CARDIORENAL SYNDROME
WHAT YOU NEED TO KNOW

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Introduction

- Cardiac and kidney diseases are prevalent and frequently co-exist.
- Primary disorders of one of these organs can result in secondary dysfunction of the other organ with significant morbidity and mortality.
- The complex interactions between the 2 organs which occur as a result of organ cross-talk has been termed Cardiorenal Syndrome.
Introduction

Although the concept of CRS was established previously, there was no consensus definition leading to non uniformity of diagnosis, treatment and preventive strategies.

In fact, treatment is often disjointed, and single-organ centred, with competing or conflicting interests amongst the different specialties.
A consensus conference was organised under the auspices of the Acute Dialysis Quality Initiative (ADQI) by bringing together key opinion leaders and experts in the fields of nephrology, critical care, cardiac surgery, cardiology and epidemiology in Venice, Italy from September 3 to 6, 2008.

Ronco et al. *Eur Heart J* 2010; 31: 703-11
## CRS - Classification

### Disorders of the heart and kidneys – the cardiorenal syndrome (CRS) and its five subtypes

**CRS, general definition**
A complex pathophysiologic disorder of the heart and kidneys where acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ.

**CRS type I (acute CRS)**
Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or acute decompensation of chronic heart failure) leading to kidney injury.

**CRS type II (chronic CRS)**
Chronic abnormalities in cardiac function (e.g. chronic heart failure) causing progressive chronic kidney disease.

**CRS type III (acute renocardiac syndrome)**
Abrupt worsening of renal function (e.g. acute kidney failure or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, or pulmonary edema).

**CRS type IV (chronic renocardiac syndrome)**
Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events.

**CRS type V (secondary CRS)**
Systemic condition (e.g. diabetes mellitus or sepsis) causing both cardiac and renal dysfunction.

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Ronco C. Cardiorenal Med 2011; 1: 3-4
Acute cardiac decompensation leading to acute kidney injury
CRS Type 1

- Acute cardiac events that may contribute to acute kidney injury include
  - acute coronary syndrome
  - cardiogenic shock
  - acute decompensated heart failure
  - cardiac surgery
CRS Type 1 - Pathophysiology

- Low cardiac output -> arterial underfilling
- Elevation of intra-abdominal and central venous pressures -> venous congestion
- Neuro-hormonal and inflammatory activation
CRS Type 1 - Pathophysiology

CRS Type 1 - Pathophysiology

Ismail Y et al. Sem Nephrol 2012; 32: 18-25
CRS Type 1 - Treatment

- Clinical challenge with no real consensus regarding its appropriate management
- Many of the therapies for heart failure including diuretics, can have deleterious effects on the kidneys
CRS Type 1 - Treatment

- It is not uncommon to have contradictory recommendations from cardiologists and nephrologists.
- From a cardiac perspective, the treatment of heart failure often relies on large doses of diuretics and afterload reduction aimed at optimising preload and afterload; as a result of volume depletion, renal function worsens.
- Conversely, treatment with volume to preserve renal function leads to pulmonary and systemic congestion and worsening heart failure.
CRS Type 1 - Treatment

- Principle: Preservation of renal function should receive the same priority as maintaining cardiac function
- Treatment should be targeted towards adequate intravascular volume management and ensuring proper renal perfusion at the same time
- Challenge is to find a delicate balance between these 2 interconnected systems
Diuretics

- Use of loop diuretics may be associated with electrolyte abnormalities, further neurohormonal activation and worsening renal function
- They may also increase the risk of developing adverse effects with concomitant medications, eg ACE-I, ARB, aldosterone antagonists
Volume control in CRS Type 1

- Ultrafiltration
- Nesiritide
- Vasopressin antagonists
- Adenosine A₁ antagonists
How can we strike a balance between removing volume to relieve congestion and yet avoiding the adverse effects of diuresis/ultrafiltration?
Is there a role for biomarkers?

Figure 3. Chronologic association of SCr and novel biomarkers in predicting renal insufficiency. (A) Time-course of decrease in GFR as compared with increase in SCr. (B) Comparison of traditional late approach versus proposed biomarker early approach in the diagnosis of post-cardiac surgery AKI. Modified from Herget-Rosenthal et al.¹⁸⁴ and Hudson et al.¹⁷²

CRS Type 1 - Fluid management

- Management of fluid balance can be aided by clinical evaluation, biomarkers, bioimpedance analysis and blood volume monitoring (for patients requiring dialysis/ultrafiltration)

CRS Type 1 - Treatment

- Inotropic agents should be considered in patients with low output states in the presence of signs of hypo-perfusion or congestion despite the use of vasodilators and/or diuretics
- Avoid nephrotoxic agents
CRS Type 2

Chronic heart failure causing progressive chronic kidney disease
CRS Type 2 - Pathophysiology

- Chronic poor forward flow from the heart leading to renal hypoperfusion
- Systemic venous congestion resulting in reduced renal perfusion
- Activation of RAAS with eventual fibrosis and negative myocardial remodelling
Therapeutic choices are often aimed at reducing congestion and volume overload, yet have the undesired effect of worsening ongoing renal dysfunction.

Drugs that inhibit the RAAS (e.g., ACE-I) reduce the progression of both heart failure and chronic kidney disease.

