Μηχανισμοί αλληλεπίδρασης μεταξύ καρδιάς και νεφρού στο <<καρδιονεφρικό σύνδρομο>>
Ορισμός, κατάταξη, Παθοφυσιολογία και επιδημιολογία.

- Κων/νος Τσιούφη
- Ιπποκράτειο Γ.Ν.Α
Cardiorenal syndrome

Facts!

- 1/3 of HF patients suffer from mild to moderate CKD and 1/4 of them develop WRF during their hospitalization for HF.
- Renal dysfunction is an independent predictor of adverse prognosis in HF.
- SCr and GFR are not useful in recognizing the early stages of WRF or identifying either tubular or glomerular damage.
- Heterogeneity of study populations—Patients with renal dysfunction were excluded from HF studies.
- The link between renal function and acute HF is not well evaluated.
# Overview of important meta-analyses of renal impairment in HF

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>Total n</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith</td>
<td>2006</td>
<td>Acute and chronic HF</td>
<td>CKD: 80 098</td>
<td>CKD present in 63% of patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WRF: 12 634</td>
<td></td>
</tr>
<tr>
<td>Tonelli</td>
<td>2006</td>
<td>CV disease, including chronic HF</td>
<td>Total: 1 371 990</td>
<td>CKD present in 33% of patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HF: 78 272</td>
<td></td>
</tr>
<tr>
<td>Damman</td>
<td>2007</td>
<td>Acute and chronic HF</td>
<td>HF: 18 634</td>
<td>WRF occurred in 25% of patients</td>
</tr>
<tr>
<td>Clark</td>
<td>2014</td>
<td>Chronic HF patients included in RAAS-inhibitor trials</td>
<td>HF: 20 573</td>
<td>WRF occurred in 13 and 9.6% with RAAS inhibitors and placebo, respectively</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CKD: 1 076 104</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WRF: 49 890</td>
<td></td>
</tr>
<tr>
<td>Damman</td>
<td>2014</td>
<td>Acute and chronic HF</td>
<td>CKD: 1 076 104</td>
<td>CKD present in 32% of patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WRF: 49 890</td>
<td></td>
</tr>
</tbody>
</table>
Overview of renal biomarker

Veldhuisen et al, Eur Heart J 2015
# RIFLE staging of acute kidney injury

<table>
<thead>
<tr>
<th>RIFLE stage</th>
<th>GFR criteria</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>$\uparrow$ SCreat x 1.5 or $\downarrow$ GFR &gt;25%</td>
<td>$&lt;0.5\text{mL/kg/h for 6h}$</td>
</tr>
<tr>
<td>Injury</td>
<td>$\uparrow$ SCreat x 2.0 or $\downarrow$ GFR &gt;50%</td>
<td>$&lt;0.5\text{mL/kg/h for 12h}$</td>
</tr>
<tr>
<td>Failure</td>
<td>$\uparrow$ SCreat x 3.0 or $\downarrow$ GFR &gt;75% or SCreat $\geq 4 \text{mg/dL}$ or absolute $\uparrow$ SCreat $\geq 0.5\text{mg/dL}$</td>
<td>$&lt;0.3 \text{mL/kg/h for 24h}$ or anuria x 12h</td>
</tr>
<tr>
<td>Loss</td>
<td>Dialysis dependence $&gt;4$ weeks</td>
<td>-</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>Dialysis dependence $&gt;3$ months</td>
<td>-</td>
</tr>
</tbody>
</table>
## Worsening renal function in AHF: definitions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Absolute change&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Relative change&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Target value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>&gt; or ≥0.3 mg/dL</td>
<td>≥25%</td>
<td>≥2 mg/dL</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>&gt; or ≥0.5 mg/dL</td>
<td>&gt; or ≥25%</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>&gt;0.3 mg/dL</td>
<td>≥1.5 × baseline</td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>&gt;5 mL/min/year</td>
<td>≥20%</td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>&gt;0.3 mg/L</td>
<td>≥25%</td>
<td></td>
</tr>
</tbody>
</table>

*Filippatos, et al. Eur Heart J 2013*
Hearth and Kidney: dangerous liaison

Regulation of perfusion pressure and flow to periphery

Electrical activity depends on electrolytes and acid-base

Hormonal function (ANP - BNP)

Regulation of volume and BP (Na\(^+\) and H\(_2\)O)

Electrolyte and acid-base balance

Hormonal function (Erythropoiesis – Vascular tone)
The need for a consensus classification and definition that describes all the clinical conditions together with the bidirectional nature of the organ cross-talk and the time frame of the insult and sequelae emerges clearly.
What is Syndrome in medicine?

