Organ Interactions and AKI

Lung & Kidney

F. Husain-Syed
Nephrology, Pulmonology and Intensive Care Medicine - Giessen/Germany
Faeq Husain-Syed

Employer: University Clinic Giessen School of Medicine and Medical Science, Germany

Disclosures: None
Objectives

Lung & Kidney

A  Fluid overload

B  The Heart in Lung-Kidney Interactions
   Cardiogenic pulmonary edema

C  The Kidney in Lung-Kidney Interactions
   Non-cardiogenic pulmonary edema and uremic lung

D  The Lung in Lung-Kidney Interactions
   Mechanical ventilation and ARDS
Lung & Kidney

A Fluid overload

B The Heart in Lung-Kidney Interactions
Cardiogenic pulmonary edema

C The Kidney in Lung-Kidney Interactions
Non-cardiogenic pulmonary edema and Uremic Lung

D The Lung in Lung-Kidney Interactions
Mechanical ventilation and ARDS

Objectives
Fluid Overload - Pediatric ICU (1)

Fluid overload and mortality in children receiving CRRT: The prospective pediatric CRRT registry

Fluid overload (\%) = \frac{\text{Fluid intake (L)} - \text{fluid output (L)}}{\text{Admission weight (kg)}} \times 100

Sutherland S et al. Am J Kidney Dis 2010
• “Is it possible that in some cases CVVH may be a prevention, rather than a treatment, for worsening degrees of fluid overload?”

• “Early initiation of CVVH to allow for sufficient blood product and nutrition administration, while preventing fluid overload may improve patient survival...”

Fluid Overload - Pediatric ICU (3)

Association between fluid balance and outcomes in critically ill children – A systemic review and meta-analysis

44 studies (7502 children)

Fluid overload associated with

→ Increased in-hospital mortality (OR 4.3)

• Each 1% FO increases odds of mortality by 6% (OR 1.06)

→ Increased risk for prolonged mechanical ventilation (OR 2.1)

→ Increased risk for AKI (OR 2.4)

Alobaidi R et al. JAMA Pediatr 2018
Fluid Overload - Adult ICU

Fluid balance and urine volume are independent predictors of mortality in acute kidney injury

Teixeira et al. Crit Care 2013
Fluid Overload - Pediatric and Adult ICU

Fluid balance in critically ill children with acute lung injury

Pediatric Acute Lung Injury and Sepsis Investigator’s Network and the ARDS Clinical Trials Network

*Positive fluid balance associated with longer ventilator-days* \((p=0.04, n=168)\)


Comparison of two fluid-management strategies in acute lung injury

ARDS Clinical Trials Network

**FACTT trial**: liberal fluid management:

- longer ventilator-days \((+2 \text{ days})\) & worse oxygenation \((p<0.0001, n=1001)\)
- No difference in 60-day mortality

Fluid balance, diuretic use, and mortality in acute kidney injury
*(FACCT trial-Comparison of two fluid-management strategies in acute lung injury)*
ARDs Clinical Trials Network

<table>
<thead>
<tr>
<th>Fluid balance / week</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conserv. strategy</strong></td>
<td>(n=503)</td>
</tr>
<tr>
<td>-136 ml (± 491)</td>
<td></td>
</tr>
<tr>
<td><strong>Liberal strategy</strong></td>
<td>(n=498)</td>
</tr>
<tr>
<td>+6992 ml (± 502)</td>
<td></td>
</tr>
</tbody>
</table>

Patients with RRT:  
- **Conservative** 10%  
- **Liberal** 14% (p=0.06)

### CVP

<table>
<thead>
<tr>
<th></th>
<th>Liberal group</th>
<th>Conservative group</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### IV furosemide

<table>
<thead>
<tr>
<th></th>
<th>Liberal group</th>
<th>Conservative group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fluid accumulation on AKI classification

AKI in patients with acute lung injury: impact of fluid accumulation on classification of AKI and associated outcomes

Post hoc analysis of FACTT trial

AKI in the first 7 days:

• **Unadjusted AKIN 1:**
  57% conservative > 51% liberal; p=0.04

• **Adjusted AKIN 1:**
  58% conservative <66% liberal; p=0.007

Liu KD et al. Crit Care Med 2011

Macedo F et al. Crit Care 2010
Recommendation:
Fluid management in ARDS (+ECMO)

ELSO Guideline for Adult Respiratory Failure – August, 2017
Extracorporeal Life Support Organization (ELSO)

- **ARDS**: return extracellular fluid volume to normal and maintain it there
- **If diuretic response not sufficient or severe AKI**: CVVH should be added (to extracorporeal ECMO circuit)
- **Sepsis and active capillary leakage**: wait till patient is hemodynamically stable (typically 12 hours), then continue diuretics until dry weight is achieved
- **If ECMO blood flow compromised by depletion of intravascular volume**: temporarily decrease output of pump rather than administering IV fluid

ELSO Adult Respiratory Failure Guidelines: www.ELSO.org
Objectives

**Lung & Kidney**

A  Fluid overload

B  **The Heart in Lung-Kidney Interactions**
   *Cardiogenic pulmonary edema*

C  **The Kidney in Lung-Kidney Interactions**
   *Non-cardiogenic pulmonary edema and uremic lung*

D  **The Lung in Lung-Kidney Interactions**
   *Mechanical ventilation and ARDS*
Heart-kidney interactions are bidirectional, time-dependent, and are mediated by several pathophysiological mechanisms.

