OBJECTIVES

• To enumerate the different types of cardiorenal syndrome
• To discuss the pathophysiology of cardiorenal syndrome
• To present the diagnostic and therapeutic approach to patients with cardiorenal syndrome
PATIENT PROFILE

• B.R.
• 25-year-old
• Male
• Admitted for the first time last April 23, 2016
• Diagnosed case of rheumatic heart disease since 2003 when he was 12 years old maintained on Phenoxyymethyl Penicillin 250 mg BID

• No intake of NSAIDs or herbal medications

• Chief Complaint: Difficulty of breathing
HISTORY OF PRESENT ILLNESS

- Cough and fever
- Difficulty of breathing
- Edema

Admitted
- Diuretics
- PHC
- EF 35%, AR, MR & TR
- Crea 3.0 eGFR 27.6

3 months 1 month 1 week Consult
• **Past Medical History**
  • Rheumatic heart disease (2003) maintained on Phenoxyethyl Penicillin 250 mg BID

• **Family History**
  • Unremarkable

• **Social History**
  • Non-smoker and non-alcoholic beverage drinker
  • Denies illicit drug use
# REVIEW OF SYSTEMS

<table>
<thead>
<tr>
<th>General</th>
<th>(-) Sweating, (+) <strong>weight gain</strong>, (+) weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>(-) Itching, (-) rashes, (-) changes in hair/nails</td>
</tr>
<tr>
<td>Eyes</td>
<td>(-) Visual impairment, (-) redness, (-) tearing, (-) pain, (-) double vision, (-) discharge</td>
</tr>
<tr>
<td>Ears</td>
<td>(-) Hearing, (-) pain, (-) discharge, (-) tinnitus</td>
</tr>
<tr>
<td>Nose, Throat, Mouth</td>
<td>(-) Hoarseness, (-) sore throat, (-) trauma, (-) frequent colds, (-) nose bleeding, (-) neck mass, (-) dental carries, (-) facial pain, (-) sinus disorder, (-) gum Bleeding, (-) toothache</td>
</tr>
<tr>
<td>Respiratory</td>
<td>(+) <strong>Non-productive cough</strong>, (-) hemoptysis</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>(-) Chest pain, (+) <strong>palpitation</strong>, (-) syncope</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>(-) Dysphagia, (-) nausea, (-) vomiting, (-) change in appetite, (-) abdominal pain, (-) melena, (-) jaundice, (-) bleeding, (-) indigestion, (-) heartburn, (-) hematemesis, (-) fatty food intolerance, (-) stool frequency/character, (-) hemorrhoids, (-) hernia</td>
</tr>
<tr>
<td>Urinary</td>
<td>(-) Dysuria, (-) retention, (-) bleeding, (-) stream, (-) nocturia, (-) stones, (-) hesitancy, (-) urgency, (-) change in color, (-) frequency, (-) dribbling</td>
</tr>
</tbody>
</table>
## REVIEW OF SYSTEMS

<table>
<thead>
<tr>
<th>System</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genito-Reproductive</td>
<td>(-) Discharge, (-) pain, (-) libido, (-) sexual difficulties</td>
</tr>
<tr>
<td>Breast</td>
<td>(-) Nipples, (-) lump, (-) pain, (-) discharge</td>
</tr>
<tr>
<td>Extremities</td>
<td>(-) Cyanosis, (-) clubbing, (-) varicosity, (-) ulcers, (-) claudication</td>
</tr>
<tr>
<td>Hematopoietic System</td>
<td>(-) Excessive bleeding/bruising, (-) pica</td>
</tr>
<tr>
<td>Nervous System</td>
<td>(-) Headache, (-) tremor, (-) fainting spells, (-) seizures, (-) neurological deficit, (-) gait disturbance, (-) dizziness/vertigo, (-) head trauma, (-) sensory perversions</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>(-) Joint pain or stiffness, (-) muscle weakness</td>
</tr>
<tr>
<td>Endocrine System</td>
<td>(-) Heat/cold intolerance, (-) thyroid problems, (-) neck surgery/irradiation, (-) proximal muscle weakness, (-) easy bruisingability</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>(-) Mood swings, (-) behavioural changes, (-) anxiety, (-) depression</td>
</tr>
</tbody>
</table>
## PHYSICAL EXAMINATION