Avoid nephrotoxic agents.
CRS Type 3

Acute kidney injury leading to acute cardiac disorders
CRS Type 3 - Pathophysiology

Figure 1. Pathophysiology of CRS type 3 and the potential vicious cycle.

Chuasuwan A et al. Sem Nephrol 2012; 32: 31-9
Prevention of Acute Kidney Injury

- Identify high risk patients
- Avoid hypotension, dehydration, nephrotoxic agents
Management Strategies for the Kidney in CRS Type 3

- Ascertain etiology of AKI & manage accordingly
- Avoid further renal insults
- Monitor and treat complications of AKI
- Appropriate drug dosing
- Avoid volume overload as continued fluid administration to fluid-overloaded AKI patients is an important mechanism of CRS Type 3
- RRT if indicated
- No specific pharmacological therapies have shown consistent benefit in preventing or attenuating AKI with or without CRS
Management Strategies for the Heart in CRS Type 3

- Core management principle is intravascular and extravascular volume control with use of either diuretics or various forms of extracorporeal therapy (isolated ultrafiltration, slow continuous ultrafiltration, continuous renal replacement therapy)
Chronic Kidney Disease leading to cardiac dysfunction
The association between CKD and increased risk for cardiac diseases has long been recognised.

Cardiovascular disease accounts for close to 50% of all deaths in all age groups of CKD patients.
CVD in CRS Type 4

- Ischemic coronary events
- Heart failure
- Left ventricular hypertrophy
- Arrhythmias
- Sudden death
Figure 2. Adjusted hazard ratios for cardiovascular events according to baseline GFR. Adjusted for multiple variables (see text). Plotted using data from Go et al.9

House A. Sem Nephrol 2012; 32: 40-8
CRS Type 4 - Pathophysiology

Figure 3. Pathophysiologic mechanisms of CRS type 4. BMI, body mass index; EPO, erythropoietin; LDL, low-density lipoprotein. Figure modification by Rob Frewell, reproduced with permission from Ronco et al.21

House A. Sem Nephrol 2012; 32: 40-8
CRS Type 4 - Treatment

- Traditional CV risk factors – obvious targets for therapy
- Additional management strategies have mostly targeted those risk factors that are peculiar or exaggerated in CKD patients eg anemia, mineral and bone disorders, albuminuria, hyper-homocysteinemia, malnutrition etc
CRS Type 4 - Treatment

- Large RCT of interventions (eg correction of anemia, lipid lowering therapies) that were predicted to be fruitful based on sound observational studies in ESRF patients have been mostly negative, or if positive, their results have been muted compared with the general population.

- It could be that CRS type 4, particularly in the ESRF population is such a complex disorder that it will be difficult for studies of single interventions to show positive results, because each targeted risk factor may represent only the tip of the iceberg.

- Perhaps aggressive management of multiple risk factors will be required to change the course of this devastating syndrome and future trials of such multi-pronged strategies are needed.
CRS Type 5

Systemic conditions causing both cardiac and renal dysfunction
There are many clinical situations in which both organs are targeted simultaneously by systemic illnesses, either acute or chronic.

This subtype does not have a primary or secondary organ dysfunction.

Aim is to identify diagnostic and interventional strategies that can address common pathways of organ injury.
## Conditions causing acute CRS Type 5

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sepsis</strong></td>
<td>Malaria, Leptospira, HIV, Parvovirus B19, Cytomegalovirus, Coxsackie virus, Schistosoma haematobium, Toxoplasmosis</td>
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<tr>
<td><strong>Infections</strong></td>
<td>SLE, Systemic sclerosis, APS</td>
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<td><strong>Connective tissue disorders</strong></td>
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<td><strong>Electric shock</strong></td>
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<td><strong>Drugs</strong></td>
<td>Cocaine, Heroin, Calcium channel blockers, Cisplatin, Methotrexate, Mitomycin</td>
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Soni S et al. *Sem Nephrol* 2012; 32: 49-56
Conditions causing acute CRS Type 5

- Thrombotic microangiopathy
- Toxins: Arsenic, Paraphenylene diamine, Snake bite, Scorpion bite
- Wegener’s granulomatosis
- Pheochromocytoma
- Burkitt’s lymphoma

Soni S et al. *Sem Nephrol* 2012; 32: 49-56
## Conditions causing chronic CRS type 5

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Tuberculosis</td>
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<tr>
<td>Sarcoidosis</td>
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<tr>
<td>Fabry’s disease</td>
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<tr>
<td>SLE</td>
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<tr>
<td>Chronic liver disease</td>
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<tr>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
</tr>
<tr>
<td>Multiple myeloma</td>
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<tr>
<td>Systemic amyloidosis</td>
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<tr>
<td>Chronic lead toxicity</td>
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<tr>
<td>Post bone marrow transplant</td>
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</tbody>
</table>

Soni S et al. *Sem Nephrol* 2012; 32: 49-56
CRS Type 5 - Treatment

- Mainstay of management is treatment of the underlying etiology
- Associated cardiac and renal complications warrant appropriate therapy as indicated
Conclusion

- A new classification of CRS is now available
- This will allow concerted and coordinated efforts in an attempt to improve diagnostic accuracy, and allow formulation of therapeutic and preventive strategies, which will hopefully reduce morbidity and mortality in patients with concurrent cardiac and renal dysfunction