MR Imaging of Renal Perfusion using arterial spin labeling (ASL)

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Motivation: Improving Diagnostic Tools

• Goal of assessing kidney function using \textit{non-invasive} diagnostic tools that allow:
  – Regional assessment
  – Earlier detection of functional change
  – Characterization of disease
  – Longitudinal assessment to determine treatment response

• Perfusion MRI is appealing:
  – Non-invasive
  – Allows longitudinal assessment
  – Functional information
  – May allow earlier detection and characterization of disease
    • e.g. BOLD\textsuperscript{1} and Perfusion\textsuperscript{2} MRI appear to differentiate ATN from rejection in renal transplants
  – ASL methods avoid toxicity of exogenous contrast agents

\textsuperscript{1}Sadowski et al. Radiology, 2005
\textsuperscript{2}Szolar et al. MRI, 1997
Background: Types of Arterial spin labeling (ASL) techniques

1. CASL – continuous ASL
2. PASL – pulsed ASL (e.g. FAIR methods)
3. PCASL (pCASL) – pseudocontinuous ASL
4. VS - Velocity selective ASL

- SNR is inherently low in ASL
  - Because the signal from the labeled inflowing blood is only 0.5%-1.5% of the full tissue signal
  - So we acquire several tag/control pairs to allow for signal averaging and boosting the SNR

- ASL Signal depends on many parameters:
  - Including flow, $T_1$ of blood and tissue, arterial transit time (i.e. blood’s travel time from the site of labeling to imaging region), and efficiency of labeling
**Background: ASL Techniques**

**Selective Slab Based** (e.g. FAIR)

- Blood in slab is inverted and moves into volume

**Slice Based** (e.g. CASL or pCASL)

- Blood that passes through plane is inverted

**Motion Based** (e.g. VS ASL)

- Blood that moves is saturated
Background: Arterial Spin Labeling (ASL) Principles

- ASL is an image subtraction technique with contrast based on differences in magnetization of water spins in blood

**Diagram:**

- **Tag:** Prep → Post Label Delay → Imaging
  - t=0
  - t=PLD
- **Control:** Prep Off → Post Label Delay → Imaging
  - t=0
  - t=PLD

**Difference (ΔS):**

- Tag image - Control image = Difference image

**Perfusion (RBF):**

- Normalization and Modeling

**Units:** ml/min/100g
Reference Image Correction
Bulk decay of signal after labeling correction
Account for label time
Account for tagging efficiency

\[ RBF = \frac{6000 \cdot \lambda \cdot (1 - \exp(-2.0s/T_{1,R})) \cdot \exp(TI/T_{1,B})}{2 \cdot TI \cdot \alpha} \cdot \frac{\Delta S}{S_0} \]

\( RBF \) is renal blood flow [ml/100g/min]
\( \lambda \) is the blood:tissue partition coefficient (0.9 mL/g)
\( T_{1,R} \) is the \( T_1 \) of the renal tissue (1.68s at 1.5T)
\( T_{1,B} \) is the \( T_1 \) of the arterial blood (1.35s at 1.5T)
\( TI \) or PLD is the inversion time; also known as Post-label delay (PLD)
\( \alpha \) is the tagging efficiently

- Careful(!): PCASL, pCASL, and VS ASL all have different ASL signal models based on how the labeling occurs and of efficiently the water spins are labeled
Methods: FAIR-bSSFP ASL for Kidney Perfusion

- **Preliminary Results in Healthy Native Kidneys**

- **Correlated with Renal Artery Stenosis Grade**

- **Feasibility in Diseased Native and Transplanted Kidneys**
  - Li et al., Kidney International Reports. 2017; 2:36-43.

- **Reproducibility in Diseased Native and Transplanted Kidneys**

- **Accuracy using an Interventional Swine Study**

- **Demonstration of longitudinal change in renal transplant living donor-recipient pairs**

- Review of ASL use for renal perfusion can be found here:
  - Nery et al., Diagnostics 2018; 8:2-15.
Methods: ASL MRI uses a FAIR tagging scheme and balanced SSFP readout

Acquisition parameters:
- 20 ms adiabatic inversion pulse, 1.2 s inversion delay, 32 control/tag pairs.
- TR/TE/α = 4.6 ms/2.3 ms/70°; Matrix = 128 x 128
- Sagittal FOV = 34 – 36 cm; Slice thickness = 8 mm
- Scan Time: 6-8 min.

