to increased sodium reabsorption in other nephron segments.

HF: heart failure.

Data from: Brater DC, Day B, Burdette A, et al. *Kidney Int* 1984;26:143-50

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Renin-Angiotensin-Aldosterone-System antagonist (RAAS)

- Standard part of the therapy for heart failure with reduced EF
- Generally not associated with improvement of renal function in CRS
- A small group of patients have a moderate reduction in GFR
- There is a dose effect
 - High dose losartan is associated with sustained reductions in eGFR compare to low-dose
 - High-dose losartan is associated with improved long-term clinical outcomes
- Clinical trials of RAAS-antagonists in HF have not focused on patients with CRS
- The beneficial effect of RAAS antagonists on clinical outcomes is not reduced by concomitant CKD
- Higher adverse events in patients with CKD compare to non-CKD patients

Vasodilators (Nitrates and Nesiritide)

Nitrates (Nitroglycerin and Nitroprusside)

Nesiritide (Recombinant human brain natriuretic peptide)

No supporting data:

- *Worsening or no change* on renal function with combination of IV diuretics and vasodilators compare to IV diuretics alone.
 - Acute Decompensated Heart Failure National Registry (ADHERE) database of almost 100,000 patients
 - ASCEND-HF and ROSE trials

Inotropic Drugs (Dobutamine, Dopamine and Milrinone)

- The role of inotropes in the treatment of CRS is uncertain
- There is no supportive data outside the subgroup of patients with cardiogenic shock or severe acute decompensated HF

Ultrafiltration

- Removal of isotonic fluid from the venous compartment across a semipermeable membrane
- May be helpful in acute decompensated HF and diuretic resistance and/or impaired renal failure
- Available evidence does not support UF as a first line therapy for acute decompensated HF with CRS

Other therapies

- Vasopressin receptors antagonists (Tovaptatan)
 - ✓ Produces water diuresis
 - ✓ Only approved for the treatment of hyponatremia in patients with HF
- Adenosine A1 receptor antagonist (Rolofylline)
 - ✓ Increase GFR and promote diuresis
 - ✓ Potential synergistically with loop diuretics
 - ✓ No difference in vascular between or rate of worsening of renal function (PROTECT trial)

END
