Οξεία Καρδιακή Ανεπάρκεια με συνοδό νεφρική ανεπάρκεια

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Disclosures

I have no actual or potential conflict of interest in relation to this presentation
Case

• 75 year old male
• Presents to the emergency department in April 2016
• Reports acutely worsened dyspnea at rest
• In last week progressively worsening dyspnea on exertion and weight gain 6kg
• No chest pain
Medical history - 1

- Coronary artery disease (3VD)
  - 2002 PCI LCX, RCA
  - 2003 Repeat PCI LCX, RCA due to ISR
  - 2007 PCI LAD
  - 2015 NSTEMI- PCI RCA- LVEF 50%

- Heart failure
  - 2015 Hospitalizations due to AHF (X2)
  - NYHA II
Medical history - 2

- Chronic kidney disease stage 4
  - Baseline creatinine 2.1mg/dl (eGFR 25-30ml/min/1.73m$^2$)
  - Albuminuria (333mg/24h)
  - Cause: diabetes, arterial hypertension, previous contrast-induced acute kidney injury
- Diabetes mellitus
- Arterial hypertension
- Dyslipidemia
- Obstructive sleep apnea syndrome
- Obesity (BMI=42 kg/m$^2$)
Chronic medications prior to admission

Medical therapy

– Valsartan 160 mg
– Furosemide 160mg, increased to 200mg since 1w
– Bisoprolol 5mg
– Simvastatin 40mg/ Ezetimibe 10mg
– Amlodipine 10mg
– Aspirin 100mg/clopidogrel 75mg
– Allopurinol
– Insulin
ER Physical exam results

- **General**: Dyspnea at rest, orthopnea
- **Vital signs**: BP 175/85 mm Hg
  - HR 75 bpm
  - RR 32 ipm
- **Neck**: Jugular vein distension, 10cm
- **Lungs**: Bilateral rales up to middle lung fields
- **Heart**: Regular, mild basal systolic murmur
- **Abdomen**: normal
- **Extremities**: Warm extremities, pitting edema up to knees
Admission ECG
Admission chest X-ray
Admission laboratory tests

Urea 91 mg/dL (NR=16.6-48.5 mg/dL)
Creatinine 2.6 mg/dL (NR=0.7-1.2 mg/dL)
Sodium 137 mEq/L (NR=136-146 mEq/L)
Potassium 5.0 mEq/L (NR=3.5-5.1 mEq/L)
Hemoglobin 12.8 mg/dL (NR=13.5-17.5 mg/dL)
NT-proBNP 2265 pg/ml

Arterial blood gas
pH 7.48 (NR =7.35-7.45)
PO₂ 65 mm Hg (NR=80-100 mm Hg)
PCO₂ 28 mm Hg (NR=35-45 mmHg)
HCO₃ 21 mEq/L (NR=21-28 mEq/L)
LA 47 mm    LVEDD 57 mm/ESD 35 mm/ LVEF (Simpson): 50%  
RVEDD (4-CH): 43, normal systolic function   TR 1/4, PASP 55mmHg
Case summary

• History
  – 75 year-old male
  – HFpEF (CAD, DM, AH)
  – Chronic renal disease stage 4

• Presentation
  – NYHA IV
  – “Wet and warm” profile (pulmonary and systemic congestion, preserved peripheral perfusion)
  – High SBP
  – Worsening renal function superimposed on chronic renal disease
Initial management

- Admission to the ward
- Bed rest, fluid restriction
- Oxygen by nasal cannula
- IV diuretics - (60 mg bolus IV, then 400 mg divided in 4 bolus doses: 2.5X the previous oral dose)
- IV nitrates (starting dose 0.5mg/h)
- ARB maintained
- Additional tests to exclude primary renal diseases (Fresh urine sediment, renal ultrasound, renal artery ultrasound)
Evolution in ward

After 2 hours

Symptomatically improved

Rales in 1/3 of lungs

Blood pressure: 145 / 85 mm Hg

Good response to initial diuretic regimen: urine output 400ml to initial 60mg bolus
Improving status: urine output
In-hospital evolution

• After 48 hours: Significant clinical improvement (no orthopnea in bed angle >30°), negative fluid balance

• After 72h:
  – ambulatory
  – switched to oral furosemide 250mg
  – IV nitrates discontinued

• Improving blood pressure (135/75mmHg)