<table>
<thead>
<tr>
<th>Gen. Survey</th>
<th>Awake, coherent, ambulatory, <strong>weak looking, speaks in phrases</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital Signs</td>
<td><strong>BP: 90/60 mmHg, HR: 99 bpm, RR: 22 cpm, Temp.: 37.6°C</strong></td>
</tr>
<tr>
<td>HEENT</td>
<td>Anicteric sclera, <strong>pale palpebral conjunctiva</strong>, no tonsillopharyngeal congestion, no cervical lymphadenopathies, <strong>prominent neck veins</strong></td>
</tr>
<tr>
<td>Chest/Lungs</td>
<td>Equal chest expansion, <strong>decrease breath sounds on bibasal lung fields, crackles on left lower lungs, no wheezing</strong></td>
</tr>
<tr>
<td>Heart</td>
<td>Adynamic precordium, normal rate, <strong>irregularly irregular rhythm</strong>, PMI displaced to 5th intercostal space at the left anterior axillary line, grade 3 holosystolic murmur</td>
</tr>
<tr>
<td>Abdomen</td>
<td><strong>Globular</strong>, normoactive bowel sounds, <strong>distended</strong>, no tenderness, no masses, (+) <strong>shifting dullness and fluid wave</strong></td>
</tr>
<tr>
<td>Extremities</td>
<td>Full and equal pulses, <strong>grade 3 bipedal edema</strong>, no cyanosis</td>
</tr>
</tbody>
</table>
SALIENT FEATURES

- 25-year-old
- Male
- Rheumatic heart disease (2003)
- CAP-MR 3 months ago
- Progressive difficulty of breathing, easy fatigability, 2 pillow orthopnea, paroxysmal nocturnal dyspnea, bipedal edema and enlarging abdomen
- EF 35%, AR, MR & TR
- Crea 3.0 eGFR 27.6
- Advised valve replacement surgery
- BP 90/60
- Prominent neck veins, irregularly irregular rhythm, PMI displaced, grade 3 holosystolic murmur
- Anasarca
PROBLEM LIST

1. Cardiorenal syndrome type 1/2?
2. Heart failure 2° VHD (RHD – AR, MR & TR)
3. Permanent atrial fibrillation

- Address volume overload
- Improve cardiac function
- Adequate anticoagulation
DEFINITION

“Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other”

The interaction is bidirectional.

Morbidity is increased in patients with heart failure (HF) who have a reduced glomerular filtration rate (GFR).

Acute or chronic systemic disorders can cause both cardiac and renal dysfunction.

CKD = ↑ atherosclerotic cardiovascular disease (CVD) and HF.

CVD = ~50% of deaths in end-stage renal disease (ESRD).
Type 1 – Acute HF results in AKI

Type 2 – Chronic cardiac dysfunction causes progressive CKD

Type 3 – Abrupt and primary worsening of kidney function causes acute cardiac dysfunction

Type 4 – Primary CKD contributes to cardiac dysfunction

Type 5 (secondary) – Acute or chronic systemic disorders that cause both cardiac and renal dysfunction
PREVALENCE

• Over 60% of patients admitted in the hospitals with ADHF had stage 3 or worse CKD ¹

• During the management of ADHF, a majority of patients develops varying degrees of worsening renal function ²

• Age, men, diabetes, ischemic etiology of HF, low BPs, worse neurohormonal and proinflammatory profiles, presence of edema, and use of higher doses of diuretics were independently associated with the presence of CKD ³

• The presence of CKD was similar in patients with preserved (34%) and depressed LV function (33%) ⁴

3. Valsartan in Heart Failure Trial (2009)
4. CHARM Trial (2006)
RISK FACTORS

CAD

High doses of diuretics

Pulmonary edema

Tachycardia

Crea 1.5 mg/dl

HPN

DM

HF

PROGNOSIS

• Types 1 and 2 CRS is associated with worse short- and long-term adverse outcomes. In the ADHERE registry, the in-hospital mortality increased from 1.9% for patients with normal renal function to **7.6%** for patients with severe renal dysfunction.¹

• Although any increase in serum creatinine during treatment of ADHF is associated with worse prognosis, an increase in creatinine of **0.3 mg/dl** was found to have the highest sensitivity and specificity for predicting in-hospital mortality and length of stay.²

• One of the factors that contribute to worse outcomes in HF is the presence or development of **renal dysfunction during management of HF**.³

• It was estimated that mortality increased by approximately **15 percent** for every **10 mL/min reduction in eGFR**.⁴

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² Gottlieb SS, et al. (2002)
³ Fonarow GC, et al. (2006)
⁴ Smith GL, et al. (1987)
PATHOPHYSIOLOGY

-↓ CO
-↓ SNS
-↓ RAAS

Renal dysfunction
Salt and water retention
Venous congestion

Drugs
Primary Renal Parenchymal Disease
Anemia

Anand IS, et al. (2005)
Arterial underfilling

- Decreased cardiac output
- Decreased effective circulating volume
- Decreased RBF, RPF
- Activation of RAAS, SNS
- Inflammatory pathways

Heart

- Decreased GFR
- Na and H₂O retention
- Increased edema, preload
- Increased afterload

Kidney

- Venous congestion and venous hypertension, raised IAP
- Decreased AV perfusion gradient
- Kidney interstitial edema
- Activation of RAAS, SNS
- Inflammatory pathways

Venous congestion

House AA (1997)
DIAGNOSIS

• The most common test used to estimate GFR is the serum creatinine concentration.

