UPDATE ON CARDIO-RENAL SYNDROME

15/05/2023

Definition

- Condition in which therapy to relieve congestive symptoms of heart failure is limited by a decline in renal function
- Previously thought to be from reduction in renal blood flow
- Cardiorenal interactions occur in both directions and in a variety of clinical settings

Classification

- Type 1 - (Acute) Acute heart failure results in acute kidney injury
- Type 2 - Chronic cardiac dysfunction causes progressive CKD
- Type 3 – Abrupt and primary worsening of kidney function (renal ischemia or GN) causes acute cardiac dysfunction (HF)
- Type 4 – Primary CKD contributes to cardiac dysfunction (CAD, HF or arrhythmia)
- Type 5 – Acute or Chronic systemic disorders (sepsis or Diabetes) that cause both cardiac and renal dysfunction.

Prevalence

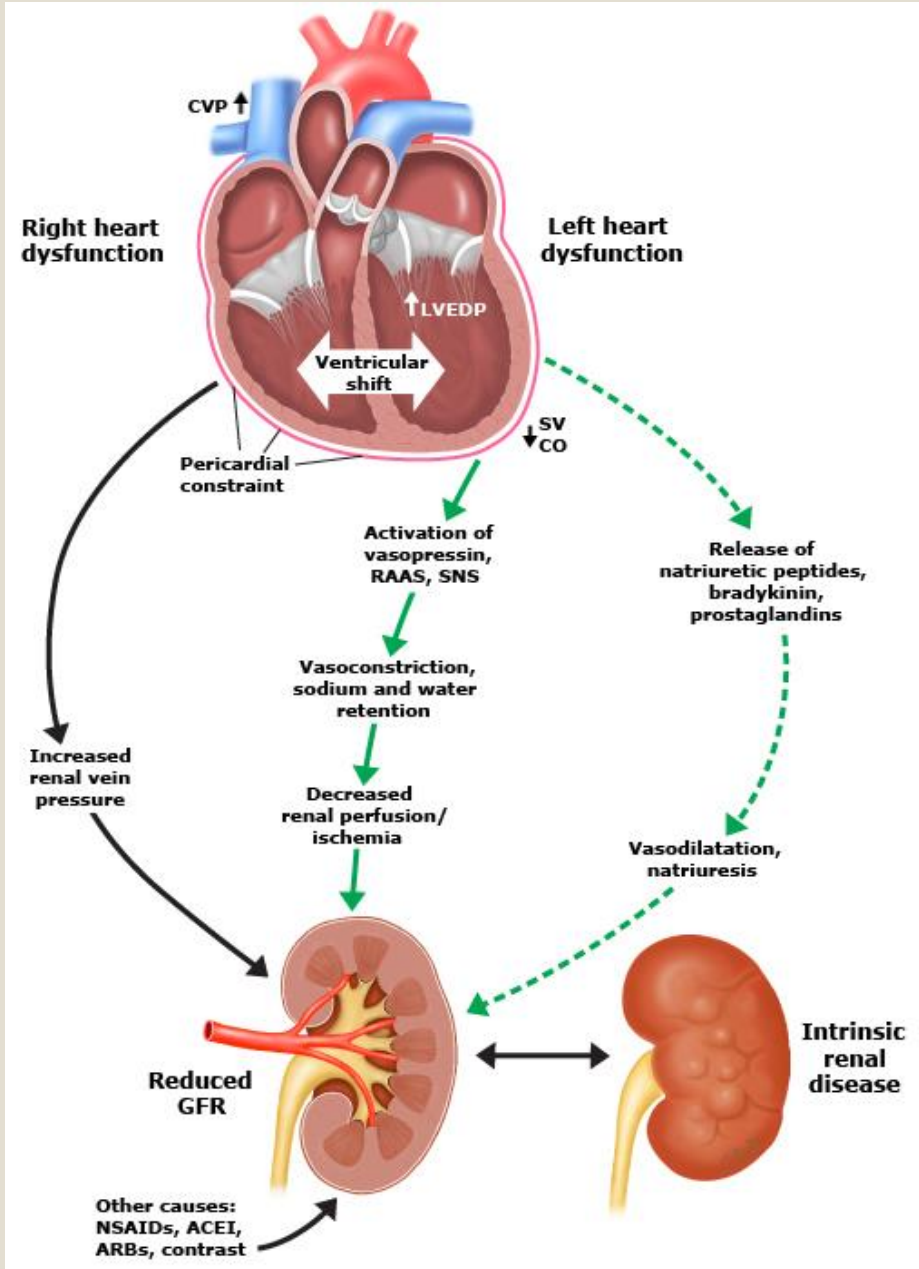
- 30 t0 60% in patients with HF have moderate to severe renal impairment (GFR <60 ml/min/1.73m2)
- Systemic review (80,000) hospitalized or nonhospitalized patients with HF have moderate to severe kidney impairment was present in 29%
- Acute Decompensated Heart Failure National Registry - >100,000 patients with HF requiring hospital admission – 30% had diagnosis of CKD)eGFR <55 ml/min/1.73m2
- Risk factors or WRF – prior history of HF, Diabetes, admission creatinine >133 umol/L, uncontrolled hypertension

