Chronic Kidney Disease and heart failure:
How to get it right!

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• Research/ travel/ educational grants:
  • Menarini, Baxter, Roche, Novartis, Amgen, Shire, Servier, Abbott
• CARI guidelines for Renovascular disease
• Principal investigator for aHUS Registry
Kevin and his partner had different ways of looking at things.

"When I pay for a second opinion, I expect it to be different!"
Figure 1 | Putative pathophysiologic connections in cardiorenal syndrome. Abbreviations: AT-II, angiotensin II; AVP, arginine vasopressin; FGF23, fibroblast growth factor 23; IAP, intra-abdominal pressure; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species.
Cardio renal syndrome: Agenda

• Burden of the problem?
• How to dissect it into sub-types
• How to apply the pathogenesis and determine logical management
• What works, what doesn't
• Individualised approach suited for particular patient
Definition: Cardio-Renal Syndrome (CRS)

• Bidirectional interaction between heart – kidney disease

• “acute or chronic dysfunction in one organ may **INDUCE (NOT JUST CO-EXISTENCE)** acute or chronic dysfunction of the other”
Burden of disease

Inpatient:
• 1 million Americans are hospitalized with acute decompensated heart failure each year
• One third have renal dysfunction (ADHERE Study: n=100,000)

Outpatient:
• One third with known cardiac failure patients (NYHA class 3-4) have CKD
• 80% of ESRF patients had cardiac diseases
  • ischemic heart disease (IHD) (39%)
  • congestive heart failure (40%)
  • arrhythmia (31%)
In-Hospital rise in creatinine in creatinine admitted with heart failure

Risk factors for CRS

• Hypertension
• Diabetes
• Severe vascular disease
• Elderly age
• Past history of:
  ➢ Heart failure
  ➢ Renal dysfunction
  ➢ Heart failure and renal dysfunction
Prognosis:

- Baseline creatinine
- Elevated creatinine at admission and worsening creatinine during hospital stay associated with prolonged hospital / HDU stay and mortality.
- Nearly half the ESRF patients die from CV events
- Nearly half the patients commenced on hemodialysis suffer acute myocardial event in the first 2 years
Previous definitions

• Bongartz et al: (2002)

  “patients with coexisting severe cardiac and renal dysfunction”

• National Heart, Lung, and Blood Institute (2004):

  “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”
**Acute Dialysis Quality Initiative (ADQI) consensus classification (2008): Ronco et al**

<table>
<thead>
<tr>
<th>CRS type</th>
<th>Name</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acute cardiorenal</td>
<td>Acute cardiac dysfunction leading to acute kidney injury</td>
<td>Acute coronary syndrome causing acute heart failure and then renal dysfunction</td>
</tr>
<tr>
<td>2</td>
<td>Chronic cardiorenal</td>
<td>Chronic heart failure leading to renal dysfunction</td>
<td>Congestive cardiac failure</td>
</tr>
<tr>
<td>3</td>
<td>Acute renocardiac</td>
<td>Acute kidney injury leading to acute cardiac dysfunction</td>
<td>Uraemic cardiomyopathy secondary to acute renal failure</td>
</tr>
<tr>
<td>4</td>
<td>Chronic renocardiac</td>
<td>Chronic renal failure leading to cardiac dysfunction</td>
<td>Left ventricular hypertrophy and diastolic heart failure secondary to renal failure</td>
</tr>
<tr>
<td>5</td>
<td>Secondary</td>
<td>Systemic condition causing cardiac and renal dysfunction</td>
<td>Septic shock, vasculitis</td>
</tr>
</tbody>
</table>
Pathophysiology

Two broad categories

• "hemodynamic factors"
  ➢ low cardiac output, low compliance of heart
  ➢ elevation of intra-abdominal and central venous pressures

• "non-hemodynamic" factors or "cardiorenal connectors"
Change in intra abdominal pressure with diuresis and serum creatinine.

