Distant organ effects of acute kidney injury

Hamid Rabb
Professor & Vice-Chairman
Department of Medicine
Johns Hopkins University
Baltimore, USA
Mortality with acute kidney injury - AKI

With availability of dialysis, patients are dying with AKI, but from extra-renal complications
Distant organs effect of AKI

Gramps M & Rabb H. *Kidney Int* August 2011
High mortality associated with combined AKI and lung injury in the ICU

- High mortality of patients in ICU with native kidney AKI remains around 50%, and has a mortality rate of >80% if associated with ventilation associated lung injury (VALI)
Mechanisms of renal influence on mortality

- Abundance of epidemiological data
- Increasing data on pathophysiology of AKI
- However,
  - Paucity of integrated organ system data
  - Lack of mechanistic data
  - e.g. Does AKI contribute to respiratory dysfunction-independent of volume overload?
Hypothesis

Acute kidney injury leads to increased pulmonary vascular permeability, a hallmark of acute lung injury (ARDS)
Transporter hypothesis

- Pulmonary edema after renal IRI is, in part, due to abnormalities in salt and water clearance/transport
Epithelial Sodium Channels (ENaC)

Sodium channels have a role in regulating the volume of liquid on airway surfaces. (*N Engl J Med* 341:156, 1999)

Sodium transport in the distal nephron is mediated by ENaC
What is the molecular signature of AKI distant lung effects?
Mice with renal IRI had increase in BAL total protein at 36 h
Genes expression lungs from mice with renal IRI or BNx

Placenta-specific 8
Histocompatibility 2, class II antigen
Scavenger receptor class B, member 1
Chemokine orphan receptor 1
Serum amyloid A 3
Phospholipase A2
Chemokine (C-C motif) ligand 6
C-type lectin domain family 4
Interferon induced protein 6
TYRO protein kinase binding protein
Interleukin 1 receptor, type II
Transforming growth factor β induced
S100 calcium binding protein A4
CD52 antigen

Synuclein, alpha
Tumor necrosis factor receptor 19
Interferon-induced protein 2
Septin 4
Prickle like 1
Endothelin 1

Am J Physiol 2007
Biological processes activated in the lung during ischemic AKI at 6 h

<table>
<thead>
<tr>
<th>GOID</th>
<th>GO Name</th>
<th>Changed Genes</th>
<th>Measured Genes</th>
<th>Genes in GO</th>
<th>Changed Genes (%)</th>
<th>Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>6955</td>
<td>Immune response</td>
<td>15</td>
<td>83</td>
<td>273</td>
<td>18.1</td>
<td>11.72</td>
</tr>
<tr>
<td>6954</td>
<td>Inflammatory response</td>
<td>14</td>
<td>57</td>
<td>178</td>
<td>24.6</td>
<td>10.50</td>
</tr>
<tr>
<td>7166</td>
<td>Cell surface receptor signaling</td>
<td>9</td>
<td>54</td>
<td>128</td>
<td>16.7</td>
<td>5.15</td>
</tr>
<tr>
<td>7186</td>
<td>G-protein coupled receptor signaling</td>
<td>9</td>
<td>70</td>
<td>1738</td>
<td>12.9</td>
<td>4.17</td>
</tr>
<tr>
<td>6935</td>
<td>Chemotaxis</td>
<td>7</td>
<td>33</td>
<td>103</td>
<td>21.2</td>
<td>8.46</td>
</tr>
<tr>
<td>6928</td>
<td>Cell motility</td>
<td>7</td>
<td>68</td>
<td>108</td>
<td>10.3</td>
<td>3.49</td>
</tr>
<tr>
<td>1558</td>
<td>Regulation of cell growth</td>
<td>6</td>
<td>50</td>
<td>75</td>
<td>12.0</td>
<td>2.27</td>
</tr>
<tr>
<td>50896</td>
<td>Response to stimulus</td>
<td>5</td>
<td>23</td>
<td>261</td>
<td>21.7</td>
<td>9.73</td>
</tr>
</tbody>
</table>
Biological processes activated in the lung during ischemic AKI at 36 h