**Syndrome:** A Greek word (sun + dromos)

Syndrome is the association of several clinical recognizable features, signs, symptoms, phenomena or characteristics that often occur together, so that the presence of one or more features alerts the physician to the possible presence of the others.

While the syndrome and the associated conditions may be statistically related, they do not have a clear cause and effect relationship, ie, there is likely to be a separate underlying problem or risk factor that explains the association.

**CRS:**
No doubt about bidirectionality
But it is a syndrome?
The Cardiorenal Syndrome

Claudio Ronco1-7, Chang-Yin Chiong3, Mikko Haapio3, Nagesh S. Anavekar2, Andrew A. House4, and Rinaldo Bellomo4

1Department of Nephrology, Ospedale San Borbori, Vicenza, Italy; 2Department of Medicine, Division of Nephrology, Helsinki, Finland; 3Department of Cardiology, The Northern Hospital, and 4Department of Intensive Care, Austin Hospital, Melbourne, Vic., Australia; 5London Health Sciences Centre, Division of Nephrology, London, Ont., Canada

Widely accepted definition

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

Acute Cardio-Renal Syndrome Type 1

Acute Heart Disease or Procedures

Acute decompensation (AF, HTN, Infection)
ACS
Coronary angiography
Cardiac surgery

Acute Kidney Injury

Renal hypoperfusion
Reduced oxygen delivery
Necrosis / apoptosis
Decreased GFR
Resistance to ANP/BNP
Chronic Cardio-Renal Syndrome (Type 2)

Chronic Heart Disease

Increased susceptibility to insults

Insult and Initiation of kidney damage

Progression of CKD

Common scenario: longstanding HF leading to progressive CKD (possibly via episodes of AKI)

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

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

Chronic hypoperfusion
Increased renal vascular resistance
Increased venous pressure
Embolism

Sclerosis - Fibrosis

Apoptosis
Cardiovascular and renal disease continuums: complex interactions

- Elderly, DM, Hypertension, Obesity
- Albuminuria
- GFR ↓
- "At Risk"

ESRD
- CHF, death

LVH

End-Stage Progression
LVH vs CKD as predictors of CV events in hypertension: a Greek 6-year-follow-up study


1652 hypertensives free of CV disease were enrolled within a period of 3 yrs (1998-2000)

3.2 Fold
Severity of LVH and renal outcome

6163 Veterans with high CV risk, followed for a period of 14 years
VA medical center, Georgetown University, Washington DC

For each 42g/m² increase in LVMI there was a 45% increase for dsCr, 52% increase for GFR<30 and 58% increase for hemodialysis

In all models, baseline sCr remained a significant determinant for all studied renal outcomes

Tsioufis, ..., Papademetriou. J Hypertension November 2010
Pathophysiology of renal failure in pts with HF

- The low-flow state hypothesis
- Intraabdominal and central venous pressure elevation
- Sympathetic overactivity
- RAAS
- Oxidative injury
- Endothelial dysfunction
- Inflammation
- Cardiorenal anemia syndrome
Pathogenetic pathways linking HF with renal dysfunction

**Inflammatory**
- Inflammation
- Anemia
- Cell death
- Fibrosis/Remodelling

**Risk factors**
- Ageing
- Diabetes
- Hypertension
- Atherosclerosis

**Neurohormonal activation**

**Heart Failure**
- High central venous pressure
- Drug therapy
- Low cardiac output
- High intra-abdominal pressure

**Renal Dysfunction**
- Low urine output
- High pressure on Bowman's capsule

- Diuretics
- RAS inhibitors
- Dilatation of efferent arteriole
- Low pressure in afferent arteriole