Ronco C et al. J Am Coll Cardiol 2008
Cardiorenal Syndromes (2)

Cardiac metabolome in mice following ischemic AKI:

- amino acid depletion, increased oxidative stress and anaerobic energy production
- significant cardiac ATP depletion
- echocardiographic evidence of diastolic dysfunction

Cardiac ATP levels

E/A ratio

Fox BM et al. Kidney Int 2018
Endothelial dysfunction
- Impaired NO vasodilation
- Myocardial leucocytes infiltration
- Pro-apoptotic cascades

Myocardial dysfunction
- Wall stress
- Oxidative stress
- Inflammation
- Neurohormonal activation

Worsening renal function
- Sodium and water retention
- Electrolyte and acid base disorder
- Peripheral vasoconstriction
- RAAS activation

The Heart in Lung-Kidney Interactions

Ronco C et al. J Am Coll Cardiol 2012
Braam B. Nat Rev Nephrol 2014
Peripheral edema, central venous pressure, and risk of AKI in critically illness

AKI incidence manifested as edema or increased CVP

12,778 ICU patients

Table 4. Admission central venous pressure and subsequent risk of AKI

<table>
<thead>
<tr>
<th>Risk</th>
<th>≤7 cm/H₂O</th>
<th>&gt;7 to ≤10 cm/H₂O</th>
<th>&gt;10 to ≤13 cm/H₂O</th>
<th>&gt;13 cm/H₂O</th>
<th>Per 1 cm H₂O positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>N, % AKI</td>
<td>275 (21)</td>
<td>275 (22)</td>
<td>227 (23)</td>
<td>312 (26)</td>
<td>—</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>Ref</td>
<td>1.06</td>
<td>1.08</td>
<td>1.18</td>
<td>1.02</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.86 to 1.29</td>
<td>0.87 to 1.29</td>
<td>0.96 to 1.33</td>
<td>0.96 to 1.33</td>
<td>1.00 to 1.03</td>
</tr>
<tr>
<td>P value</td>
<td>0.57</td>
<td>0.46</td>
<td>0.09</td>
<td>0.09</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Objectives

Lung & Kidney

A  Fluid overload

B  The Heart in Lung-Kidney Interactions
   Cardiogenic pulmonary edema

C  The Kidney in Lung-Kidney Interactions
   Non-cardiogenic pulmonary edema and uremic lung

D  The Lung in Lung-Kidney Interactions
   Mechanical ventilation and ARDS
Uremic Lung –
Non-Cardiogenic Pulmonary Edema (1)

Pulmonary Changes in Uremia*

Hyman E. Bass, David Greenberg, Emanuel Singer
and Milton A. Miller

Bass HE et al. JAMA 1950
Uremic Lung –
Non-Cardiogenic Pulmonary Edema (2)

Following ischemic AKI / bilateral nephrectomy:
- ↑pulmonary vascular permeability, neutrophil infiltration, cellular apoptosis and alveolar hemorrhage

Uremic Lung – Non-Cardiogenic Pulmonary Edema (3)

- Serum IL-6 (and IL-8) increase in mice and patients with AKI
- Lung injury occurs in mice with AKI
- Lack of IL-6 protects against lung injury in mice with AKI
- Increased serum IL-6 (and IL-8) predicts prolonged mechanical ventilation (>24h) in patients with AKI (ROC-AUC 0.95)

Liu KD et al. Crit Care 2009
In AKI impaired resolution of lung edema by down-regulation of lung ENaC and aquaporin 5, and activation of NKCC1

Grams ME et al. Kidney 2012
Solymosi EA et al. Proc Natl Acad Sci U S A 2013
Fluid Management of Combined AKI & ARDS

- Complete recovery with fluid removal
- Partial recovery with fluid removal but failure to be quickly extubated
- Fluid removal does little to improve oxygenation

Faubel S, Edelstein CL. Nat Rev Nephrol 2015
AKI and the Lung

Traditional complications

- Fluid overload
- Electrolyte/Acid base disorder
- Uremic solute retention
- Renal anemia
- Respiratory work load
- Endothelial dysfunction
- Pulmonary hypertension
- ↑RV stress

Non-traditional complications

- Remote lung injury and apoptosis
- Non-cardiogenic pulmonary edema
- ↑Circulating IL-6, DAMPs
- ↑caspase 3, TNF-α
- ↓ENaC, Na,K-ATPase, aquaporin 5

Husain-Syed et al. Am J Respir Crit Care Med 2017
Objectives

Lung & Kidney

A  Fluid overload

B  The Heart in Lung-Kidney Interactions
   Cardiogenic pulmonary edema

C  The Kidney in Lung-Kidney Interactions
   Non-cardiogenic pulmonary edema and uremic lung