Central venous pressure (CVP) and estimated GFR

Pathophysiology

Two broad categories

- "hemodynamic factors"
  - low cardiac output, low compliance of heart
  - elevation of intra-abdominal and central venous pressures

- “non-hemodynamic” factors or "cardiorenal connectors"
  - Neuro - hormonal (Renin-angiotensin-system activation and sympathetic activation)
  - NO-ROS dysbalance, Inflammatory factors etc....
Case 1:

- 65-year-old male
- Background of severe heart failure and chronic kidney disease (baseline creatinine 190 mmol/L, eGFR of 23 mLs/min)
- Admitted with acute decompensated heart failure (ADHF).
- Creatinine on admission was similar to baseline,
- Week 2: urea 51.1 mmol/L, creatinine 503 mmol/L
- Needed inotropic support and haemofiltration in high dependency.
- Week 7: Succumbed to progressive pump failure

Cardio renal syndromes type 1 and 2
Acute Cardio renal syndrome (Type 1)
Chronic Cardio renal syndrome (Type 2)
Case 2:

- 53 year male
- 2 weeks history of low urine output, lethargy, nausea and haemoptysis
- Exam: flaps and pulmonary oedema
- Creatinine: 1135 mcmol
- Echo: Global systolic dysfunction: EF = 35%
- Renal biopsy: Crescentic Glomerulonephritis (Pred and Cyclophosphamide)
- Haemodialysis for 3 weeks: stopped
- Echo: EF: 55%, normal systolic function

Reno-cardiac syndrome (type 3)
Acute Reno-cardiac syndrome (Type 3)
Case 3:

- 62 year old lady
- Diabetic End stage kidney disease on peritoneal dialysis
- Pre-dialysis ECHO: Severely impaired systolic dysfunction
- 6 months later: ECHO: Markedly improved systolic function

Cardio renal syndrome type 4
Chronic reno-cardiac syndrome type 4
Cardiomyopathy in CKD

LV Pressure overload

Hypertension
Arteriosclerosis
Aortic stenosis

AV fistula
Anaemia
Volume overload

Uraemic state

LV Volume overload

CKD

Maladaptive cardiomyocytes
Cardiomyocytes death

Diminished perfusion
Malnutrition
Uraemia
Hyperparathyroidism

LV dilatation >>>> Systolic dysfunction
Myocardial fibrosis >>> Diastolic dysfunction
Molecular pathogenetic mechanisms of Uraemic Cardiomyopathy

- Increase in circulating cardiotonic steroids (Ouabain and Marinobufagenin)
- Diabetes, CKD, ESRD
- Activation of PI3K- Akt pathway
- Insulin resistance
- Cell survival, growth proliferation, cell migration, angiogenesis
- LVH, Uraemic cardiomyopathy

Molecular insights into uremic cardiomyopathy: cardiotonic steroids and Na/K ATPase signaling
Kennedy DJ, Malhotra D, Shapiro JI, Cell Mol Biol (Noisy-le-grand), 2006
Case 4:

• 30 year old lady
• Uro-septic shock, on inotropic support and antibiotics
• Echo: Severely impaired systolic function
• Recovered

Secondary Cardio renal syndrome
Secondary cardio renal syndrome (type 5)
Management:
Depends to certain extent on the type of CRS

**Acute**
- Diuretics
- Renin-angiotension- aldo axis blockade
- Vasodilators
- Aquaresis and Ultrafiltration
- Dialysis
- ? Inotropes

**Chronic**
- Diuretics
- Renin-angiotension- aldo axis blockade
- Correction of anaemia
- Correction of Fe deficiency
- Dialysis
Diuretics

• Mainstay with option of loop diuretics or sequential diuretics or mineralocorticoid blockade
• Limited clinical data
• Chronic use leads to neurohumoral activation (RAAS, Sympathetic NS)
• Diuretic resistance and ‘Braking Phenomenon’
• Progressive and gradual diuresis rather than aggressive diuresis
• Bolus lasix vs IV infusion: Cochrance review: Salvador et al, 2004
  ➢ Better urine output
  ➢ Less ototoxicity was less
  ➢ Reduced duration of hospitalization
• Can be combined with salt poor albumin / hypertonic saline