<table>
<thead>
<tr>
<th>GOID</th>
<th>GO Name</th>
<th>Changed Genes</th>
<th>Measured Genes</th>
<th>Genes in GO</th>
<th>Changed Genes (%)</th>
<th>Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>6512</td>
<td>Ubiquitin cycle</td>
<td>23</td>
<td>180</td>
<td>338</td>
<td>12.8</td>
<td>2.61</td>
</tr>
<tr>
<td>6915</td>
<td>Apoptosis</td>
<td>16</td>
<td>142</td>
<td>265</td>
<td>11.3</td>
<td>2.94</td>
</tr>
<tr>
<td>7264</td>
<td>Small GTPase mediated signaling</td>
<td>14</td>
<td>120</td>
<td>220</td>
<td>11.7</td>
<td>2.43</td>
</tr>
<tr>
<td>122</td>
<td>Negative regulation of transcription</td>
<td>10</td>
<td>54</td>
<td>120</td>
<td>18.5</td>
<td>4.01</td>
</tr>
<tr>
<td>1558</td>
<td>Regulation of cell growth</td>
<td>9</td>
<td>50</td>
<td>75</td>
<td>18.0</td>
<td>3.50</td>
</tr>
<tr>
<td>7186</td>
<td>G-protein coupled receptor signaling</td>
<td>9</td>
<td>70</td>
<td>1738</td>
<td>12.9</td>
<td>3.05</td>
</tr>
<tr>
<td>7283</td>
<td>Spermatogenesis</td>
<td>9</td>
<td>59</td>
<td>164</td>
<td>15.3</td>
<td>2.80</td>
</tr>
<tr>
<td>45449</td>
<td>Regulation of transcription</td>
<td>9</td>
<td>71</td>
<td>165</td>
<td>12.7</td>
<td>2.21</td>
</tr>
<tr>
<td>7166</td>
<td>Cell surface receptor linked signaling</td>
<td>8</td>
<td>54</td>
<td>128</td>
<td>14.8</td>
<td>5.17</td>
</tr>
<tr>
<td>6954</td>
<td>Inflammatory response</td>
<td>8</td>
<td>56</td>
<td>178</td>
<td>14.3</td>
<td>2.13</td>
</tr>
<tr>
<td>7507</td>
<td>Heart development</td>
<td>7</td>
<td>44</td>
<td>89</td>
<td>15.9</td>
<td>2.67</td>
</tr>
<tr>
<td>16481</td>
<td>Negative regulation of transcription</td>
<td>6</td>
<td>51</td>
<td>83</td>
<td>11.8</td>
<td>3.06</td>
</tr>
<tr>
<td>7169</td>
<td>Transmembrane receptor PTK signaling</td>
<td>6</td>
<td>29</td>
<td>84</td>
<td>20.7</td>
<td>2.70</td>
</tr>
<tr>
<td>45786</td>
<td>Negative regulation of cell cycle</td>
<td>5</td>
<td>29</td>
<td>50</td>
<td>17.2</td>
<td>2.22</td>
</tr>
</tbody>
</table>
Two Nodes: TNFR and Caspase

Am J Physiol 2009
Increased lung TUNEL staining during ischemic AKI

Am J Physiol 2009
Increased caspase 3 positive cells and activity in AKI

A

Sham

IRI

BNx

B

Active Caspase-3 (cells/hpf)

Sham

IRI

BNx

C

p19

p17

Active Caspase-3

β-actin

D

Caspase-3 Activity (RFU × 10^3)

Sham

IRI

BNx

Am J Physiol 2009
Lung endothelial cells are the primary apoptotic cell during AKI
Protection from lung protein leak and apoptosis during AKI by Z-VAD-FMK