Diagnosis

- Serum creatinine/eGFR
- Distinction between underlying CKD and CRS may be difficult
- Some may have both
- Proteinuria, casts, small kidneys on imaging – CKD
- Elevated BUN/Creatinine ratio – HF is a cause of pre-renal
- U Na - <25 mmol/L expected with HF (concurrent diuretic use)
- U Na profiling – can predict diuretic responsiveness

Pathophysiology

- Incompletely understood
- Likely a diverse group of pathophysiologically distinct process with worsening renal function as common pathway
- Prognosis is likely dependent on mechanism behind a rising creatinine
- Major mechanisms include
  - Neurohumoral adaptation
  - Reduced renal perfusion
  - Increased renal venous pressure and right ventricular dysfunction


CVP
Right heart dysfunction
Left heart dysfunction
LVEDP
Ventricular shift
SV
CO
Pericardial constraint
Activation of vasopressin, RAAS, SNS
Release of natriuretic peptides, bradykinin, prostaglandins
Vasoconstriction, sodium and water retention
Increased renal vein pressure
Decreased renal perfusion/ ischemia
Vasodilatation, natriuresis
Reduced GFR
Intrinsic renal disease
Other causes: NSAIDs, ACEI, ARBs, contrast

Neurohumoral adaptations

- Impaired LV function - reduced stroke volume, cardiac output, arterial underfilling, elevated atrial pressures, and venous congestion
- Trigger a variety of compensatory neurohormonal adaptations
- Sympathetic nervous system and RAS, increases vasopressin (antidiuretic hormone), and endothelin-1 which promote salt and water retention and systemic vasoconstriction
- Preservation of perfusion to vital organs (the brain and heart) via arterial vasoconstriction in other circulations, including the renal circulation and by increasing myocardial contractility and heart rate

Chloride Handling

- Plays important role in fluid homeostasis, neurohormonal activation and diuretic resistance
- Primary modulator of tubuloglomerular feedback
- Evidence suggests primary determinant of changes in plasma volume and in activation of RAS
- In acute HF receiving diuresis, hypochloremia is frequently accompanied with metabolic alkalosis leads to inappropriately attributed to intravascular volume depletion
- Characterized by elevated urinary chloride level