Licata et al, Amer Heart Journal 2003
Paterna et al, Eur J of Heart fail, 2000
Fliser et al, Kidney Int, 2005
Diuretic infusion dose based on GFR

<table>
<thead>
<tr>
<th>Diuretic</th>
<th>Moderate renal insufficiency</th>
<th>Severe renal insufficiency</th>
<th>Heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximal intravenous dose (mg)</td>
<td>IV Loading dose (mg)</td>
<td>Infusion rate (mg/hr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl &lt;25 ml/min</td>
<td>CrCl 25–75 ml/min</td>
</tr>
<tr>
<td>Furosemide</td>
<td>80–160</td>
<td>40–80</td>
<td>20 then 40</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>4–8</td>
<td>1–2</td>
<td>1 then 2</td>
</tr>
<tr>
<td>Torsemide</td>
<td>20–50</td>
<td>10–20</td>
<td>10 then 20</td>
</tr>
</tbody>
</table>
Treatment - ACE inhibitors and AT-2 antagonist, renin antagonist, aldosterone antagonist

• Vasodilators: if hypertensive (decrease pre and/or afterload)
• SOLVD and CONSENSUS trials: CHF with moderate renal insufficiency,
• Improved outcomes if intra-vascular volume depletion can be avoided
• Cease if hypotension, intolerance, refractory hyperkalemia or sustained rise in creatinine
Treatment: Vasodilators:

- if hypertensive (decrease pre and/or afterload)
- Nitoglycerine infusion

- Nesiritide: Recombinant BNP
  - dilates arteries and veins, induces sodium excretion, and suppresses the RAAS
  - Improved cardiac failure symptoms but no change in renal function
  - no significant effect on outcome or quality of life

- Low dose dopamine

VMAC trial, Fusion I and II trials
Treatment: Inotropes

- If severe low cardiac output and renal hypoperfusion
- Dobutamine, milrinone, levosimendin
- May exacerbate myocardial ischemia and oxygen demand
- No proven benefit (OPTIME-CHF Study)
Anaemia and Cardiomyopathy
Cardio renal syndrome Type 2

Reduced endogenous erythropoetin (Epo)

Decreased marrow responsiveness to Epo

TNF α, IL 6

Functional Fe deficiency

Anemia
Anemia and CRS: Role of erythropoietin

• Increased mortality, length of hospital stay, and hospital readmission rates compared with non-anaemic patients with HF
• Heart Failure (OPTIMIZE-HF) registry, 51% of the nearly 50 000 patients with HF had hemoglobin \( \leq 12 \text{ g/dL} \)
• Hemoglobin is an antioxidant
• HEART: Erythropoietin can prevent apoptosis and increase the number of cardiomyocytes
• KIDNEYS: Erythropoietin has on nitric oxide synthesis, it does appear to decrease oxidative stress
Does correction of anaemia help CRS?

- Correction of Hb to > 12 g/L with Epo and iv Iron Sucrose
  - NYHA and LVEF improved *
  - Serum creatinine did not change
  - Rate of hospitalization fell *
  - Reduced mortality *
  - Reduced doses of oral and IV furosemide *
  - Reverses LVH and LVMI *

Silverberg et al, J Amer Coll Cardiol 2001
Stenvinkel et al, 2003
Fe deficiency - Cardiomyopathy
Fe deficiency ------ Cardiomyopathy

- Anemia leads to compensatory increase in cardiac output to maintain oxygen delivery
- Transition from a high-output cardiac state to a state of LV dysfunction appears to begin at a Hb of 70 g/L. Pegelow et al 1977
- Cardiomyopathy also occurred in iron-deficient rats that were not anemic.
- Fe deficient cardiomyopathy animal models has low myocardial Fe concentrates.
- Iron moieties also bind to myoglobin, a total-body iron deficit could impair myocytes’ ability to extract oxygen from circulating hemoglobin.
- FAIR-HF trial: IV Iron associated with improved functional status

Anker et al, NEJM, 2009
Ultrafiltration? Peritoneal dialysis? Hemodialysis?