• Weight loss of 8kg at discharge
In-hospital improvement of renal function
Effective decongestion: reduction of natriuretic peptide levels
Pre-discharge and discharge management

- At 4\textsuperscript{th} day valsartan increased to 240mg
- Discharge at 7\textsuperscript{th} day
- Scheduled for outpatient clinic evaluation in the next 2-3 weeks
- Scheduled for a consultation with a nephrologist and diabetologist

**Oral CV meds at discharge**

- Valsartan 240 mg
- Furosemide 250mg
- Bisoprolol 5mg
- Isosorbide Mononitrate 60mg
- Amlodipine 10mg
- Simvastatin 40mg/ezetimibe 10mg
- Aspirin 100mg/clopidogrel 75mg
Clinical profiling in AHF

ESC HF guidelines 2016

Hypoperfusion **is not synonymous** with hypotension, but often hypoperfusion is accompanied by hypotension.
SBP at presentation: incidence and prognosis

SBP >140mmHg: 43-50%
SBP 90-140mmHg: 48-50%
SBP < 90mmHg: 2-8%

Renal dysfunction in AHF

Sample = All AHF patients (4,953) vs ADCHF (3,161) vs De Novo AHF patients (1,792)

## Predictors of WRF

<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&lt;sup&gt;a&lt;/sup&gt;</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&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5</td>
<td>13 502</td>
<td>1.52 (1.07–2.15)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
# Worsening renal function in AHF: definitions

## Table 1: Definitions of worsening renal function that can be found in the literature

<table>
<thead>
<tr>
<th>Variable</th>
<th>Absolute change(^a)</th>
<th>Relative change(^a)</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></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>&gt;0.3 mg/dL</td>
<td>&gt; or ≥25%</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>≥1.5 × baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>≥20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>≥25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>&gt;5 mL/min/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystatin C</td>
<td>&gt;0.3 mg/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Filippatos, Farmakis, Parissis Eur Heart J 2013
Pathophysiology of worsening renal function in AHF

Ronco et al. JACC 2012;60:1031-1042
Prognostic significance of WRF: early vs late onset

Breidthardt et al. Critical Care 2012
Prognostic impact of WRF and its interaction with congestion in AHF

Marco Metra et al. Circ Heart Fail. 2012;5:54-62
ESC therapeutic algorithm of AHF

PATIENT WITH ACUTE HEART FAILURE

Bedside assessment to identify haemodynamic profiles

PRESENCE OF CONGESTION?

YES
(95% of all AHF patients)

‘Wet’ patient

NO
(5% of all AHF patients)

‘Dry’ patient

ADEQUATE PERIPHERAL PERFUSION?

YES

‘Wet and Warm’ patient
(typically elevated or normal systolic blood pressure)

Vascular type – fluid redistribution
Hypertension predominates

- Vasodilator
- Diuretic

Cardiac type – fluid accumulation
Congestion predominates

- Diuretic
- Vasodilator
- Ultrafiltration (consider if diuretic resistance)

NO

‘Dry and warm’
Adequately perfused = Compensated

- Adjust oral therapy

‘Dry and cold’
Hypoperfused, Hypovolemic

- Consider fluid challenge
- Consider inotropic agent if still hypoperfused

‘Wet and Cold’ patient
Systolic blood pressure <90 mm Hg

YES

- Inotropic agent
- Consider vasopressor in refractory cases
- Diuretic (when perfusion corrected)

NO

- Vasodilators
- Diuretics
- Consider inotropic agent in refractory cases

Consider mechanical circulatory support if no response to drugs
Vasodilators or Diuretics Driven Treatment in Acute Hypotensive HF?

- 110 AHF pts
- Group A: Furosemide 40mg - ISDN 3mg iv every 3min
- Group B: Furosemide 80mg every 15min, ISDN 1mg/h, +1mg every 10min
- Mechanical ventilation: 13% (A) vs 40% (B), p=0.0041
- AMI: 17% vs 37%, p=0.047
- Mortality: 1/3, p NS
- Composite primary EP: 25% vs 46%, p=0.041

*Cotter et al, Lancet 1998*
Vasodilation Is Required to Normalize Cardiac Filling Pressures

IV Diuretic Monotherapy Causes Reflex Vasoconstriction, Increased Afterload, and Decreased Cardiac Index

25 class IV patients: furosemide alone or with IV nitroprusside.

