CARDIORENAL SYNDROME: CASE PRESENTATION AND BRIEF OVERVIEW

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Presentation Outline/Goals

- Convince you that having combined LV dysfunction and AKI carries a very high mortality and why its so important to **treat their congested state despite increasing serum creatinine.**
- Define cardiorenal syndrome and discuss a case of Type 1 CRS through a clinical vignette.
- Use the case to discuss evidence based medicine for some common medical treatments available
- Summary remarks.
- Have some fun

Type 2 CRS: Look Familiar ?

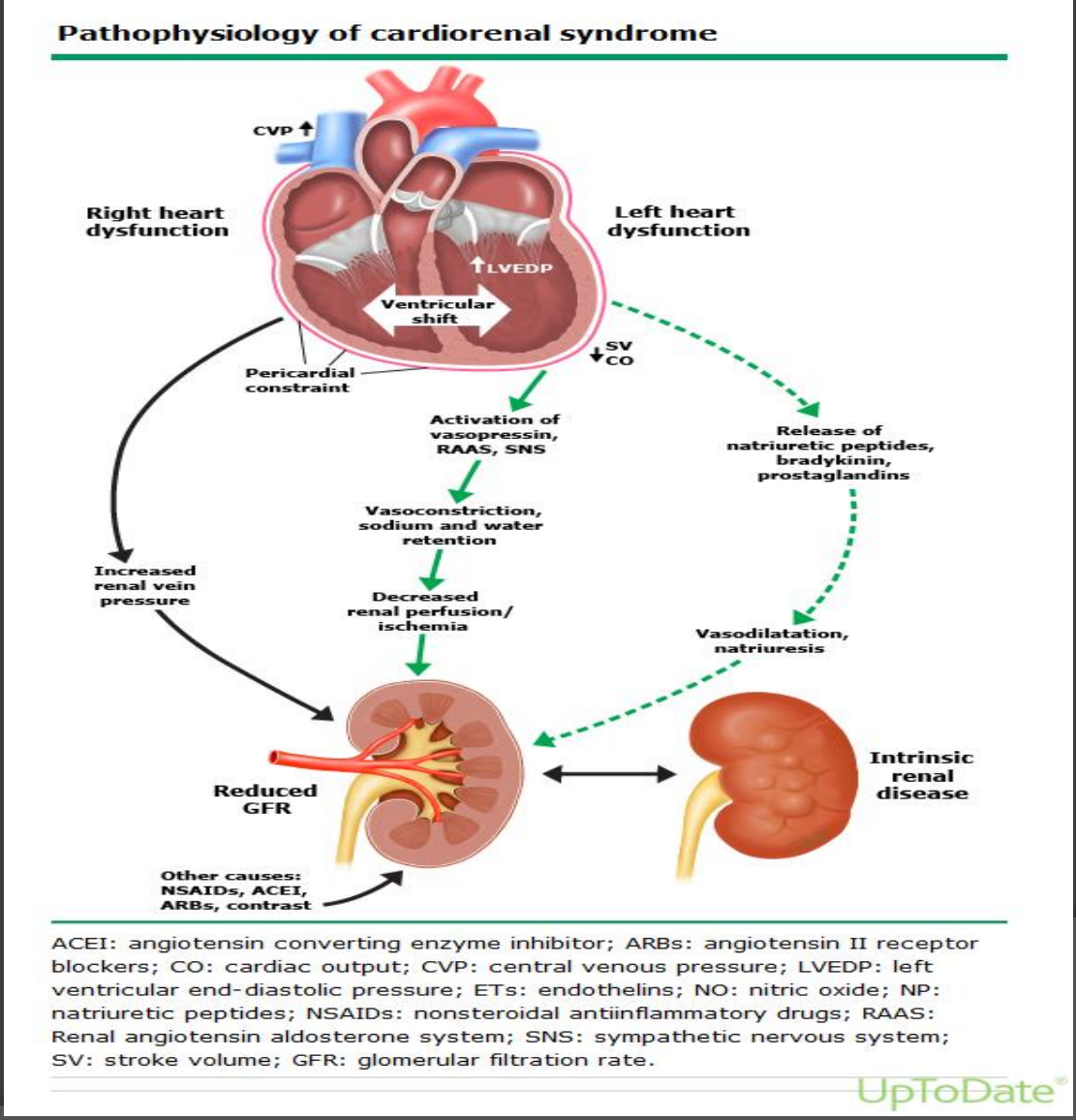
Observations

- There are a number of important interactions between heart disease and kidney disease.
- The interaction is bidirectional, as acute or chronic dysfunction of the heart or kidneys can induce acute or chronic dysfunction in the other organ.
- The clinical importance of such relationships is illustrated by the following observations:

Observations

- Mortality is increased in patients with heart failure (HF) who have a reduced glomerular filtration rate. *Renal impairment and outcomes in heart failure: systematic review and meta-analysis.AUSmith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, Krumholz HM SOJ Am Coll Cardiol. 2006;47(10):1987. Epub 2006 Apr 24*
- Patients with chronic kidney disease have an increased risk of both atherosclerotic cardiovascular disease and HF, and cardiovascular disease is responsible for up to 50 percent of deaths in patients with renal failure. *Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey.AUCoresh J, Astor BC, Greene T, Eknoyan G, Levey AS SOAm J Kidney Dis. 2003;41(1):1.*

Pathophysiology: I will Spare You !



Definitions

- A 2004 report from the National Heart, Lung, and Blood Institute defined CRS as a condition in which therapy to relieve congestive symptoms of HF is limited by a decline in renal function as manifested by a reduction in GFR.