I don’t care what day it is. Four hours is four hours.
Why treat?

• LVH is the earliest stage of UC
• LVH independent risk factor morbidity and mortality
• Regression associated with improved survival
• Hemodialysis regresses LVH, improves systolic function and LVEF

Ultrafiltration (UF) or aquapheresis:

- Diuretic resistance
- Larger and faster removal of fluid without inducing hypotension
- ‘CARRESS-HF’ trial (2012):
  - Inferior to diuretics: recruitment stopped
- ‘UNLOAD’ trial (2007):
  - Reduced rate of readmission
  - Did not improve renal perfusion, urine output or GFR
When should we commence long term dialysis
Lower eGFR at dialysis initiation is associated with lower mortality

Kaplan–Meier survival curves in subgroups based on quintile levels of eGFR at dialysis initiation.

Hwang et al, NDT 2010

“Lower eGFR at dialysis initiation is associated with lower mortality”
Early vs late initiation of dialysis

Higher eGFR at dialysis initiation was associated with higher mortality

2012: Initiating Dialysis Early and Late (IDEAL) trial: Cooper et al

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Early-Start Group (N = 404)</th>
<th>Late-Start Group (N = 424)</th>
<th>Hazard Ratio with Early Start (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Events</td>
<td>No. of Events/100 Patient-Yr</td>
<td>No. of Events/100 Patient-Yr</td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td>Primary outcome: death from any cause</td>
<td>152</td>
<td>155</td>
<td>1.04 (0.83–1.30)</td>
<td>0.75</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite cardiovascular events</td>
<td>139</td>
<td>127</td>
<td>1.23 (0.97–1.56)</td>
<td>0.09</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>63</td>
<td>71</td>
<td>0.94 (0.67–1.32)</td>
<td>0.70</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>47</td>
<td>37</td>
<td>1.39 (0.91–2.15)</td>
<td>0.13</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>33</td>
<td>29</td>
<td>1.21 (0.73–2.00)</td>
<td>0.45</td>
</tr>
<tr>
<td>Hospitalization with new-onset angina</td>
<td>42</td>
<td>39</td>
<td>1.15 (0.75–1.78)</td>
<td>0.52</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>9</td>
<td>4</td>
<td>2.36 (0.73–7.68)</td>
<td>0.15</td>
</tr>
<tr>
<td>Composite infectious events</td>
<td>148</td>
<td>174</td>
<td>0.87 (0.70–1.08)</td>
<td>0.20</td>
</tr>
<tr>
<td>Death from infection</td>
<td>39</td>
<td>28</td>
<td>1.46 (0.90–2.38)</td>
<td>0.12</td>
</tr>
<tr>
<td>Hospitalization for infection</td>
<td>135</td>
<td>170</td>
<td>0.81 (0.65–1.02)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

“elective earlier initiation of dialysis was not associated with improved clinical outcomes or quality of life”
Proposed benefits of peritoneal dialysis therapy for heart failure

- Continuous gentle ultrafiltration with minimal impact on hemodynamic status
- Improvement in functional status and symptoms of volume overload
- Reduction in number of days of heart failure-related hospitalizations
- Restoration of diuretic responsiveness
- Reduction in weight and improvement in volume status
- Improvement in left ventricular ejection fraction
- Sodium sieving effect and possibility of better control of natremia
- Removal of pro-inflammatory mediators (medium-sized molecules)
- Reduction in intra-abdominal pressure in patients with severe ascites
- Improvement in quality of life
- Improved atherogenic lipid serum profile
- Lack of impact on neurohormonal activity (renin-angiotensin-aldosterone system and sympathetic nervous system)
- Improved control of serum potassium level (hence providing the opportunity to use medications such as aldosterone receptor blockers)
- Reduction in healthcare cost
## Role of peritoneal dialysis in heart failure