Methods: Motion Compensation

- Respiratory triggering and coaching
- Retrospective Image Registration
  - Images aligned for each kidney separately using Normalized Mutual Information (NMI)

- Magnetization Compensation
  - Respiratory Rate $\leq$ 12 breaths/min
Methods: Retrospective Image Registration

Transplant Example 1

Average

Unregistered
Registered

Average

Transplant Example 2

Unregistered
Registered
Results: ASL vs. Fluorescent Microspheres

- Interventional Swine Study
  - 11 female swine (34-38 kg)
  - Microsphere and ASL perfusion (cortex only) measured at four time points

- 2 back-to-back injections of microspheres at each time point
- ASL scanning and processing: same as previous studies

Results: ASL Perfusion Maps

- **Baseline**
- **Acetylcholine Challenge**
- **Iced Kidney**
- **Initial Isoflurane**
- **Prolonged Isoflurane**

/ml/100g/min
Results: Individual RBF Responses
Results: Normalized Perfusion vs Intervention

Averaged for 11 Swine (22 kidneys)
Results: Test/Retest and Reproducibility Study Design

- Human Subjects (n = 24 subjects)
  - 10 with native kidneys, 14 with transplanted kidneys
    - Broad range of renal function
    - All subjects were stable
      - serum creatinine levels varied < 0.3 mg/dL between visits
      - no events changed their clinical status during the interim
    - Refrained from fluids for 4 hrs

- Assessing Reproducibility at 1.5T
  - Same Visit – exams repeated back-to-back (test/re-test)
    - subject remained in scanner
  - Separate Visits – exams repeated at least 24 hours apart

- Statistics
  - Intra-class Correlation Coefficient (ICC)
  - Coefficient of Variation (CV)

- Substudy (N = 5) comparing coached vs. free-breathing ASL MRI in transplant patients

Reproducibility – Cortical Perfusion

<table>
<thead>
<tr>
<th></th>
<th>Same Visit</th>
<th>Separate Visits</th>
<th>ICC</th>
<th>CV(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Native Right</strong></td>
<td>337</td>
<td>339</td>
<td>0.94</td>
<td>7.6</td>
</tr>
<tr>
<td><strong>Native Left</strong></td>
<td>337</td>
<td>336</td>
<td>0.94</td>
<td>13.1</td>
</tr>
<tr>
<td><strong>Transplant</strong></td>
<td>269</td>
<td>275</td>
<td>0.96</td>
<td>6.0</td>
</tr>
</tbody>
</table>

* Perfusion listed in ml/min/100g
## Reproducibility – Medullary Perfusion

### Measures of reproducibility

<table>
<thead>
<tr>
<th></th>
<th>Same Visit</th>
<th>Separate Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ICC</strong></td>
<td>0.78</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>CV(%)</strong></td>
<td>16.7</td>
<td>26.7</td>
</tr>
</tbody>
</table>

### Native Right Mean Perfusion

<table>
<thead>
<tr>
<th></th>
<th>Scan 1</th>
<th>Scan 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perfusion</strong></td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td><strong>ICC</strong></td>
<td>0.78</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>CV(%)</strong></td>
<td>16.7</td>
<td>26.7</td>
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### Native Left Mean Perfusion

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<tr>
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<th>Scan 1</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Perfusion</strong></td>
<td>72</td>
<td>57</td>
</tr>
<tr>
<td><strong>ICC</strong></td>
<td>0.72</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>CV(%)</strong></td>
<td>23.8</td>
<td>26.7</td>
</tr>
</tbody>
</table>

### Transplant Mean Perfusion

<table>
<thead>
<tr>
<th></th>
<th>Scan 1</th>
<th>Scan 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perfusion</strong></td>
<td>38</td>
<td>43</td>
</tr>
<tr>
<td><strong>ICC</strong></td>
<td>0.77</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>CV(%)</strong></td>
<td>16.7</td>
<td>26.7</td>
</tr>
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</table>