- The reduction in GFR was initially thought to result from a reduction in renal blood flow. However, various studies have demonstrated that cardiorenal interactions occur in both directions and in a variety of clinical settings.
- Not a simple as this. A new definition is required

Ronco Classification

- Type 1 (acute) – Acute HF results in acute kidney injury (previously called acute renal failure).
- Type 2 – Chronic cardiac dysfunction (eg, chronic HF) causes progressive chronic kidney disease (CKD, previously called chronic renal failure).
- Type 3 – Abrupt and primary worsening of kidney function due, for example, to renal ischemia or glomerulonephritis causes acute cardiac dysfunction, which may be manifested by ADHF.

Ronco Classification

- Type 4 – Primary CKD contributes to cardiac dysfunction, which may be manifested by coronary disease, HF, or arrhythmia.
- Type 5 (secondary) – Acute or chronic systemic disorders (eg, sepsis or diabetes mellitus) that cause both cardiac and renal dysfunction.

***Cardiorenal syndrome.AURonco C, Haapio M, House AA, Anavekar N, Bellomo R SOJ Am Coll Cardiol. 2008;52(19):1527*.**

For purposes of time in this brief overview, we will discuss type 1 CRS

(in other words you will fall asleep and forget everything and throw things at me if I discuss all 5 types !!!!)

A 73-year-old patient with known severe systolic heart failure(LVEF 25 percent) and chronic kidney disease (baseline creatinine 1.9 mg/dL (estimated glomerular filtration rate (eGFR) 23 mLs/min) was admitted to LMH with acute decompensated heart failure (ADHF) do to AMI. Creatinine on admission was similar to baseline, but over the next week renal function deteriorated significantly (urea 51.1 meq/L, creatinine 5.03 mg/dL, eGFR 8) requiring inotropic support and then CVVHDF.

Her inpatient stay lasted 3 weeks, of which over half was spent in the intensive care unit. Unfortunately, she died from progressive multi system organ failure several weeks after discharge.

