Pathophysiology of Cardio-Renal Interactions
Pathophysiology of Cardio-Renal Interactions

• Heart-Kidney Interactions:
  ➢ Bidirectional
  ➢ Temporally regulated (Acute and Chronic)
  ➢ Mediated by different mechanisms
  ➢ Different outcomes in specific populations
  ➢ Functional vs structural organ damage
- ADHF leading to AKI
- Cardiac Surgery
- Cardiac procedures
  - CIN
  - CPB
  - Valve replacement

- Chronic HF (systolic or diastolic) leading to:
  - CKD
  - CKD progression
  - Diuretic resistant oliguria

- Acute Kidney Injury leading to AHF
  - Volume/uremia-induced ADHF
  - Renal ischemia-induced ADHF
  - Sepsis/cytokine induced AKI and HF

- Chronic HF increasing cardiovascular mortality
- CKD increasing cardiovascular morbidity
- Chronic HF progression due to CKD
  - Uremia related HF
  - Volume related HF
Cardio-Renal Interactions
Basically a vicious circle

Primary Insult

ADHF - CHF

Physiological derangements

AKI - CKD

Renal dysfunction

Primary Insult

AKI - CKD

Physiological derangements

ADHF - CHF

Heart dysfunction
Heart-Kidney Scenarios

- CKD secondary to chronic heart failure (HF)
- AKI secondary to coronary angiography contrast induced nephropathy (CIN)
- AKI secondary to cardiopulmonary bypass (CPB)
- AKI secondary to acute or acute on chronic heart failure

Cardiovascular morbidity and mortality increased by end stage renal disease (ESRD)
- Chronic HF progression due to kidney dysfunction
  - Uremia related HF
  - Volume related HF
- Acute HF due to acute kidney dysfunction
  - Volume/uremia-induced AHF
A widely accepted classification

Cardiorenal Syndrome

Claudio Ronco, MD, ‡ Mikko Haapio, MD, † Andrew A. House, MSc, MD, ‡ Nagesh Anavekar, MD, ‡ Rinaldo Bellomo, MD, ‡
Vicenza, Italy; Helsinki, Finland; London, Ontario, Canada; and Melbourne, Australia

European Heart Journal

Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative

Claudio Ronco,1,2‡, Peter McCullough3, Stefano D. Anker4,5, Inder Anand6, Nadia Aspromonte7, Sean M. Bagshaw8, Rinaldo Bellomo9, Tomas Bert19, Ilona Bobek1, Dinna N. Cruz1,2, Luciano Daliento11, Andrew Davenport12, Mikko Haapio13, Hans Hillege14, Andrew A. House15, Nevin Katz16, Alan Maisel17, Sunil Mankad18, Pierluigi Zanco19, Alexandre Mebazaa18, Alberto Palazzuoli19, Federico Ronco11, Andrew Shaw20, Geoff Sheinfeld21, Sachin Soni21,22, Giorgio Vescovo23, Nereo Zamarreto24, Piotr Ponikowski25, Claudio Ronco and for the Acute Dialysis Quality Initiative (ADQI) consensus group

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Definition and classification of Cardio-Renal Syndromes: workgroup statements from the 7th ADQI Consensus Conference

Andrew A. House1, Inder Anand2, Rinaldo Bellomo3, Dinna Cruz4, Ilona Bobek5, Stefano D. Anker5, Nadia Aspromonte6, Sean Bagshaw7, Tomas Bert8, Luciano Daliento9, Andrew Davenport10, Mikko Haapio11, Hans Hillege12, Peter McCullough13, Nevin Katz14, Alan Maisel15, Sunil Mankad16, Pierluigi Zanco17, Alexandre Mebazaa18, Alberto Palazzuoli19, Federico Ronco20, Andrew Shaw20, Geoff Sheinfeld21, Sachin Soni21,22, Giorgio Vescovo23, Nereo Zamarreto24, Piotr Ponikowski25, Claudio Ronco26 and for the Acute Dialysis Quality Initiative (ADQI) consensus group