### Native Left Mean Perfusion

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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Perfusion</strong></td>
<td>72</td>
<td>65</td>
</tr>
<tr>
<td><strong>ICC</strong></td>
<td>0.63</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>CV(%)</strong></td>
<td>19.8</td>
<td>19.8</td>
</tr>
</tbody>
</table>

### Native Right Mean Perfusion

<table>
<thead>
<tr>
<th></th>
<th>Visit 1</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Perfusion</strong></td>
<td>79</td>
<td>77</td>
</tr>
<tr>
<td><strong>ICC</strong></td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>CV(%)</strong></td>
<td>28.1</td>
<td>28.1</td>
</tr>
</tbody>
</table>

### Transplant Mean Perfusion

<table>
<thead>
<tr>
<th></th>
<th>Visit 1</th>
<th>Visit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perfusion</strong></td>
<td>36</td>
<td>40</td>
</tr>
<tr>
<td><strong>ICC</strong></td>
<td>0.46</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>CV(%)</strong></td>
<td>37.0</td>
<td>37.0</td>
</tr>
</tbody>
</table>

* Perfusion listed in ml/min/100g

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### Graphs

- **Same Visit**
  - Equations:
    - Scan 1: $y = 0.72x + 14$
    - Scan 2: $y = 0.78x + 14$
  - ICC: 0.79, *p < 0.001*
  - CV(%): 16.7
- **Separate Visits**
  - Equations:
    - Visit 1: $y = 0.80x + 12$
    - Visit 2: $y = 0.65x + 12$
  - ICC: 0.65, *p < 0.001*
  - CV(%): 23.8
Results: Coached/Triggered vs Free Breathing

<table>
<thead>
<tr>
<th></th>
<th>Triggered/Coached</th>
<th>Free Breathing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical</td>
<td>382 ml/min/100g</td>
<td>344 ml/min/100g</td>
</tr>
<tr>
<td>Medullary</td>
<td>36 ml/min/100g</td>
<td>13 ml/min/100g</td>
</tr>
</tbody>
</table>
Results: Coached/Triggered vs Free Breathing

- Data trend toward lower perfusion values under free-breathing.
- The trend was not statistically significant but $N = 5$. 
Regional perfusion heterogeneity observed in 3 transplant subjects
Results: Longitudinal Study in Transplant Living Donor-Recipient Pairs

Donors (n = 15)

Recipients (n = 15)

No losartan (LOS-)

25-50 mg/day losartan (LOS+)

Results: Losartan in recipients was associated with a higher cortical perfusion.  

\[ 62 \text{ ml/min/100g} \]

\[ P < 0.05 \text{ LOS- vs. LOS+} \]

\[ P < 0.05 \text{ vs. baseline} \]
### Results: Changes in Estimated GFR and FE\textsubscript{Na}

<table>
<thead>
<tr>
<th></th>
<th>Baseline (B)</th>
<th>Δ(B → 3 mo)</th>
<th>Δ(B → 1 y)</th>
<th>Δ(B → 2 y)</th>
<th>Δ(LOS- → LOS+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion, cortex, mL/min per 100 g</td>
<td>412 ± 19</td>
<td>-92 ± 18*</td>
<td>-121 ± 21*</td>
<td>-141 ± 21*</td>
<td>62 ± 24†</td>
</tr>
<tr>
<td>Perfusion, medulla, mL/min per 100 g</td>
<td>41 ± 7</td>
<td>-2 ± 9</td>
<td>-9 ± 10</td>
<td>-14 ± 10</td>
<td>3 ± 10</td>
</tr>
<tr>
<td>Rs*, cortex, s(^{-1})</td>
<td>11.6 ± 0.3</td>
<td>0.7 ± 3.0</td>
<td>0.2 ± 0.4</td>
<td>0.4 ± 0.4</td>
<td>0.1 ± 0.4</td>
</tr>
<tr>
<td>Rs*, medulla, s(^{-1})</td>
<td>18.1 ± 0.6</td>
<td>-1.4 ± 0.6†</td>
<td>-1.5 ± 0.7†</td>
<td>0.3 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m(^2)§</td>
<td>43.9 ± 3.1</td>
<td>11.6 ± 3.6†</td>
<td>9.4 ± 4.2†</td>
<td>14.6 ± 4.3</td>
<td>1.6 ± 4.5</td>
</tr>
<tr>
<td>FE\textsubscript{Na}, %</td>
<td>0.6 ± 0.2</td>
<td>0.4 ± 0.2†</td>
<td>0.6 ± 0.2†</td>
<td>0.2 ± 0.2</td>
<td>-0.2 ± 0.2</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SE. Δ for time points represents the difference with respect to baseline. Δ(LOS- → LOS+) represents the difference between recipient groups and includes both 1 year and 2 years.

