Cardiorenal Syndrome
*a famous unknown cluster*

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**Overview**
- Introduction
- Risk factors of CVD: Role of CKD
- CRS syndrome
  - Classification: definition and pathophysiology
  - Biomarkers – current and future
  - Preventive approaches
- Conclusions

CVD – cardiovascular disease, CKD – chronic kidney disease, CRS – cardiorenal syndrome

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**Introduction**
- The heart – kidney interaction is far more complex and intricate than that of a simple pump and filter
- Epidemiological data have demonstrated a close relationship between cardiorenal disease and clinical outcome

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**Introduction**
- Chronic kidney disease (CKD) has remained largely a 'silent' epidemic
  - May be regarded as a clinical model of accelerated vascular disease and premature ageing, and
  - Risk-factor profile changes during the progression from mild/moderate CKD to ESRD

ESRD – end stage renal disease


**Introduction**
- Cardiovascular disease remains the major cause of mortality and morbidity in patients with advanced CKD
  - The mechanisms for cardiotoxicity are multiple
  - Identifying high-risk patients remains a challenge

*J Ren Care. 2010 May;36 Suppl 1:68-75*
Introduction

Given, the poor long-term outcome of dialysis patients who do not receive renal transplantation and the lower supply of donor kidneys relative to demand, optimal selection of renal transplantation candidates is crucial. This requires a clear understanding of the validity of cardiac tests in this patient group.

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Introduction

Premature cardiovascular disease (CVD), including:

- stroke
- peripheral vascular disease
- sudden death
- coronary artery disease and
- congestive heart failure is a notorious problem in patients with chronic kidney disease.


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Cardiovascular Risk Factors in CKD—A Complicated Puzzle with Many Pieces

Figure. Schematic presentation of traditional and novel (or uremia-specific) cardiovascular risk factors in chronic kidney disease.


List of cardiovascular risk factors in CKD (proven or hypothesized)

<table>
<thead>
<tr>
<th>Traditional risk factors</th>
<th>Chemical Risk Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>—</td>
</tr>
<tr>
<td>Male gender</td>
<td>—</td>
</tr>
<tr>
<td>Hypertension</td>
<td>—</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>—</td>
</tr>
<tr>
<td>Smoking</td>
<td>—</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>HbA1c [32] glucose [33]</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Oleic acid [34] fatty acid [35]</td>
</tr>
</tbody>
</table>

HbA1c, glycated hemoglobin; Lp(a), lipoprotein(a);

Figure 1. The frequency and time course of developing an increase in creatinine in patients hospitalized with HF. The percent of patients with an increase (by that time in the hospitalization) in creatinine of at least the value indicated is shown.

Figure 2. The relationship between changes in IAP with diuresis and the change in serum creatinine.

Figure 3. Distribution of central venous pressure (CVP) and the relationship between CVP and estimated GFR in 2507 patients.

Figure 4. The change in blood pressure after radiofrequency ablation of renal sympathetic nerves.

Figure 5. Postulated mechanisms underlying the relationship between HF and renal dysfunction.

Cardiorenal syndrome (CRS)

- CRS:
  - Conventionally defined as...
  - Condition characterized by the initiation and/or progression of renal insufficiency secondary to HF
  - Also used to describe the negative effects of reduced renal function on the heart and circulation (more appropriately named renocardiac syndrome)
Cardiorenal syndrome (CRS)

Definitions...

However,
- Older definitions of CRS have been challenged recently as advances in the basic and clinical sciences have changed our understanding of organ crosstalk and interactions.
- Of interest is that some therapies may have efficacy in the prevention and treatment of both cardiac and renal injury.

Recently, a new definition has been proposed which focuses on the complexity of the interrelationship of heart and kidney,
- including an emphasis on which organ is the initiator of functional damage and which organ is indirectly affected.
- To address the inherent complexity of cardiorenal functional deficits and to stress the bi-directional nature of these heart-kidney interactions,
  - This new classification of the CRS includes five subtypes whose terminology reflects their primary and secondary pathology, time frame and simultaneous cardiac and renal dysfunction.

The CRS can thus be generally defined as a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of one organ may induce acute or chronic dysfunction of the other...

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

CRS: Types

Type I: Definition
- An abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive HF) leading to AKI.