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The Cardiorenal Syndrome

Claudio Ronco a Chang-Yin Chiong a Mikko Haapio b Nagesh S. Anavekar c
Andrew House e Rinaldo Bellomo d

aDepartment of Nephrology, Ospedale San Bortolo, Vicenza, Italy; bHUCH Meiliaht Hospital, Division of Nephrology, Helsinki, Finland; cDepartment of Cardiology, The Northern Hospital, and dDepartment of Intensive Care, Austin Hospital, Melbourne, Vic., Australia; eLondon Health Sciences Centre, Division of Nephrology, London, Ont., Canada
Cardio-Renal syndromes

General Definition:
*Pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ induces acute or chronic dysfunction in the other*

CRS Type I (Acute Cardiorenal Syndrome)
*Abrupt worsening of cardiac function leading to acute kidney injury*

CRS Type II (Chronic Cardiorenal Syndrome)
*Chronic abnormalities in cardiac function causing progressive and permanent chronic kidney disease*

CRS Type III (Acute Renocardiac Syndrome)
*Abrupt worsening of renal function causing acute cardiac disorders*

CRS Type IV (Chronic Renocardiac Syndrome)
*Chronic kidney disease contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events*

CRS Type V (Secondary Cardiorenal Syndrome)
*Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction*
Markers of Function
BUN, Creatinine, GFR/eGFR

Markers of Damage
NGAL, Cystatin C, KIM 1
Cardio-Renal Syndrome Type 1

Hemodynamically mediated damage

Exogenous Factors
Contrast media
ACE inhibitors
Diuretics

Decreased CO
Decreased perfusion
Increased venous pressure

Sympathetic Activation

Neuro-mediated damage

RAA activation, Na + H2O retention, vasoconstriction

Hormonal factors

Natriuresis

Immune mediated damage

Cytokine secretion

Caspase activation
Apoptosis

Monocyte Activation
Endothelial activation

Acute Heart Disease

Acute decompensation
Ischemic insult
Coronary angiography
Cardiac surgery

Acute Kidney Injury

Renal hypoperfusion
Reduced oxygen delivery
Necrosis / apoptosis
Decreased GFR
Resistance to ANP/BNP

Humoral signalling
Cardio-Renal Syndrome Type 1
LCOS and Congestion

• Upon initial recognition, AKI induced by primary cardiac dysfunction implies inadequate renal perfusion until proven otherwise. This should prompt clinicians to consider the diagnosis of a low cardiac output state (LCOS) and/or marked increase in venous pressure leading to kidney congestion.
• It is important to remember that central venous pressure translated to the renal veins is a product of right heart function, blood volume, and venous capacitance which is largely regulated by neuro-hormonal systems.
• Specific regulatory and counter-regulatory mechanisms are activated with variable effects depending on the duration and the intensity of the insult.
Cardio-Renal Syndrome Type 1
Hemodynamic mechanisms

**Diseased heart**
- Increased preload
- Decreased cardiac output

**Compensatory Mechanisms**
- Vasoconstriction
- Vasodilatation

**Arterial**
- Underfilling

**Venous**
- Congestion
- Increased pressure

**Vasocostriction**

**Decreased perfusion pressure**

**Functional (Pre-renal)**

**AKI**

**Parenchymal**
Cardio-Renal Syndrome Type 1
Compensatory mechanisms in HF

Natriuresis
Afterload

HF

Natriuresis
Afterload

Compensatory
Mechanisms

Vasocostriction

Sympathetic Nervous System
R-A-A System
Arginin Vasopressin
Endothelin

Water excretion
Sodium excretion
Urea readsorption

Vasodilatation

Natriuretic Peptides
Chinin-kallicrein System
Prostaglandins
Endothelial Relaxin Factor

Water excretion
Sodium excretion
Urea readsorption
RAA SYSTEM
ANP - BNP
SYMPATHETIC NS
VASOPRESSIN
AVP in normal and failing heart