* \(P < 0.001\) LOS- versus baseline.
\(P < 0.05\) LOS- versus LOS+.
† \(P < 0.05\).
§ Baseline value is listed as 0.5 \(\times\) (total eGFR) for comparison with subsequent single-kidney measurements.
\| \(P < 0.01\).

- eGFR increases overall by ~30% in the transplant kidney at 2 years
- FE\textsubscript{Na} % also increases overall 50-100% initially but stabilized at 2 years
Summary/Conclusions

• ASL MRI in the kidney provides a time-averaged* estimate of cortical and medullary perfusion responsive to interventions and changes in function
  – Medullary perfusion more challenging due to prolonged transit time
    • Additional complexity due to the possibility of perfusion shunting
• Measures have negligible bias, provide regional information and are highly repeatable.
• ASL FAIR provides a useful and robust tool for longitudinal study of kidney disease

*Doesn’t capture absolute perfusion as measured by microspheres, possibly due to short-term fluctuations
Recommendations for Future Work

• Need for assessing pCASL vs pASL performance in the kidneys and across field strengths
  – What are the tradeoffs in robustness to motion, spatial resolution, and SNR for applications in the kidney?

• Implementation of accelerated acquisition methods to optimize inversion delay
  – Robust against bias due to delayed arterial arrival times in disease and with age
  – Perhaps can improve robustness for estimating medullary perfusion

• More thorough exploration of the benefits of independent tissue $T_1$ measurement on a per patient basis.
Thank you.

Departments of Radiology and Medical Physics

Recruitment and Safety Monitoring:
• Jan Yakey, RN
• Amanda Kolterman, LVN

Regulatory and Protocol:
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• Donna McGrew

Technologists:
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• Sara John RT
• Jenelle Fuller RT

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Extra Slides
Main messages

• ASL perfusion is an attractive non-invasive tool for evaluating renal function
  – Non-Gd for Fe contrast agent approach is favorable in light of renal insufficiency
  – Captures time averaged cortical perfusion; less robust for medullary perfusion
  – Technically simple using FAIR in our experience

• Low bias and coefficient of variation for repeated measures

• Can be performed repeatedly for longitudinal assessment
Outline

• Motivation
  – Oxygen delivery paradigm
  – Cortical/medullary perfusion anatomy
  – Benefits of endogenous contrast
    • risks of contrast agents in renal insufficiency
    • longitudinal assessment

• Background review
  – ASL methodology and prior work
  – Limitations
    • Signal to noise ratio
    • Fixed inversion delay
    • Finite label and medullary perfusion

• Methods
  – FAIR ASL approach
    • Simple implementation – slice label
    • Robust to different kidney positioning
    • Signal averaging and motion compensation

• Results
  – Pre-clinical microsphere study
  – Repeatability in healthy and diseased kidneys
  – Longitudinal study in transplant donor-recipient pairs

• Conclusions
Donors showed a small decline in cortical perfusion at 2 years.

* $P < 0.05$ vs. baseline
Donors showed a lower cortical $R_2^*$ (higher $pO_2$) at 1 year.

* $P < 0.05$ vs. baseline
Losartan did not affect $R_2^*$ in recipients.

* $P < 0.05$ vs. baseline