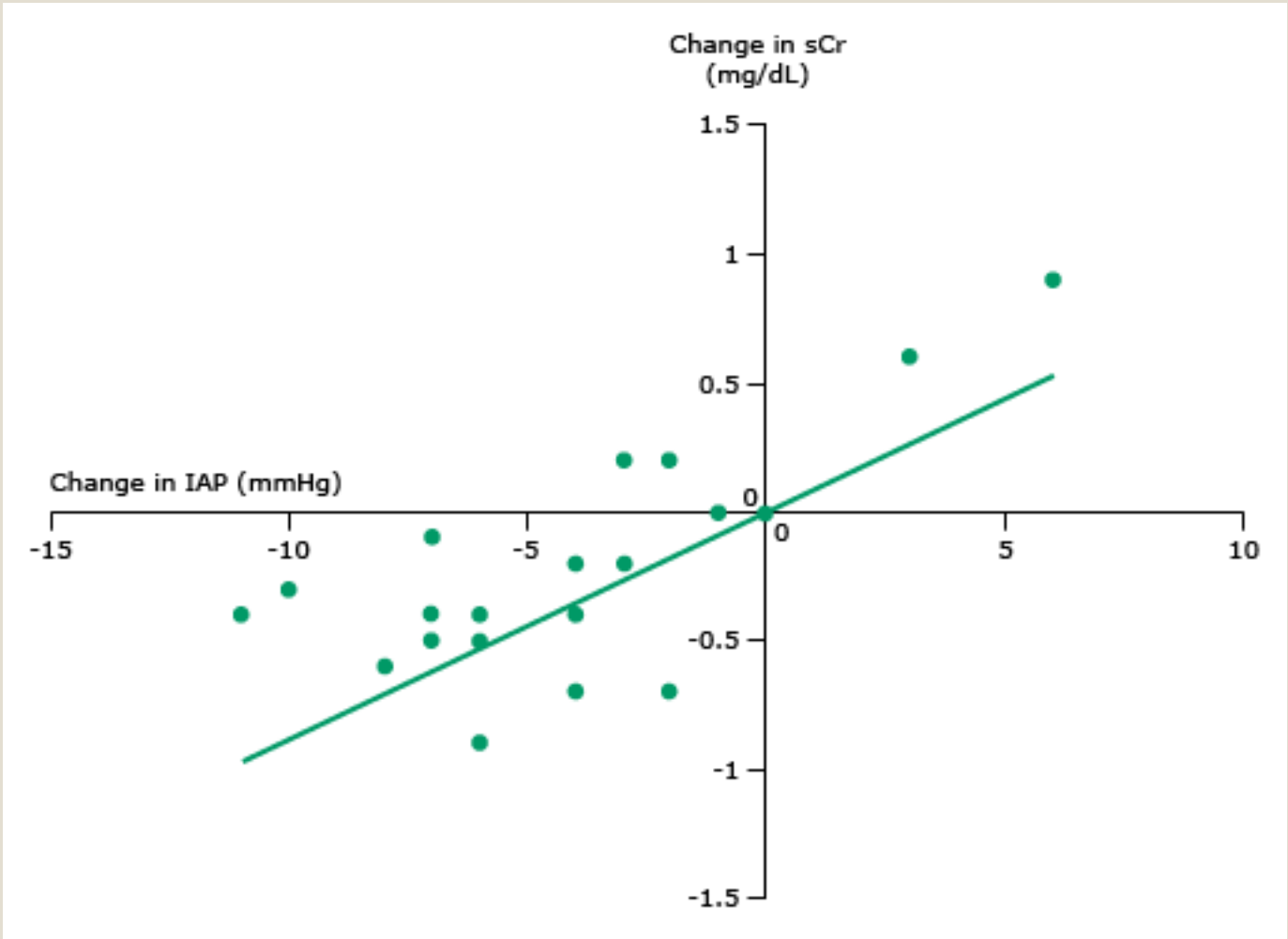
- Coadministration of acetazolamide with loop diuretics can reduce chloride loss

Reduced renal perfusion

- Reduced systemic blood pressure – associated with WRF
- Reduced cardiac index is not the primary driver
- ESCAPE trial - no correlation between the cardiac index and either the baseline GFR or worsening kidney function
- ESCAPE trial - weak but significant inverse correlation between cardiac index and estimated GFR (eGFR), higher cardiac index was paradoxically associated with worse eGFR
- ADHERE registry (>100,000 patients), 50% had a systolic blood pressure of 140 mmHg or higher, while less than 2% had a systolic blood pressure below 90 mm/Hg

Increased renal venous pressure
Right ventricular dilation and dysfunction

- Both animal and human studies have shown that increasing intra-abdominal or central venous pressure, which should also increase renal venous pressure, reduces the GFR
- mechanisms by which increased renal venous pressure might lead to a reduction in GFR are not well understood
- Right ventricular dilation and dysfunction - impairs left ventricular (LV) filling, and therefore forward output
- Increased pressure within a distended RV increases LV extramural pressure, reducing LV transmural pressure for any given intracavitary LV pressure and inducing leftward interventricular septal bowing, thereby diminishing LV preload and distensibility and reducing forward flow


Change in sCr
(mg/dL)
1.5
1
0.5
0
-0.5
-1
-1.5
Change in IAP (mmHg)
-15
-10
-5
0
5
10

Associations with heart failure with preserved ejection fraction

- Renal dysfunction is frequently seen in patients with HFpEF
- Endothelial dysfunction and a proinflammatory state have emerged as important mediators
- Renal dysfunction can lead to metabolic derangements resulting in systemic inflammation and microvascular dysfunction, which can cause cardiomyocyte stiffening, hypertrophy, and interstitial fibrosis
- Study shows association between WRF and reduced RV function and increased RV free wall thickness - ?causality