DOSE trial
Dyspnea scale and Creatinine changes at 72 hours:
Low vs High diuretic dose

Felker, NEJM 2011
Maximal doses of loop diuretics in patients with diminished response to initial IV treatment

<table>
<thead>
<tr>
<th>Maximal Intravenous Dose (mg)</th>
<th>Moderate Renal Insufficiency</th>
<th>Severe Renal Insufficiency</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>80-160</td>
<td>160-200</td>
<td>40-80</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>4-8</td>
<td>8-10</td>
<td>1-2</td>
</tr>
<tr>
<td>Torsemide</td>
<td>20-50</td>
<td>50-100</td>
<td>10-20</td>
</tr>
</tbody>
</table>

Maximal Intravenous continuous infusion rate of loop diuretics

<table>
<thead>
<tr>
<th>Diuretic</th>
<th>IV Loading Dose (mg)</th>
<th>CrCl &lt; 25 ml/min</th>
<th>CrCl 25-75 ml/min</th>
<th>CrCl &gt; 75 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>40</td>
<td>20 then 40</td>
<td>10 then 20</td>
<td>10</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>1</td>
<td>1 then 2</td>
<td>0.5 then 1</td>
<td>0.5</td>
</tr>
<tr>
<td>Torsemide</td>
<td>20</td>
<td>10 then 20</td>
<td>5 then 10</td>
<td>5</td>
</tr>
</tbody>
</table>

Specific reno-protective strategies in AHF?
Not here yet!

Ularitide (TRUE-AHF)

Dopamine (ROSE/DAD-HF-II)

Serelaxin (RELAX-AHF-2)

Rolofylline (PROTECT)
What is diuretic resistance?

1. Non-response or inadequate response to loop diuretics, or

2. Persistent congestion despite adequate and escalating doses of diuretic with >80 mg furosemide per day, or

3. FeNa <0.2%, or

4. Failure to excrete at least 90 mmol of sodium within 72 hours of a 160-mg oral furosemide dose given twice daily
Therapeutic strategies for diuretic resistance

1. Loop diuretic
2. Switch loop diuretic
3. Intravenous administration
4. Combination diuretic therapy
   - Add thiazide and/or mineralocorticoid receptor antagonist at natriuretic doses
   - If not tolerated/contraindicated consider:
     - Add metolazone
     - Add acetazolamide
     - Add mannitol

- Tolvaptan
- Nesiritide
- Ularitide
- Levosimendan
- Glucocorticoids
- Rolofylline
- Serelaxin
- Hypertonic saline
- Dopamine
- Ultrafiltration

Ter Maaten, et al. Nat Rev Cardiol 2015
Ultrafiltration in AHF with WRF and persistent congestion: CAREESS-HF

188 patients with acute decompensated heart failure, worsened renal function, and persistent congestion

Treatment arms:
A. Stepped pharmacologic therapy (94 patients)
B. Ultrafiltration (94 patients).

Primary endpoint: change in serum creatinine and body weight (96 hours)

Bart et al. NEJM 2012

Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrafiltration may be considered for patients with refractory congestion, who failed to respond to diuretic-based strategies.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Renal replacement therapy should be considered in patients with refractory volume overload and acute kidney injury.</td>
<td>IIA</td>
<td>C</td>
</tr>
</tbody>
</table>

Bart et al. NEJM 2012
Take home messages

Acute heart failure with worsening renal function

- Strongest risk factor is pre-existing chronic renal disease
- Confers worse prognosis only with persistent congestion
- Management
  - Determine patient profile (“wet and warm” vs “wet and cold”).
  - “Wet and warm” patients are treated with vasodilators plus diuretics
  - High dose diuretics achieve more rapid symptomatic improvement without adverse renal effects
  - Consider reduction/pause of RAAS inhibitors
  - Specific effective renal protective therapeutic strategies currently not available
  - Stepped approach in diuretic resistance
  - Ultrafiltration reserved for congested patients with inadequate response to diuretics. Classical indications for renal replacement therapy apply.
Criteria for ICU/CCU admission

• Need for intubation
• Signs/symptoms of hypoperfusion
  • $\text{SaO}_2 < 90\%$ (despite supplemental $\text{O}_2$)
  • RR > 25/min, use of accessory muscles
  • SBP < 90 mmHg, 40 > HR > 130 bpm
Effect of levosimendan on renal function in AHF: Comparison with dobutamine

Yilmaz et al. Cardiovasc Drugs Ther 2007