• Serum cystatin C may be a better marker of GFR because it is less dependent upon muscle mass and therefore less influenced by nutritional status.

• Distinguish between underlying kidney disease and impaired kidney function due to the cardiorenal syndrome.
  • Significant proteinuria, an active urine sediment with hematuria with or without pyuria or cellular casts, and/or small kidneys on radiologic evaluation.

• An elevation in BUN is also associated with increased mortality in patients with HF since disproportionate increase in BUN is often seen with a reduction in renal perfusion (prerenal azotemia).
TREATMENT

- Improve Cardiac Function
- Diuretics
- RAAS Antagonism
- Vasodilators
- Inotropes
- Ultrafiltration
- Investigational Therapies
Continuous-Flow LVADs

- Improvements in eGFR were noted within one month of LVAD implantation and persisted over a two-year period of follow-up \(^1\)
- Early improvements in eGFR with LVAD use were transient and typically only sustained for a period of weeks to months \(^2\)

Cardiac Resynchronization Therapy

- Improved the LV ejection fraction and the eGFR in selected patients with HF and moderately reduced baseline eGFR (eGFR 30 to 59 mL/min) \(^3\)

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DIURETICS

- Loop diuretics are first-line therapy for managing volume overload in patients with HF
  - Cardiac filling pressures, CO & renal perfusion decrease
  - Creatinine increases

- Reduction in serum creatinine
  - Reductions in intraabdominal and renal venous pressures
  - Reduction in right ventricular dilatation, which may improve LV filling and function via ventricular interdependence

- AHA/ACC (2013) - goal of diuretic therapy is to eliminate clinical evidence of fluid retention such as an elevated jugular venous pressure and peripheral edema

DIURETICS

- Diuretic Optimization Strategies Evaluation (DOSE-HF) \(^1\) – high-dose loop diuretics are associated with better symptom improvement than low-dose loop diuretics at the cost of some renal impairment, while continuous diuretic infusions are no better than intermittent diuretic boluses.

- Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) \(^2\) - the diuretic strategy yielded similar outcomes in terms of fluid loss and symptom control, mortality or re-hospitalizations did not differ but the ultrafiltration group experienced more serious adverse events.

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DIURETICS - SHORTCOMINGS

- Direct activation of the RAA system
- Deterioration in renal function
- Electrolyte abnormalities
- Suboptimal natriuresis (hypotonic urine)
- Development of diuretic resistance
- Unpredictability of the therapeutic response
- Lack of clarity on the practical aspects of use
- Nonrenal adverse effects

Kazory A (2013)
RAAS ANTAGONISM

• Angiotensin inhibition with an ACEI or an ARB is a standard part of the therapy of HF with reduced ejection fraction, being associated with symptomatic improvement, reduced hospitalization for HF, and enhanced survival.

• They are not generally associated with an improvement in renal function, most have a moderate reduction in GFR that can often be ameliorated by reducing the intensity of diuretic therapy, additionally, there is a dose effect.

• The beneficial effect of RAAS antagonism on clinical outcomes is not mitigated by concomitant CKD.

• The risk of adverse events including hyperkalemia and worsening renal function is higher in patients with CKD.

Fig. 3 The impact of neurohormones on the glomerulus: normal, heart failure, and treated heart failure. AA afferent arteriole, EA efferent arteriole, RBF renal blood flow, GC glomerular capillary, NE norepinephrine, AII angiotensin-II, AVP arginine vasopressin.
Fig. 4 Approach for initiation of RAS blockade in patient vulnerable to renal insufficiency. 
Ct creatinine; BP blood pressure
ANGIOTENSIN–NEPRILYSIN INHIBITION

• **PARADIGM-HF**
  
  • Treatment with an angiotensin receptor-neprilysin inhibitor reduces CV and all-cause mortality or HF hospitalizations when compared to enalapril
  
  • The LCZ696 group had higher proportions of patients with hypotension and non-serious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group

VASODILILATORS

- **ADHERE Database**\(^1\) - the rate of worsening renal function was significantly higher when intravenous diuretics were given with nitroglycerin or nesiritide compared with intravenous diuretics alone, however, a causal effect could not be distinguished from patients requiring combination therapy having more severe HF

