BOLD & Diffusion MRI for Evaluating Renal Oxygenation & Fibrosis in CKD

Pottumarthi V. Prasad, Ph.D.
Sr. Research Scientist
NorthShore University HealthSystem
Professor of Radiology (part time)
Pritzker School of Medicine, University of Chicago
Motivation: Need for Novel Markers

- **Chronic Kidney Disease (CKD)** is a slow and progressive loss of renal function
  - Based on current clinical marker (estimated GFR), 30 million people in US are classified to have CKD
  - About 120 K per year will progress to ESRD where the options will be limited to replacement
    » Need for markers for progressive CKD
Motivation: Role for Oxygenation & Fibrosis in CKD

- **Chronic Hypoxia Hypothesis**
  - Fine LG et al., *Kidney Int Suppl* 1998; 65:S74-8
  - Initiating glomerular injury leads to loss of microvasculature, leading to development of hypoxia and fibrosis …
  - Translation to humans require non-invasive methods
    - there are no non-invasive markers for renal oxygenation
    - Histology remains the only accepted method to evaluate renal fibrosis
Blood Oxygenation Level Dependent (BOLD) MRI

TE=3.1  TE=7.0  TE=10.9  TE=14.9  TE=18.8  TE=22.7  TE=26.6  TE=30.5

Signal Intensity vs. Echo Time (s)

- Medulla: $R^*_2 = 23.6 \text{ s}^{-1}$
- Cortex: $R^*_2 = 18.6 \text{ s}^{-1}$

Magnetic susceptibility of OxyHb ≈ tissue Field uniform MFI signal high
Magnetic susceptibility of deOxyHb >> tissue Field non-uniform MRI signal low

$pO_2$ range:

MRI signal range:
BOLD MRI: Replicates Invasive Measurements

Effect of furosemide

Am J Physiol. 1994;267:F1059

Invest Radiol. 2006 Feb;41(2):181
Diffusion MRI

b s/mm² = 200
300
500
700
1000

ADC = \(1.72 \times 10^{-3}\) mm²/s
Diffusion: Dependence of fibrosis

Kidney


Renal BOLD & Diffusion MRI: Current Status

• Both sequences readily available on major vendor platforms
  – Independent verification by investigators world-wide

• Both applied together in the context of CKD
  – Inoue T et al., *JASN*. 2011;22(8):1429-34
Renal BOLD & Diffusion MRI: Current Status

- Both sequences readily available on major vendor platforms
  - Independent verification by investigators world-wide
- Both applied together in the context of CKD
  - Inoue T et al., JASN. 2011;22(8):1429-34
  - Prasad P et al., PloS one. 2015;10(10):e0139661
- Highly reproducible – comparable when repeated on the same day or up to 18 months apart
  - Li L et al., JMRI 2018 [in press]
- Preliminary data supporting use in multicenter trials
  - Prasad P et al., Kidney Int. Reports 2018 [in press]
## Data from Multiple Sites in Advanced CKD

<table>
<thead>
<tr>
<th></th>
<th>Control/CKD</th>
<th>n</th>
<th>Mean±sd</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Cortex R2</em> (s⁻¹)</em>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>13</td>
<td>18.8±2.4</td>
<td></td>
<td>0.022</td>
</tr>
<tr>
<td>CKD</td>
<td>123</td>
<td>20.6±3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em><em>Medulla R2</em> (s⁻¹)</em>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>13</td>
<td>29.0±3.9</td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CKD</td>
<td>123</td>
<td>23.8±3.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em><em>Medulla ΔR2</em> (s⁻¹)</em>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>13</td>
<td>6.3±3.5</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>CKD</td>
<td>54</td>
<td>2.5±2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ADC x10⁻³ mm²/s</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>13</td>
<td>1.67±0.08</td>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CKD</td>
<td>126</td>
<td>1.45±0.17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Renal BOLD & Diffusion MRI: Current Status

- Both sequences readily available on major vendor platforms
  - Independent verification by investigators world-wide
- Both applied together in the context of CKD
  - Inoue T et al., *JASN*. 2011;22(8):1429-34
- Highly reproducible – comparable when repeated on the same day or up to 18 months apart
  - Li L et al., *JMRI* 2018 [in press]
- Preliminary data supporting use in multicenter trials
- Data supporting sensitivity to disease progression
  - Li L et al., Poster #9
  - Srivastava et al., Poster #17
Progression in CKD: Cortical $R_2^*$, $\Delta$(Med-Cor) $R_2^*$

### Associations with yearly change in eGFR

<table>
<thead>
<tr>
<th></th>
<th>Fully adjusted* $\beta$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex $R_2^*$ (s$^{-1}$)</td>
<td>-0.44(-0.76 to -0.11)</td>
<td>0.009</td>
</tr>
<tr>
<td>$\Delta$(Med-Cor) $R_2^*$</td>
<td>0.45 (0.11 to 0.80)</td>
<td>0.01</td>
</tr>
<tr>
<td>Proteinuria (g/24 hr)</td>
<td>-1.49 (-2.65 to -0.33)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, diabetes, eGFR, proteinuria, and use of RAS blockers

<table>
<thead>
<tr>
<th></th>
<th>Progressors</th>
<th>Non-progressors</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex $R_2^*$</td>
<td>21.3±2.6</td>
<td>20.2±1.9</td>
<td>0.033</td>
</tr>
<tr>
<td>$\Delta$(Med-Cor) $R_2^*$</td>
<td>7.3±2.8</td>
<td>8.2±2.9</td>
<td>0.038</td>
</tr>
</tbody>
</table>

*Progressors: eGFR decline $> 3$ ml/min/yr

*Kidney Int. 2018 Apr;93(4):932-940*
Progression in CKD: Medulla $\Delta R2^*$

$y = 0.48 x + 5.16$
$R = 0.42$

<table>
<thead>
<tr>
<th>$\Delta R2^*$ s$^{-1}$</th>
<th>Progressors</th>
<th>Non-progressors</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulla $\Delta R2^*$ (s$^{-1}$)</td>
<td>1.90±2.53</td>
<td>5.39±3.65</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Li et al, Poster # 9
Progression in CKD: ADC

Srivastava et al, Poster # 17
What else do we need?

• Even though proof-of-concept evidence is available, further investigations necessary to
  – improve sensitivity and/or specificity
    » Important to translate to clinic where decisions need to be made on an individual basis
    » Reason to look at contrast agents for fibrosis
  – Demonstrate whether these markers can be used to monitor interventions
  – Include more non-invasive measures
    » PARENCHIMA includes ASL, T1, PC-BF
  – Develop objective analytical tools