Independent Effect of CKD on CVD Morbidity / Mortality

N=1,120,295 adults
*Age-standardized rates
†Cardiovascular event defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease per 100 person-years

Prognostic impact of WRF in ADHF

- WRF in relation to clinical status

  Hypotension, hypovolemia

  Ongoing renal venous congestion

- WRF in relation to RAAS/ACEI initiation

- WRF in relation to nephrotoxicity of drugs

- WRF in relation to diagnostic contrast agent

- WRF in relation to acute tubular necrosis
28 studies (49890 patients) investigating WRF and outcome in HF
28 studies (49890 patients) investigating WRF and outcome in HF

Predictors of the occurrence of worsening renal function in meta-analysis across studies

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Number of studies</th>
<th>Number of patients</th>
<th>Adjusted HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CKD</td>
<td>9</td>
<td>5477</td>
<td>2.17 (1.79-2.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
<td>11 611</td>
<td>1.36 (1.08-1.71)</td>
<td>0.009</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5</td>
<td>11 081</td>
<td>1.23 (1.12-1.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>5</td>
<td>9993</td>
<td>1.38 (1.14-1.68)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diuretic use</td>
<td>5</td>
<td>13 502</td>
<td>1.52 (1.07-2.15)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Impact of WRF on Clinical Outcomes in Patients With acute HF

Both elevated SCr on admission and WRF during hospitalization predict prolonged hospitalization, re-hospitalization and death

Hillege et al, Circ 2000;102:203-210
Forman et al, JACC 2004;43:61-67

Aronson D, Burger AJ. J Cardiac Fail 2010
The Role of Congestion and Its Interaction With Renal Function in Patients With Acute HF

Outcome for 1-year death or urgent heart transplantation

Congestion
Persistence of 1 or more signs or symptoms of fluid overload at discharge

- Third heart sound
- Pulmonary rales
- Jugular venous stasis
- Hepatomegaly
- Peripheral edema

26% of patients had haemoconcentration (>3% increase in Ht)
Haemoconcentration was correlated with greater risk of in-hospital WRF but renal parameters returned to baseline within 4 weeks post discharge

Kaplan–Meier curves for all-cause mortality (A) and cardiovascular mortality or hospitalization for heart failure (B) by absolute in-hospital haematocrit change quartile. Times to events were compared using log-rank tests.
Determinants and forms of WRF in HF

Filippatos et al, Eur Heart J 2014;35:416-18
Practice guidelines on RAA treatment

- An increase in creatinine of up to 50% above baseline, or 266μmol/L (3 mg/dL)/eGFR <25mL/min/1.73m², whichever is the smaller, is acceptable.

- An increase in potassium to ≤5.5mmol/L is acceptable

- If urea, creatinine, or potassium does rise excessively, consider stopping concomitant nephrotoxic drugs (e.g.NSAIDs) and other potassium supplements or K⁺ retaining agents (triamtreren, amiloride) and if no signs of congestion, reducing the dose of diuretic.

- If greater rises in creatinine or potassium than those outlined above persist despite adjustment of concomitant medications, the dose of the ACE-I (or ARB) should be halved and blood chemistry re-checked within 1-2 weeks; if there is still an unsatisfactory response, specialist advice should be sought.

- If potassium rises to >5.5mmol/L or creatinine increases by >100% or to >310μmol/L (3.5mg/dL) /eGFR <20mL/min/1.73m², the ACE-I (or ARB) should be stopped and specialist advice sought.

- Blood chemistry should be monitored frequently and serially until potassium and creatinine have plateaued.

History of research in cardiorenal interaction

Gaps in evidence
Limitations in our understanding of heart-kidney associations

Have an experienced nephrologist as a good friend

10ο Συμπόσιο
Καρδιαγγειακές Παθήσεις και Νεφρική Δυσλειτουργία 2018
με διεθνή συμμετοχή

Σάββατο 20
Ιανουαρίου 2018
Ιδρυμα Ευγενίδου,
Αθήνα

Workshop
Ο σακχαρώδης διαβήτης στην εποχή της συνδυασμένης αντιμετώπισης καρδιαγγειακών και νεφρικών νόσων
Παρασκευή
19 Ιανουαρίου, 2018