Prognosis

- Reduced baseline GFR – mortality rate increases with mild to moderate and severe reduction in eGFR
- Estimated that mortality increased by 15% for every 10 ml/min reduction in eGFR
- Change in GFR during therapy for HF – all cause mortality higher in patients with WRF compared to those with unchanged or slightly increased 43 vs 36%
- Blood urea nitrogen – associated with increased mortality in patient with HF
- Microalbuminuria – increased in event rates in patients with HFrEF but not with ARNI associated UACR

Management

- No medical therapies shown to directly increase GFR in patients with HF
- Reduced eGFR could primarily be a marker of more severe cardiac disease.
- Improving cardiac function in type 1 and 2 CRS suggests reversible components
- LVADs (INTERMACS) and cardiac resynchronization therapy (MIRACLE) improves serum creatinine and eGFR

Diuretics

- Loop diuretic as first-line therapy for patients with volume over load (peripheral or pulmonary oedema)
- Decongestive efficacy is better with urine out-put guided diuretic adjustment over standard therapy – greater weight change (more net fluid loss after 24 hours
- Effect of diuretic-induced fluid removal on GFR is variable

– Some: increase in creatinine (reduced renal perfusion)

-- Some: no change ion creatinine (flat curve of starling curve)

-- Some: reduction in creatinine – (reduction in intraabdominal and renal venous pressure +/- reduction in RV dilation

Evidence

- Best outcomes may occur with aggressive fluid removal even if associated with mild to moderate WRF
- ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness)

  - Hemoconcentration was associated with WRF (OR 5.3), but also associated with lower 180 day mortality (HR 0.16)

- EVEREST (Efficacy of Vasopressin Antagonism in heart Failure Outcome Study with Tovaptan)

  - Hemoconcentration was associated with in-hospital WRF but return to normal 4 weeks post discharge with reduced all cause mortality (HR 0.81)

RAS antagonists

- ACE inhibitor, ARNI (angiotensin receptor-nephrilysin inhibitor) or ARB – standard part of therapy for HF with reduced EF
- Associated with symptomatic improvement, reduced hospitalization for HF, enhanced survival
- Not generally associate with improvement in renal function
- Most have moderate reduction in GFR – can be ameliorated by reducing diuretic dosing.
- Threshold of eGFR decline after initiation of RAS antagonists remains a challenging question.
- SOLVD – up to 15% eGFR decline with enalapril was still associated with significant mortality benefit!

ARNI (PARADIGM -HF trial)

- Decrease in eGFR compared to ACE inhibitor was less with ARNI (PARADIGM-HF)
- Slower rate of of decreased in eGFR compared with Enalapril (7.8 vs 10.2 ml/min)
- Benefit was consistent in patients with or without CKD (including CKD3B)
- Sacubitril-Valsartan was well tolerated with similar adverse events compared to Irbersartan

Sodium-glucose co-transporter 2 inhibitor

- In patients with HFrEF but not HFpEF SGLT2 inhibitors reduce risk of cardiovascular and kidney outcomes
- EMPEROR-Reduced (Empagliflozin) and DAPA-HF (Dapagliflozin) - combined renal end point was reduced in SGLT2 inhibitor arm (HR 0.62, 95% CI 0.43 – 0.01; p = 0.013)
- In patients with HFpEF treatment with Empagliflozin was not found to improve renal outcome.

Primary pharmacologic therapy for heart failure with reduced ejection fraction

- Angiotensin receptor-neprilysin inhibitor (ARNI, ie, sacubitril-valsartan); ACE inhibitor, or ARB
- Beta blocker
- Mineralocorticoid receptor antagonist (MRA)
- Sodium-glucose co-transporter 2 (SGLT2) inhibitor
- Sequence of therapy – add drug sequentially
- Adding an agent before dose optimization - the addition of other agents (ie, MRAs, SGLT2 inhibitors) may have a greater effect on reducing mortality in HFrEF

Summary

- CRS is increasingly recognized
- Maximize HF treatment is essential for prognosis
- Congestion should be treated regardless of WRF
- Urine out put guided diuretic treatment is preferred
- Urinary Na profiling may be helpful if available