Type I: Pathophysiology and definition

Acute cardio-renal syndrome (type I): acute worsening of heart function leading to kidney injury and/or dysfunction.

Type I: Pathophysiology
**CRS: Types**

- **Type II: Definition**
  - Chronic abnormalities in cardiac function (e.g. chronic congestive HF) causing progressive chronic kidney disease...

- **Type II: Pathophysiology**

- **Type III: Definition**
  - An abrupt worsening of renal function (e.g. acute kidney ischaemia or glomerulonephritis) causing an acute cardiac disorder (e.g. HF, arrhythmia, ischaemia).
CRS: Types

- **Type IV: Definition**
  - State of chronic kidney disease (e.g., chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events

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- **Type IV: Pathophysiology**

  *International Journal of Nephrology* Volume 2011, Article ID 762590

- **Type V: Definition**
  - Systemic condition (e.g., sepsis) simultaneously causing both cardiac and renal dysfunction.

  *Circ J* 2010; 74: 1274 – 1282

- **Type V: Pathophysiology**

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The complicated puzzle of uremic CVD

Red – traditional (i.e., Framingham) risk factors
Blue – inflammatory biomarkers
Green – endothelial dysfunction
Orange – vascular ossification
Brown – surrogate oxidative markers
Purple – adiopkines
Grey - others

Laboratory Biomarkers in Heart Failure

Cardiac biomarkers in CKD
- Identifying serum biomarkers that are useful in
- profiling cardiovascular risk and
- enabling stratification of early mortality and cardiovascular risk is
  an important goal in the treatment of patients with CKD

Current biomarkers in CRS

BNP and NT-proBNP
- BNP belong to a family of vasopeptide hormones that have major role in regulating BP and volume through direct effects on the kidney and systemic vasculature and represent a favorable aspect of neurohumoral activation
- Three different families:
  - A-type (atrial) natriuretic peptide
  - B-type (brain) natriuretic peptide (BNP) and
  - C-type natriuretic peptide

BNP and NT-proBNP
- BNP is synthesized as an amino acid precursor protein and undergoes intracellular modification to a prohormone (proBNP) that
  - Comprises 108 amino acids and is secreted from the left ventricle (LV) in response to increased myocardial wall stress
  - On release into the circulation, proBNP is cleaved in equal proportions into
    - the biologically active 32–amino acid BNP, which represents the C-terminal fragment, and
    - the biologically inactive 76–amino acid N-terminal fragment (NTpro- BNP)
BNP and NT-proBNP

In the systemic circulation, BNP mediates different biologic effects through interactions with the natriuretic peptide receptor type A, causing intracellular cGMP production, and is eliminated from plasma by binding to the natriuretic peptide receptor type C or through proteolysis by neutral endopeptidases.

Although these enzymes are found in the kidney, glomerular filtration has only a minor role in the elimination of BNP.


Mean BNP as it relates to GFR.

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Cardiac troponins

- Troponins T, I, and C are components of the contractile apparatus of muscle
- Specific forms of troponin T and I are present in the heart muscle, namely cTnT and troponin I (cTnI), and are released into the circulation with myocardial injury
- Thus, measuring circulating cTnT and cTnI levels using high-sensitivity assays has become the gold standard approach in diagnosing acute myocardial necrosis

Mechanisms of Elevated Cardiac Troponins in Patients with ESRD

- There is emerging evidence that
  - Increases in cTnT in asymptomatic patients with ESRD indicate subclinical myocardial necrosis or injury

N-Acetyl-β-(D)Glucosaminidase (NAG)

- Recognized over thirty years ago, NAG is a lysosomal brush border enzyme found in proximal tubular cells
- It is a large protein (>130 kD) and is therefore not filtered through the glomerular membrane
- NAG has been shown to function as a marker of AKI, reflecting particularly the degree of tubular damage
- It is not only found in elevated urinary concentrations in AKI and CKD but also in diabetic patients, patients with essential hypertension and heart failure

Other markers

- The overproduction and release of pro-inflammatory cytokines, particularly tumour necrosis factor-alpha, interleukin (IL)-1 and IL-6, have been shown to exert an effect on ongoing myocardial cell injury
- However, due to the non-specific nature of many of these cytokines as well as difficulty in measurement, they are not routinely used in the clinical arena
Other markers