This is NOT atypical for this disease

Mortality Statistics

- Many studies in JACC and JASN have shown close to 30 percent inpatient mortality for type 1 CRS
- If your lucky to survive hospitalization, roughly another 50 percent die within the next 6 months after discharge
- Development of AKI is a powerful predictor of survival for patients admitted with decompensated heart failure and STEMI

Good Clinical Way to Approach

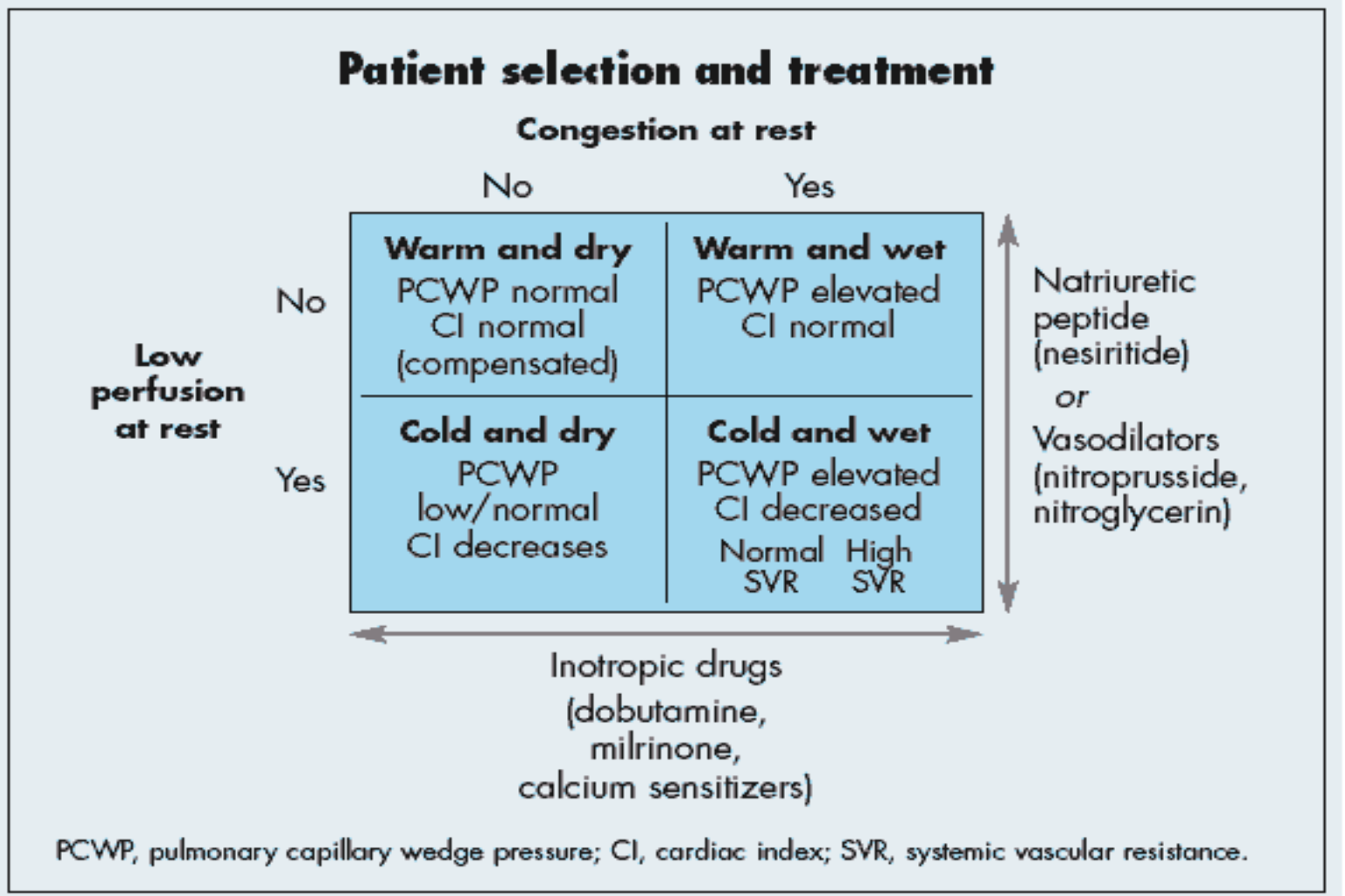


Figure – Patient selection and treatment are based on physical findings of congestion and perfusion state. (Adapted from Nohria A et al. *JAMA*. 2002.[2])