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Mean age (yr)</th>
<th>Male gender</th>
<th>NYHA class</th>
<th>EF</th>
<th>Renal function</th>
<th>Main findings</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koch et al[11]</td>
<td>Prospective</td>
<td>118</td>
<td>73.2</td>
<td>60.2%</td>
<td>III (49.2%)</td>
<td>43.5%</td>
<td>Creatinine clearance 19.2 mL/min</td>
<td>Significant improvement in body weight and NYHA class</td>
<td>Negligible incidence of peritonitis and catheter dysfunction</td>
</tr>
<tr>
<td>Núñez et al[8]</td>
<td>Prospective</td>
<td>25</td>
<td>75.1</td>
<td>72%</td>
<td>III or IV (100%)</td>
<td>40%</td>
<td>eGFR 33 mL/min per 1.73 m²</td>
<td>Significant improvement in patients' clinical status and NYHA class</td>
<td>Marked reduction in the number of days hospitalized for acute heart failure</td>
</tr>
<tr>
<td>Bertoli et al[12]</td>
<td>Multicenter retrospective</td>
<td>48</td>
<td>74</td>
<td>81%</td>
<td>II (6%)</td>
<td>30%</td>
<td>eGFR 21 mL/min per 1.73 m²</td>
<td>Significant improvement in NYHA class and reduction in the number of days hospitalized</td>
<td>Significant reduction in pulmonary artery pressure and improvement in EF</td>
</tr>
<tr>
<td>Courivaud et al[10]</td>
<td>Retrospective</td>
<td>126</td>
<td>72</td>
<td>69%</td>
<td>N/A</td>
<td>38%</td>
<td>eGFR 33.5 mL/min per 1.73 m²</td>
<td>Significant reduction in the number of days hospitalized for acute heart failure</td>
<td>Improvement in cardiac function in patients with an EF of 30% or less</td>
</tr>
</tbody>
</table>
Future in treatment

• Ability to diagnose early with biomarkers may hold the key
  • Neutrophil gelatinase-associated lipocalin, cystatin C, kidney injury molecule-1, N-acetyl-β-(D)glucosaminidase, and interleukin-18

• Vaptans:
  • CRS > Increase in AVP from post pituitary > V2 receptor > Na + water retention
  • Tolvaptan: EVEREST Study (2007)
  • Weight loss and reduced dyspnoea
  • But no mortality or morbidity difference
Future: contd

• Adenosine A1 antagonist:
  • KW-3902, Rolophyline
  • Adenosine levels increased in CRS > renal afferent vasoconstriction
  • ‘PROTECT ‘Study (2008): no benefit

• Hypertonic saline:
  • CRS: expanded extracellular fluid volume and contracted arterial blood volume with resultant regional perfusion abnormalities
  • Osmotic shift of extravascular fluid into intravascular space
  • Adjunct to diuretics
  • Achieves salt and water removal, lower morbidity and mortality in small trials

Licata et al, Amer Heart Journal 2003
Paterna et al, Eur J of Heart fail, 2000
Take home messages:

• Cardio renal syndrome: an umbrella term for mutually propagating disease and **NOT** just association

• **Classification** helps understand the pathophysiology and define specific management plan

• Mainstay would be **RAAS blockade and diuretics**

• Most interventions have achieved to improve symptomatology but **none till date to improve renal function**

• Individualised prescription based on specific clinical scenario.

• Logical therapeutic maneuvers have failed to show clinical benefit

• Have we understood the disease spectrum well enough?
“The people who bind themselves to systems are those who are unable to encompass the whole truth and try to catch it by the tail; a system is like the tail of truth, but the truth is like a lizard; it leaves its tail in your fingers and runs away knowing full well that it will grow a new one in a twinkling.” (Ivan Turgenev to Leo Tolstoy)