**Normal Heart**

- AVP
- Sympathetic tone decrease
- Vasodilat.
- BNP
- INCREASED ATRIAL PRESSURE

**Failing Heart**

- AVP
- Vasodilat.
- RAA
- Non-osmotic AVP release
- V1a-mediated vasocostriction
- RAA
- Water excretion
- Sodium excretion
- Urea readsorption
- Arterial underfilling
OVERHYDRATION
Time windows for AKI management

- Fluids
- Drugs
- Diuretics
- Nephroprotection?
RIFLE max and AKI outcomes

Days after hospital admission

P<0.001 (Log Rank)
The RIFLE criteria and mortality in acute kidney injury: A systematic review

Z Ricci¹, D Cruz²,³ and C Ronco²,³

¹Department of Pediatric Cardiosurgery, Bambino Gesù Hospital, Rome, Italy; ²Department of Nephrology, Dialysis and Transplantation, S Bortolo Hospital, Vicenza, Italy and ³International Renal Research Institute Vicenza (IRRIV), Vicenza, Italy

Increase in All-Cause Mortality with worse RIFLE Class

N=71,527 patients
Biology of AKI by Time-Zones

Ischemia/reperfusion → Toxicity → Damage → Cell death

Biomarkers

- Necrosis
- Apoptosis

Multiple Timezone Organ Damage Clock Display

Delayed biomarkers for kidney injury

- ↑ Serum creatinine
- ↑ Blood urea nitrogen

The clinical clock is always late
Clinical Continuum of AKI

Devarajan, Biomarkers Med 4:265-80, 2010
Structural AKI Biomarkers

• Early diagnosis of evolving AKI could result in prevention and/or earlier changes in management:
  – Prevention of disease progression either stopping harmful interventions or mitigating/avoiding exposure to the insult
  – Early therapeutic interventions designed to protect the kidney

• More accurate differential diagnosis of AKI could direct appropriate therapy of AKI (pre-renal vs renal)

• More accurate staging of AKI could help prognostic stratification and therapy of AKI
  – Serial staging of phases of AKI (evolution of the syndrome)
  – Assessment of current and future severity of injury
AKI Biomarkers

McIlroy et al, Anesthesiology 2010; 112: 998-1004
Cardio-Renal Syndrome Type 1

Hemodynamically mediated damage

Decreased CO

Decreased perfusion

Increased venous pressure

Toxicity
Vascocostriction.

Humorally mediated damage

RAA activation, Na + H2O retention, vasoconstriction

Hormonal factors

BNP

Natriuresis

Cytokine secretion

Humoral signalling

Monocyte Activation

Endothelial activation

Caspase activation

Apoptosis

Acute Heart Disease

Acute Kidney Injury

Renal hypoperfusion
Reduced oxygen delivery
Necrosis / apoptosis
Decreased GFR
Resistance to ANP/BNP

Diuretics & UF
Time Course of worsening of renal function (Creatinine increase) in hospitalized HF patients

Gotlieb et al, JACC 2008
Overhydration & congestion

Management with the “Five B”

B - Balance & BW
B - Blood Pressure
B - Biomarkers
B - Bioimpedance
B - Blood Volume
HF, Diuretics and NGAL

Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5

Diuretics

Creatinine

NGAL Warning

Stop Diuretics "5B"

NGAL

Diuretics

BNP

Diuresis

NGAL | BNP | Diuresis

0 | 500 | 1000 | 1500 | 2000

0 | 1.2 | 1.4 | 1.6 | 1.8

International Renal Research Institute Vicenza
Cardio-Renal Syndrome Type 1

Acute Heart Disease

Exogenous factors
Contrast media
ACE inhibitors
Diuretics

Humorally mediated damage

Hormonal factors

Immuno mediated damage

Caspase activation
Apoptosis

Monocyte Activation
Endothelial activation

Cytokine secretion

Natriuresis

Increased venous pressure

Toxicity
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Sympathetic Activation

Decreased CO

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Hemodynamically mediated damage