Management Strategies

Management Strategies for Type 1 HRS: The cold, wet patient

- There are **no** medical therapies that have been shown to directly increase the GFR (manifested clinically by a decline in serum creatinine) in patients with HF.
- On the other hand, improving cardiac function can produce increases in GFR, indicating that types 1 and 2 CRS have substantial reversible components

Evidence suggesting that improvement in cardiac function is associated with improved renal function in patients with types 1 and 2 CRS comes from studies of left ventricular assist devices (LVADs) and cardiac resynchronization therapy:

A study of 4917 patients with continuous-flow LVADs enrolled in the INTERMACS registry demonstrated improvements in serum creatinine and reductions in blood urea nitrogen (BUN) among patients with baseline moderate or severe renal dysfunction. Improvements in estimated GFR (eGFR) were noted within one month of LVAD implantation and persisted over a two-year period of follow-up [15]. However, a separate analysis of data from the INTERMACS registry found that early improvements in eGFR with LVAD use were transient and typically only sustained for a period of weeks to months. *Prevalence and prognostic importance of changes in renal function after mechanical circulatory support.AUBrisco MA, Kimmel SE, Coca SG, Putt ME, Jessup M, Tang WW, Parikh CR, Testani JM SOCirc Heart Fail. 2014;7(1):68. Epub 2013 Nov 8.*

Analysis of data from an observational study and from the MIRACLE trial found that 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) ie type 2 CRS*Response to cardiac resynchronization therapy in patients with heart failure and renal insufficiency.AUAdelstein EC, Shalaby A, Saba S SOPacing Clin Electrophysiol. 2010;33(7):850.*

Pharmacotherapy

Diuretics

- The effect of diuretic-induced fluid removal on the glomerular filtration rate (usually estimated from the serum creatinine) is variable in patients with HF
  - Some patients have an increase in serum creatinine that is presumed to be mediated at least in part by a reduction in renal perfusion due to a decline in cardiac output induced by the fall in cardiac filling pressures
  - Some patients have no change in serum creatinine that may reflect maintenance of cardiac output perhaps because they are on the flat part of the Frank-Starling curve where changes in LV end-diastolic pressure have little or no effect on cardiac performance

Some patients have a reduction in serum creatinine mediated perhaps in part by one or both of the following mechanisms:

- Reductions in intraabdominal and renal venous pressures.
- Reduction in right ventricular dilatation, which may improve LV filling and function via ventricular interdependence (alleviation of the reverse Bernheim phenomenon).

Among patients with decompensated HF, the best outcomes occur with aggressive fluid removal even if associated with mild to moderate worsening of renal function. Support for aggressive fluid removal comes from the following studies:

Trials of Diuretic Therapy

- A study of 336 patients with decompensated HF in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial found that hemoconcentration(accomplished with diuretics) was associated with worsening renal function as well as a lower mortality rate
- An analysis of data from the EVEREST (Efficacy of Vasopressin Antagonism in heart Failure Outcome Study with Tolvaptan) trial demonstrated that hemoconcentration was associated with greater risk of in hospital worsening renal function, though renal parameters generally returned to baseline within four weeks of discharge [37]. **Despite this association, every 5 percent increase in-hospital hematocrit change was associated with a decreased risk of all-cause mortality**