D  The Lung in Lung-Kidney Interactions
   Mechanical ventilation and ARDS
MECHANICAL VENTILATION

Hyperinflation

Blood gas disturbances
Hemodynamic & neurohormonal alterations
Systemic release of mediators

↓ RENAL BLOOD FLOW
↓ FREE WATER CLEARANCE
↓ SODIUM EXCRETION

ARDS

Inflammation

Remote lung injury and apoptosis
Non-cardiogenic pulmonary edema

↑ Circulating IL-6, DAMPs
↑ caspase 3, TNF-α

↓ ENaC, Na,K-ATPase, aquaporin 5

CELL INFILTRATION
ENDOTHELIAL DYSFUNCTION
MICROVASCULAR DYSREGULATION
ARDSNet $V_T$ Trial Outcomes

Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome

The Acute Respiratory Distress Syndrome Network

**Table 4. Main Outcome Variables.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group Receiving Lower Tidal Volumes</th>
<th>Group Receiving Traditional Tidal Volumes</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death before discharge home and breathing without assistance (%)</td>
<td>31.0</td>
<td>39.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Breathing without assistance by day 28 (%)</td>
<td>65.7</td>
<td>55.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of ventilator-free days, days 1 to 28</td>
<td>12±11</td>
<td>10±11</td>
<td>0.007</td>
</tr>
<tr>
<td>Barotrauma, days 1 to 28 (%)</td>
<td>10</td>
<td>11</td>
<td>0.43</td>
</tr>
<tr>
<td>No. of days without failure of nonpulmonary organs or systems, days 1 to 28</td>
<td>15±11</td>
<td>12±11</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Probability of survival

**Graph:**
- Lower tidal volumes
- Traditional tidal volumes
- Survival
- Discharge
Mechanical Ventilation and Kidney (1)

Hemodynamic

- PPV increased intrathoracic pressure $\Rightarrow$ compression of pulmonary vasculature $\Rightarrow$ low CO, pulmonary hypertension, right heart failure and venous congestion
- Increased PPV and PEEP associated with decreased renal blood flow, GFR, sodium excretion and urinary output
- Non-invasive ventilation may better preserve renal function

Drury DR et al. J Clin Invest 1947
Annat G et al. Anesthesiology 1983
Steinhoff H et al. Intensive Care Med 1982
Mechanical Ventilation and Kidney (2)

- Neurohormonal

  - ↑ sympathetic nervous system, RAAS, ADH

    - fluid/salt retention, vasoconstriction, and decreased renal blood flow

Kuiper JW et al. Crit Care Med 2005
Blood gas disturbances

- Hypercapnia and/or hypoxemia (SaO2 ~83%–87%): decrease RBF and GFR, while these increase when hypercapnia improves
- Acute hypercapnia increases pulmonary vascular resistance and can lead to right ventricular dysfunction
- During hypercapnia, loss of renal vasodilatory response to various stimuli (e.g., dopamine, L-arginine, amino acids)

Hildebrandt W et al. J Appl Physiol 1985
Sharkey RA et al. Chest 1999
Mechanical Ventilation and Kidney (4)
Kidney-Lung Protective Ventilation?

→ Biotrauma

• ARDSNet Tidal Volume Trial

In addition to improved survival and ventilator-free days, low $V_T$ group had more days without circulatory, coagulation and renal failure (renal 20±11 vs. 18±11 days, p=0.005)


• Lung-Protective Mechanical Ventilation Strategy

Less inflammation in lung-protective strategy group

Ranieri VM et al. JAMA 1999

Fewer patients with organ system failure and markedly fewer with renal failure (p<0.04) in lung-protective strategy group

Ranieri VM et al. JAMA 2000
AKI Biomarkers in Patients with ARDS

→ Biotrauma

• Secondary analysis of an 876 patient ARDSNet trial

• Tested association of several baseline biomarkers with subsequent AKI

• AKI (AKIN Stage 1) developed in 209 (24%), association with 180-days mortality (vs. 28% without AKI, p<0.001)

• Urine IL-18, IL-6, sTNFR-1/2, and PAI-1 levels independently associated with AKI


Biotrauma
Lung-kidney interactions in critically ill patients:
Consensus report of the Acute Disease Quality Initiative (ADQI) 21 Workgroup

Joannidis M et al. *Under Review*
Conclusions (1)

✓ Avoid positive cumulative fluid balance ("in ARDS being emptier is probably better than overfilled")

✓ Right ventricular dysfunction and venous congestion can reduce renal perfusion pressure, leading to a spiral of impaired cardio-pulmonary-renal axis

✓ AKI leads to pulmonary edema by both high pressure and low pressure mechanisms

✓ AKI is associated with lung injury and down-regulation of lung water/salt channels (correlate for “uremic lung”)

✓ During lung-injurious ventilation, pro-inflammatory mediators can translocate into the systemic circulation and amplify distant organ damage
Reducing mortality in AKI will require more than managing fluid, potassium, anemia and acidosis (traditional complications).

Must recognize that AKI has many other systemic effects (non-traditional complications).

Must move beyond RRT in order to improve mortality in AKI.

Does RRT remove beneficial metabolites and proteins essential for optimal organ function?