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Resistance to ANP/BNP

Acute Kidney Injury

INFLAMMATION
Current issues in AKI management

- Repair and differentiation
- Apoptosis
- Inflammation
- ATP depletion
  - Cellular injury
- Hemodynamic

GFR

Prerenal  Initiation  Extension  Maintenance  Recovery

Days
Cardiorenal Syndrome Type 1 May Be Immunologically Mediated: A Pilot Evaluation of Monocyte Apoptosis

Grazia Maria Virzi, Rossella Torregrossa, Dinna N. Cruz, Chang Y. Chionh, Massimo de Cal, Sachin S. Soni, Massimo Dominici, Giorgio Vescovo, Mitchell H. Rosner, Claudio Ronco

Department of Nephrology, Dialysis and Transplant, and Internal Medicine, St Bortolo Hospital, and IRRI - International Renal Research Institute Vicenza, Vicenza, and Division of Oncology, University of Modena and Reggio Emilia, Modena, Italy; Division of Nephrology, University of Virginia Health System, Charlottesville, Va., USA

Key Words
Cardiorenal syndrome • Acute heart failure • Apoptosis • Acute kidney injury
Cardio-Renal Syndrome Type 1
Inflammation/humoral theory

Heart Failure Patient

Plasma
Monocyte Cell Culture

Cytokines
Supernatant
R T C Colture

Apoptosis

Apoptosis
Evaluation of apoptosis and Caspase-8 activity in U937 cells after incubation with plasma from CRS Type 1 patients and healthy volunteers. Results (median, interquartile range) are given as percentage of apoptotic cells/field for apoptosis at 72h and 96h or signal to background (S/B) ratio for Caspase-8 activity at 24h.
APOPTOSIS STUDY IN CRS T.1 and CONTROLS

Evaluation of percentage of apoptosis in Monocytic cells after incubation with plasma from CRS Type 1 patients and Controls
**Fig. 3.** Evaluation of TNF-α in plasma from CRS type 1 patients and healthy volunteers.

**Fig. 4.** Evaluation of IL-6 in plasma from CRS type 1 patients and healthy volunteers.
RTC APOPTOSIS STUDY IN CRS T.1

Evaluation of percentage of apoptosis in RTC cells after incubation with supernatant from Monocytes incubated with plasma from Heart Failure Patients developing CRS Type 1 (HF/AKI) or not (HF/No AKI)

<table>
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<tr>
<th></th>
<th>MW</th>
<th>CTR</th>
<th>1B</th>
<th>2B</th>
<th>1A</th>
<th>2A</th>
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<td>16,5%</td>
<td>28,0%</td>
<td>30,8%</td>
<td>36,8%</td>
<td>47,0%</td>
<td>58,8%</td>
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</table>

- HF/No AKI: n.6
- HF/AKI: n.6

p=0.008
p=0.006
p=0.006
p=0.05
Cardio-Renal Syndrome: possible pathophysiological mechanisms of AKI following HF

Hemodynamic deterioration (congestion, ↓CO, ↓ perfusion)

Myocardial damage injury

HF progression

Neurohormonal & cytokine activation

Renal dysfunction (AKI)
CARDIORENAL SYNDROME: TYPE 2

Chronic Heart Disease

- Anemia
- Sodium and H2O retention
- Uremic solute retention
- Ca and P abnormalities
- Hypertension

Anemia, hypoxia
- RAA and sympathetic activation
- Na and H2O retention
- Ca and P abnormalities
- Hypertension, LVH

Increased susceptibility to insults

Insult and Initiation of kidney damage

Chronic hypoperfusion
- Apoptosis

Progression of CKD

Low cardiac output (CO)
- Subclinical inflammation
- Endothelial dysfunction
- Accelerated atherosclerosis

Genetic risk factors
- Acquired Risk factors
- Low cardiac output (CO)

Chronic hypoperfusion
- Increased renal vascular resistance
- Increased venous pressure
- Embolism

Sclerosis - Fibrosis
CARDIORENAL SYNDROME: TYPE 3

Acute Kidney Injury
- Glomerular diseases
- Interstitial diseases
- Acute tubular necrosis
- Acute pyelonephritis
- Acute urinary obstruction