Am J Physiol 2009
**Experimental AKI leads to pulmonary changes**

<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Kramer &amp; Rabb, KI 1999</td>
</tr>
<tr>
<td>2.</td>
<td>Rabb &amp; Soleimani, KI 2003</td>
</tr>
<tr>
<td>3.</td>
<td>Hassoun &amp; Rabb, AJP 2007</td>
</tr>
<tr>
<td>4.</td>
<td>Grigoryev, &amp; Rabb, JASN 2008</td>
</tr>
<tr>
<td>5.</td>
<td>Hoag &amp; Rabb, AJP 2008</td>
</tr>
<tr>
<td>6.</td>
<td>Dodd-O &amp; Rabb, AJP 2009</td>
</tr>
<tr>
<td>7.</td>
<td>Hassoun &amp; Rabb, AJP 2009</td>
</tr>
<tr>
<td>8.</td>
<td>Feltes &amp; Rabb, Shock 2011</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Nath, AJPath, 2005</td>
</tr>
<tr>
<td>3.</td>
<td>Kim &amp; Woo, Respiration 2006</td>
</tr>
<tr>
<td>4.</td>
<td>Zarbock &amp; Singbartl, JASN 2006</td>
</tr>
<tr>
<td>5.</td>
<td>Awad &amp; Okusa, KI 2009</td>
</tr>
<tr>
<td>9.</td>
<td>Awad &amp; Okusa, KI 2009</td>
</tr>
<tr>
<td>10.</td>
<td>Campanholle &amp; Camara, Inflam Res 2010</td>
</tr>
</tbody>
</table>
AKI and Brain-clinical

1. Central nervous system changes, from decreased mental status to seizures, are one of the classic indications to begin dialysis during AKI.

2. Despite the well-known association of acute severe kidney dysfunction with neurological changes, the underlying mechanisms are poorly understood.
Experimental design

C57BL/6 mice → Renal ischemia 60m → Reperfusion 24h → Ischemic AKI

End points

Brain harvest → Mouse brain → Sagittal dissection → Histology (H&E, IHC) → Snap frozen (gene array; protein array)

Liu & Rabb, JASN 2008
Mice with AKI had increased pyknotic neuronal cells in brain hippocampus (CA1)

Fig. 1. Pyknotic neuronal cells were significantly increased in the brain hippocampus in mice with severe ischemic AKI at 24 h.
AKI leads to increased number of microglia in the hippocampus of the brain.
Mice with AKI at 24h had increased glial fibrillary acidic protein (inflammatory marker) in astrocytes.

Sagittal Section

A: Corpus Callosum
B: Cerebral Cortex

![Sham and AKI sections with positive pixel count/field graphs for GFAP in Corpus Callosum and Cerebral Cortex.](image)
An open field test evaluates locomotor activity, exploratory behaviors and anxiety.

Novelty-induced activity was assessed over a 30-min period using the activity chambers lined with infrared photo beams.

Data are presented as photo beams breaking times over each interval or over total duration.
Mice with AKI at 24 h had significantly reduced locomotor activity compared to sham animals that underwent laparotomy and renal pedicle dissection.
AKI increases albumin permeability into brain (Left) and loosens blood brain barrier endothelial cells contacts (Right)

ASN abstract 2009
Does AKI reduce brain threshold for a “second hit” e.g. stroke?
Procedure of permanent middle cerebral artery occlusion (pMCAO)
AKI exacerbates outcomes of subsequent ischemic Stroke

ASN abstract 2009
CONCLUSIONS

- AKI results in important changes to distant organs – to-date best studied mechanistically in the lung, but also in other organs

- AKI causes brain genomic, molecular, cellular, inflammatory and functional changes.

- AKI lowers the injury threshold for ischemic stroke

- Further discovery and targeting AKI-distant organ communication pathways should help improve outcomes from AKI
Summary

• AKI/ARF has an average mortality of 50% in the ICU despite dialysis

• AKI can lead to molecular changes and organ dysfunction in lung, heart and brain

• Detailed studies of classic inflammatory and transport pathways, plus novel pathways identified by systems biology tools, can reveal novel therapeutic targets and biomarkers of organ cross talk in critically ill patients with AKI.

• Improved dialysis techniques will hopefully lessen the effects of AKI on distant organ dysfunction
Distant organs effect of AKI

Kidney Int 2011