Loop Diuretic: Bolus or Drip

- No single intravenous dosing regimen (bolus versus continuous infusion; high dose versus lower dose) has been shown to be superior to others.
- The best data come from the DOSE trial, which was included in the NICE meta-analysis [3]. The trial randomly assigned 308 patients to receive furosemide administered intravenously via either a bolus every 12 hours or continuous infusion and at either a low dose (equivalent to the patient's previous oral dose) or a high dose (2.5 times the previous oral dose).
  - There was no significant difference in efficacy or safety end points for bolus versus continuous infusion. Patients assigned to intravenous bolus therapy were more likely to require a dose increase at 48 hours; however, the total dose of furosemide over 72 hours in the bolus group was not significantly different from that in the continuous infusion group (592 versus 480 mg, p = 0.06).
  - High-dose furosemide, compared with low-dose furosemide, produced greater net fluid loss, weight loss, and relief from dyspnea but also more frequent transient worsening of renal function (23 versus 14 percent). There was no significant difference in patients' global assessment of symptoms in the high-dose group (p = 0.06); the mean change in the serum creatinine was less than 0.1 mg/dL (9 micromol/L) in both groups.

- Just give diuretics to remove volume !

These findings provide support for the recommendation included in the 2013 American College of Cardiology/American Heart Association HF guidelines that the goal of diuretic therapy is to eliminate clinical evidence of fluid retention such as an elevated jugular venous pressure and peripheral edema. The rapidity of diuresis can be slowed if the patient develops hypotension or worsening renal function. However, the goal of diuretic therapy is to eliminate fluid retention even if this leads to asymptomatic mild to moderate reductions in blood pressure or renal function.

ACE Inhibitors/ARNI

- Clinical trials of renin-angiotensin-aldosterone system (RAAS) antagonists in HF have not specifically focused on patients with the type 1 CRS.
- Subgroup analyses of patients with and without chronic kidney disease (CKD) as well as cohort studies have demonstrated that the beneficial effect of RAAS antagonism on clinical outcomes is not mitigated by concomitant CKD. (in other words, give them if and when you can) ***Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure.AUAnand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN SOCirculation. 2009;120(16):1577. Epub 2009 Oct 5.***

ACE Inhibitors

- While RAAS antagonists retain their clinical benefit in HF among patients with CKD, the risk of adverse events including hyperkalemia and worsening renal function is higher than in patients without CKD. *2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines.AUYancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL SOCirculation. 2013;128(16):1810.*

- **Monitor electrolytes frequently in the acute and chronic setting !!**

ACE inhibitors/Summary

- Use them if you can do to activation of RAAS system in the failing heart leading to Na resorption/retention. Guided by hemodynamics
- Limited role in the cold hypotensive congested patient in shock.
- Be on the lookout for hyperkalemia and oliguric AKI
- If they survive their cardiogenic shock, make every attempt to Rx on discharge with close attention to electrolytes within 5 days of discharge or sooner if CKD.

Nitroglycerin: Vasodilators

- (ADHERE) database of almost 100,000 patients defined worsening renal function as a rise in serum creatinine between admission and discharge of more than 0.5 mg/dL (44 micromol/L) or more than 0.3 mg/dL (27 micromol/L) with a serum creatinine more than 1.5 mg/dL (133 micromol/L)
- The rate of worsening renal function was significantly higher when intravenous diuretics were given with nitroglycerin or nesiritide compared with intravenous diuretics alone (relative risk 1.20 and 1.44, respectively). **However, a causal effect could not be distinguished from patients requiring combination therapy having more severe HF**.
- Makes sense to use them including nitroprusside in certain clinical settings. Hypertensive crisis, acute AR/MR, septal rupture, etc.

Nesiritide

- Randomized trials have yielded conflicting results on the effect of nesiritide therapy on renal function in the treatment of acute decompensated HF.
- The largest trial, ASCEND-HF, found no change in risk of worsening renal function with nesiritide therapy (continuous infusion at 0.01 microg/kg per min with an optional initial loading dose of 2 microg/kg) [46]. Similarly, the Renal Optimization Strategies Evaluation (ROSE) trial 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
- ***Gottlieb SS, Stebbins A, Voors AA, et al. Effects of nesiritide and predictors of urine output in acute decompensated heart failure: results from ASCEND-HF (acute study of clinical effectiveness of nesiritide and decompensated heart failure). J Am Coll Cardiol 2013; 62:1177***

Nesiritide

- For most patients hospitalized with acute HF, recommendation is **not** treating with nesiritide (Grade 1A).
- In carefully selected patients with appropriate hemodynamics (without hypotension or cardiogenic shock) who remain symptomatic despite routine therapy, a trial of nesiritide may be helpful as an alternative to other vasodilator therapy (nitroglycerin or nitroprusside).