Acute Heart Dysfunction
- Acute decompensation
- Acute heart failure
- Ischemic insult
- Arrhythmias
- Decreased CO

Humoral Signalling
- Caspase activation
- Apoptosis

Cytokine secretion
- Caspase activation
- Apoptosis

Endothelial activation
- Monocyte Activation

Electrolyte, acid-base & coagulation imbalances

Na + H2O retention

Hypertension

Sympathetic Activation

Volume expansion

Increased pre-load

Decreased GFR

RAA activation, vasoconstriction

Volume expansion
CARDIORENAAL SYNDROME: TYPE 4

CKD Stage 1-2
- Glomerular/interstitial damage

CKD Stage 3-4
- Sclerosis - Fibrosis

CKD Stage 5 - Dialysis
- Endothelial dysfunction
- Smooth muscle proliferation
- LDL oxidation
- Vascular calcification
- Oxidant stress
- Accelerated atherosclerosis

Biomarkers
- Cardiac troponin
- Natriuretic peptides
- Asymmetric dimethylarginine
- Ischemia modified albumin
- Acute phase proteins
- Serum amyloid protein A
- C-reactive protein

Anemia
- Uremic toxins
- Ca and P abnormalities
- Nutritional status, BMI
- Salt and water overload
- Chronic inflammation

Bone remodeling
- ↑ Muscle catabolism
- ↓ Appetite
- Adipocytokine production

Smoking
- Obesity
- Hypertension
- Dyslipidemia
- Homocysteinemia
- Chronic inflammation

Genetic risk factors
Acquired risk factors
Primary nephropathy
Diabetes mellitus

Cardiac remodelling
- Neurohormonal abnormalities
- Increased ischemic risk
- Left ventricular hypertrophy
- Left diastolic dysfunction
- Decreased coronary perfusion
- Inflammation
- Coronary and tissue calcification

Chronic inflammation
- Cytokine production
- Endothelial dysfunction
- Smooth muscle proliferation
- LDL oxidation
- Vascular calcification
- Oxidant stress
- Accelerated atherosclerosis

Artificial surfaces
- Contaminated fluids
- monocyte stimulation
- Cytokine production
- Insulin resistance
- Adipocytokine production

Glomerular/interstitial damage
- Sclerosis - Fibrosis
- Bone remodeling
- Acute phase reactants
- EPO resistance
- Uremic toxins
- Chronic inflammation

Nutritional status, BMI
- Salt and water overload
- Ca and P abnormalities
- Soft tissue calcification
- Na – H2O overload
- EPO resistance
- Uremic toxins
- Chronic inflammation
- Bone remodeling
- Muscle catabolism
- Appetite
CARDIORENAAL SYNDROME: TYPE 5

Systemic diseases
- Diabetes
- Amyloidosis
- Vasculitis
- SEPSIS

Heart failure
- Sympathetic system activation
- Neurohumoral stress
- Inflammation
- Hemodynamic changes
- Hypoperfusion
- Perfusion pressure ↓, RVR ↑
- Ischemia/reperfusion

Hypoxia
- Oxidative stress
- Toxemia

Exogenous toxins
- Heme proteins
- Antibiotics, contrast media
- LPS/endotoxin
- Monocyte activation
- Cytokines

Renal Insufficiency

Organ damage/dysfunction
## Cardiorenal Syndrome

### Risk Factors

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Women</td>
<td>1.41</td>
<td>(1.12-1.77)</td>
<td>.003</td>
</tr>
<tr>
<td>HTN</td>
<td>1.64</td>
<td>(1.12-2.40)</td>
<td>.003</td>
</tr>
<tr>
<td>Rales&gt;Bases</td>
<td>1.28</td>
<td>(1.02-1.61)</td>
<td>.03</td>
</tr>
<tr>
<td>HR &gt;100 bpm</td>
<td>1.34</td>
<td>(1.06-1.68)</td>
<td>.01</td>
</tr>
<tr>
<td>SCr ≥1.5 mg/dL</td>
<td>1.77</td>
<td>(1.42-2.22)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SBP &gt;200 mm Hg</td>
<td>1.63</td>
<td>(1.13-2.35)</td>
<td>.009</td>
</tr>
</tbody>
</table>