- Catalytic Iron
- Neutrophil Gelatinase-Associated Lipocalin (NGAL)
- Cystatin C
- Kidney Injury Molecule 1 (KIM-1)
- Liver Fatty Acid-Binding Protein (L-FABP)
- Tubular Enzymuria

Markers for AKI

- AKI may be
  - Primary event that leads to cardiac dysfunction (type III CRS), or
  - Result from acute cardiac dysfunction (type I CRS)
  - Condition with an increasing incidence in hospital and ICU patients
    - Using the recent RIFLE consensus definitions and its Injury and Failure categories, AKI has been identified in close to 9% of hospital patients and,
    - Large ICU database, AKI was observed in more than 35% of critically ill patients
CRS: Preventive approaches

Type I
The basic principles include
- Avoidance of volume depletion,
- Removal of superimposed renal toxic agents (nonsteroidal anti-inflammatory agents, aminoglycosides),
- Minimization of the toxic exposure (iodinated contrast, time on cardiopulmonary bypass), and
- Possibly the use of antioxidant agents such as
  - N-acetylcysteine (for contrast exposure) and B-type natriuretic peptide in the perioperative period after cardiac surgery.

Type I
More broadly across all forms of CRSs Type I, consideration should be given for forms of
- Continuous renal replacement therapy (CRRT) in the period of time surrounding the renal insult.
  - Conceptually, the use of CRRT provides 3 important protective mechanisms that cannot be achieved pharmacologically as follows:
    1. Ensures euvolemia and avoids hypo- or hypervolemia,
    2. Provides sodium and solute (nitrogenous waste products) removal, and
    3. By both mechanisms above, it may work to avoid both passive renal congestion and a toxic environment for the kidneys and allow their optimal function during a systemically vulnerable period.

Type II
As a general axiom,
- Pharmacologic therapies that have been beneficial for chronic CVD have been either neutral/favorable to the kidneys including use of
  - Renin angiotensin aldosterone system (RAAS) antagonists,
  - Beta-adrenergic blocking agents, and
  - Statins.

Type II
Other strategies
- Modestly beneficial from a cardiac perspective have even a larger benefit on microvascular injury to the kidneys includes
  - Glycemic control in diabetes and
  - Blood pressure control in those with hypertension.

There is some support from clinical trials that
- Fibric acid derivatives may preferentially reduce rates of microalbuminuria in patients with CKD
  - The long-term clinical implications of these observations are unknown.
CRS: Preventive approaches

Type III
The major management principle concerning this syndrome is
- Intra- and extravascular volume control with either
  - Use of diuretics and
  - Forms of extracorporeal volume and solute removal
    - CRRT, ultrafiltration, hemodialysis

In the setting of AKI,
- Prevention of left ventricular volume overload is critical to
  - Maintain adequate cardiac output and systemic perfusion
  - Avoid the viscous downward spiral in both cardiac and renal function

Type IV
Optimal treatment of CKD with
- Blood pressure and glycemic control,
- RAAS blockers, and
- Disease-specific therapies, when indicated, are the best means of preventing this syndrome

Morbidities of CKD, including
- Bone and mineral disorder and anemia, should be managed according to CKD guidelines; however,
- Clinical trials have failed to demonstrate that treatment of these problems influences CVD outcomes

Type V
There are no proven methods to prevent or ameliorate this form of CRSs at this time
- Randomized trials of early versus later intervention with CRRT have shown no differential benefit
- Supportive care with a judicious intravenous fluid approach and the use of pressor agents as needed to avoid hypotension are reasonable but
  - Cannot be expected to avoid AKI or cardiac damage

Conclusions
- We summarized a newly proposed framework for CRSs in order to better understand five possible subtypes
- A description of possible heart-kidney interactions is critical to our understanding and will guide future investigations into pathophysiology, screening, diagnosis, prognosis, and management
Conclusions

- Recent studies have identified and characterized several novel biomarkers for CRSs
- It is anticipated that these biomarkers will help make an earlier diagnosis of CRSs as well as identify its specific type and potentially its pathophysiology

Conclusions

- It remains to be seen whether or not effective prevention and treatment of CRSs will improve hard renal and cardiac outcomes including
  - ESRD, hospitalizations, and death

Thank You!