- **ASCEND-HF**\(^2\) – found no change in risk of worsening renal function with nesiritide therapy

- **Renal Optimization Strategies Evaluation (ROSE) Trial**\(^3\) – found that low-dose nesiritide (0.005 mcg/kg/min without bolus for 72 h) did not enhance decongestion or alter renal function when added to diuretic therapy

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INOTROPES

• Dobutamine, dopamine, and milrinone — cardiogenic shock
• Short-term intravenous therapy and prolonged therapy with oral inotropic drugs other than digoxin have been associated with an increase in mortality
• DAD-HF Trial ¹ — combination of dopamine 5 mcg/kg/min plus low-dose furosemide (5mg/h continuous infusion) produced similar urine output as high-dose furosemide (20 mg/h) with reduced risk of worsening renal function
• Renal Optimization Strategies Evaluation (ROSE) Trial ² — low-dose dopamine did not enhance decongestion or improve renal function when added to diuretic therapy

ULTRAFILTRATION

- **UNLOAD** \(^1\) and **RAPID-CHF** \(^2\) – UF was associated with a significantly greater rate of fluid loss than diuretic therapy but no difference in serum creatinine.

- **CARESS-HF** \(^3\) – UF was compared to stepped pharmacologic therapy in patients with worsening renal function and persistent congestion, although weight loss was similar, UF caused an increase in serum creatinine and a higher rate of adverse events.

- **AHA/ACC (2009)** \(^4\) – UF is reasonable for patients with refractory congestion not responding to medical therapy.

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5. Managing the Kidney when the Heart is Failing (2012)
<table>
<thead>
<tr>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ renal venous congestion and improvement in renal hemodynamics</td>
</tr>
<tr>
<td>Rapid and adjustable removal of fluid and improvement in symptoms of congestion</td>
</tr>
<tr>
<td>Higher mass clearance of sodium</td>
</tr>
<tr>
<td>Decreased risk of electrolyte abnormalities</td>
</tr>
<tr>
<td>Lack of neurohormonal activation</td>
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<tr>
<td>Sustainability of the beneficial effects</td>
</tr>
<tr>
<td>Improvement in diuretic resistance, natriuresis, and urine output</td>
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<tr>
<td>Decreased rate of heart failure–related rehospitalizations</td>
</tr>
<tr>
<td>Decreased hospital length of stay</td>
</tr>
<tr>
<td>Availability of dedicated ultrafiltration devices</td>
</tr>
</tbody>
</table>

Kazory A (2013)
<table>
<thead>
<tr>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of protective effect on renal function</td>
</tr>
<tr>
<td>Lack of effect on markers of mortality</td>
</tr>
<tr>
<td>Possible need for placement of midline or central venous catheter</td>
</tr>
<tr>
<td>Need for additional training for staff and physicians</td>
</tr>
<tr>
<td>Need for anticoagulation</td>
</tr>
<tr>
<td>Complications related to extracorporeal circuit</td>
</tr>
<tr>
<td>Lack of widely accepted guidelines for its use</td>
</tr>
<tr>
<td>Lack of knowledge on the long-term outcomes</td>
</tr>
<tr>
<td>High cost</td>
</tr>
</tbody>
</table>

Kazory A (2013)
INVESTIGATIONAL THERAPIES – TOLVAPTAN

- **Selective vasopressin 2 receptor antagonist** that produces a water diuresis
- **EVEREST Outcome Trial**
  - No effect on all-cause mortality, HF hospitalization or seven-day patient global assessment
  - **Increase in urine output** resulting in reduced dyspnea and edema and an increase in serum sodium
  - Greater increase in serum creatinine
  - Treatment of hyponatremia in patients with HF

INVESTIGATIONAL THERAPIES – ROLOFYLLINE

- Adenosine, acting on the adenosine A1 receptor, constricts the afferent glomerular arteriole, thereby reducing the GFR, and increases tubular sodium reabsorption

- **Selective adenosine A1 receptor antagonism** can increase GFR and promote a diuresis, potentially acting synergistically with loop diuretics

- **PROTECT Trial**
  - No difference cardiovascular outcomes or in the rate of persistent worsening of renal function
  - Rolofylline therapy was associated with a higher rate of neurologic events (seizure and stroke)

GOING BACK TO THE PATIENT

Dobutamine
Warfarin
Furosemide
Metolazone
HD
PHC
SUMMARY

TREATMENT

- Improve Cardiac Function
- Diuretics
- RAAS Antagonism
- Vasodilators
- Inotropes
- Ultrafiltration
- Investigational Therapies
THANK YOU FOR LISTENING!