Beta-Blockers

- The mechanism of benefit from beta blocker therapy in patients with heart failure with reduced ejection fraction (HFrEF) is likely related to reducing detrimental effects of catecholamine stimulation and HF such as elevated heart rate, increased myocardial oxygen demand, production of inflammatory cytokines, adverse remodeling, downregulation of myocardial beta-1-receptor density, arrhythmia promotion, and stimulation of vasoconstrictors.
- Use of certain beta blockers (carvedilol, metoprolol succinate, or bisoprolol) in patients with HFrEF reduces hospitalizations for HF and improves survival.

Beta-Blockers

- For patients with severe decompensation (eg, severe volume overload and/or requiring inotropic support), suggest withholding beta blockers.
- For patients with moderate-to-severe decompensation or hypotension, suggest decreasing or withholding beta blocker therapy.
- For patients with mild decompensation without hypotension or evidence of hypoperfusion, we suggest continuation of beta blocker as tolerated.

Inotropes

- Intravenous administration of inotropic drugs, such as dobutamine, dopamine, and milrinone, has a role in the treatment of cardiogenic shock in a subset of patients with acute decompensated heart failure.
- However, both routine use of short-term intravenous therapy in patients with acute decompensated HF and prolonged therapy have been associated with an increase in mortality.

Dopamine

- The clinical efficacy and safety of dopamine for preservation of renal function in patients with HF has not been established.
  - The Renal Optimization Strategies Evaluation (ROSE) trial also tested the hypothesis of whether low-dose dopamine (2mcg/kg/min) (n = 122) would improve urine output and renal function compared to placebo (n = 119) among patients hospitalized with HF and concomitant renal disease [47]. **Low-dose dopamine did not enhance decongestion or improve renal function when added to diuretic therapy.**

Inotropes

- An adverse mortality effect of milrinone was also suggested in a retrospective analysis from the Acute Decompensated Heart Failure (ADHERE) national registry [11].
- After attempted adjustment for differences in risk, milrinone and dobutamine were associated with increased mortality compared to patients who were treated with nitroglycerin or nesiritide.
- However, since sicker patients were treated with the inotropes, one cannot know if the adjustments were sufficient.
- *In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE).AUAbraham WT, Adams KF, Fonarow GC, Costanzo MR, Berkowitz RL, LeJemtel TH, Cheng ML, Wynne J, ADHERE Scientific Advisory Committee and Investigators, ADHERE Study Group SOJ Am Coll Cardiol. 2005;46(1):57.*

Use in cardiogenic Shock: Cold hypotensive, wet patient

- The role of inotropes in patients with CRS is uncertain and the routine use of inotropes cannot be recommended given their lack of proven efficacy and their association with adverse events when used outside of selected patients with cardiogenic shock or acute decompensated HF.

Ultrafiltration/Hemodialysis

UF/HD

- Three randomized trials (UNLOAD, RAPID-CHF, and CARESS-HF) compared ultrafiltration to diuretic therapy in patients with acute decompensated HF
  - In UNLOAD and RAPID-CHF, ultrafiltration was associated with a significantly greater rate of fluid loss than diuretic therapy but no difference in serum creatinine.
  - In CARESS-HF, ultrafiltration was compared to stepped pharmacologic therapy (including bolus plus high doses of continuous infusion loop diuretics, addition of thiazide diuretic [metolazone], and selected intravenous inotrope and/or vasodilator therapy) in patients with worsening renal function and persistent congestion [54]. Although weight loss was similar in ultrafiltration and stepped pharmacologic therapy groups, ultrafiltration therapy caused an increase in serum creatinine and a higher rate of adverse events.