N=1,681

Risk of Cardiorenal Syndrome by Number of Risk Factors

Obesity and cardiometabolic changes

- Diabetes
  - Sleep Apnea
  - Heart Disease
- G.I. Tract Disorders
- Kidney Disease
- Obesity
- High Blood Pressure

Lean adipose tissue ➔ Obese adipose tissue

- TNF-α
- IL-6
- FFA
- Crosstalk
- Leptin
- Resistin
- Adiponectin

- Inflammation
- CRP
- Atherosclerosis
- Apoptosis
- Dysmetabolic syndrome
- Coronary artery disease
- Cardiac remodelling
- LVH-Dilatation
- Chronic ischemia
- CKD
- Fibrosis-sclerosis
CARDIO-RENAL CACHEXIA SYNDROMES

CRS TYPES 1-2
Low Cardiac output
Na and fluid overload
Chronic hypoperfusion
Embolism
Venous Congestion
Chronic inflammation
Cardiac Remodeling
Endothelial Dysfunction
Acceler. Atherosclerosis

CRS TYPES 3-4
Na and fluid overload
Chronic inflammation
Uremic Toxins
Malnutrition
Anemia
EPO resistance
pH abnormalities
Ca-P abnormalities
Lack of VDR activation
Soft Tissue calcifications

Non-oedematous weight loss of >6% of total body weight over a period of 6 or more months

Malnutrition, loss of >10% of lean tissue or percent of ideal weight <90%

CKD Progression, Apoptosis
Necrosis, Fibrosis, Sclerosis

Heart Failure, Systolic/diastolic dysfunction, Myoc.Remodelling
Cardio-Renal Syndrome

Anemia and Iron deficiency

AKI

- ↑ Arterial diameter and volume
- ↑ Arterial wall tension
- Eccentric remodelling of the arterial system

Cardiac Work
- ↑ Cardiac Output

Reduction Blood Viscosity
- Decreased Oxygen Delivery
- Increased Sympathetic Activity
- Hyperdynamic circulation

↑ Left ventricle hypertrophy
↑ Left Ventricle wall tension
Left ventricle eccentric remodelling

CKD
Cardio-Renal Syndrome

CKD and UREMIA

Acquired Risk factors
Primary nephropathy

Anemia
Uremic toxins
Ca/P abnormalities
Nutritional status, BMI
Na – H₂O overload
Chronic Inflammation

Glomerular-interstitial damage

Sclerosis - Fibrosis

Unfriendly milieu
Inflammation

Anemia & malnutrition
Ca/P abnormalities
Na – H₂O overload
Unfriendly milieu Inflammation
Cardio-Renal Syndrome
The unfriendly uremic milieu

Uremia retention products

- Insulin resistance
- Acute phase reactants
- Fetuin-A
- Adipokine production
- Appetite
- Respiratory Exchange Ratio (REE)
- Bone remodeling
- Muscle catabolism
- Endothelial dysfunction
- Monocyte adhesion
- Smooth muscle cell proliferation
- LDL oxidation
- Vascular calcification
- Oxidant stress
Cardio-Renal Syndrome
CKD and UREMIA

$$CVR_{CKD} = CVR_b \times f \left( \frac{CKD + HD}{HD \text{ techno/Dr}} + X \right)$$
Heart-kidney interactions are bidirectional, time-dependent, and the are mediated by several pathophysiological mechanisms. Pre-existing or concomitant pathological conditions represent important risk factors for developing CRS.
CONCLUSIONS

- Recognize patient subsets and risk factors
- Consider biomarkers for early identification
- Understand precipitating factors
  - Medications
  - Procedures
- Explore new avenues for CRS prevention and organ protection based on pathophysiological mechanisms