Thus, although ultrafiltration may be helpful for fluid removal in acute decompensated HF in patients unresponsive to diuretic therapy, the available evidence does not establish ultrafiltration as first line therapy for acute decompensated HF or as an effective therapy for CRS

Two New Actors

- Two other classes of drugs have been evaluated in the treatment of HF, with no proven effect on kidney function: antagonists of the vasopressin receptors, which mediates the antidiuretic response, and antagonists of the adenosine A1 receptor.
  - The effect of tolvaptan on cardiovascular outcomes and decongestion in patients with acute HF was evaluated in the EVEREST Outcome trial [57]. **Tolvaptan had no effect on the co-primary end points of all-cause mortality, mortality or HF hospitalization, or seven-day patient global assessment.** However, there were significant benefits in a number of secondary end points including an increase in urine output, resulting in reduced dyspnea and edema and an increase in serum sodium

Adenosine Antagonists

- Adenosine, acting on the adenosine-1 receptor, constricts the afferent glomerular arteriole, thereby reducing the GFR, and increases tubular sodium reabsorption [58]. Thus, selective adenosine A1 receptor antagonism can increase GFR and promote a diuresis [59], potentially acting synergistically with loop diuretics.
- In the PROTECT trial, 2033 patients hospitalized with HF and impaired renal function (mean creatinine clearance 51 mL/min) were randomly assigned to the experimental selective A1 adenosine antagonist rolofylline or to placebo [60]. **During the study period, there was no difference between the groups in cardiovascular outcomes or in the rate of persistent worsening of renal function, which was defined as an increase in serum creatinine of 0.3 mg/dL (27 micromol/L). In addition, rolofylline therapy was associated with a higher rate of neurologic events (seizure and stroke).**

Summary

- Given the limitations imposed by impaired renal function on the ability to correct volume overload and the strong association between impaired or worsening renal function and adverse clinical outcomes in patients with HF, it is possible that effective treatment of the cardiorenal syndrome (CRS) would improve patient outcomes.
- On the other hand, the worse prognosis associated with CRS could primarily reflect a reduced GFR being a marker of more severe cardiac disease. In this setting, improving renal function alone would not necessarily improve patient outcomes.
- **Still much to be done and learned**.

Summary

- Reduced glomerular filtration rates (GFR) are common in patients presenting with heart failure (HF) and are associated with increased mortality.
- A systematic review found that mortality increased by approximately 15 percent for every 10 mL/min reduction in estimated GFR.
- These patients are **sick !!!**

Summary

- A fall in GFR during treatment of HF has often been associated with increased mortality in clinical studies in which the mortality risk increased progressively with the degree of worsening renal function.
- However, other evidence suggests that patient outcomes may be improved with aggressive fluid removal even if accompanied by a rise in serum creatinine.

Summary

- There are no medical therapies that have been shown to directly increase GFR in patients with the CRS.
- On the other hand, improving cardiac function can produce increases in GFR, indicating that types 1 and 2 CRS have substantial reversible components.
  - LVAD, Cardiac Resynchronization

Summary

- ICU monitoring
- Oxygen, opiates, mechanical ventilation, nitrates, nitroprusside(hypertensive crisis and acute valvular/septal emergencies)
- Diuretics – Bolus/Gtt no difference. Just give them.
- No unique role for Nesiritide
- Hemodynamics guide choices about beta-blockade, ACE inhibitors, Inotropes
- RRT and Uf for selected patients with azotemia, uremia, acidosis, diuretic resistance, etc.

Summary

- Think outside the box
  - Revascularization
  - IABP
  - Pericardial Procedures
  - Cardioversion/Pacing
  - LVAD
  - Sick patients – reach out to your nearest friendly cardiologist !!!!

Patron Saint of Nephrology

Thank You