DEPARTMENT OF Medical Physics

University of Wisconsin SCHOOL OF MEDICINE AND PUBLIC HEALTH

NIH National Institute of Diabetes and Digestive and Kidney Diseases

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

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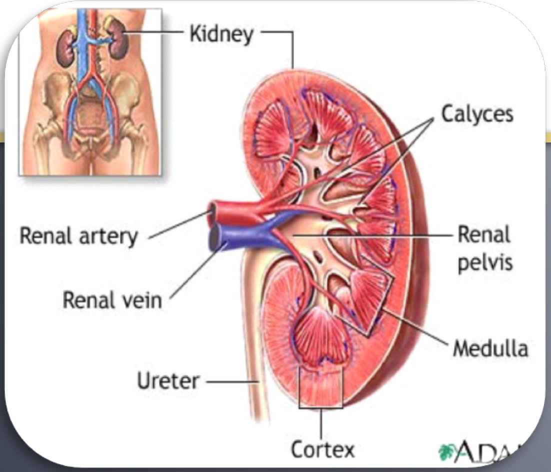
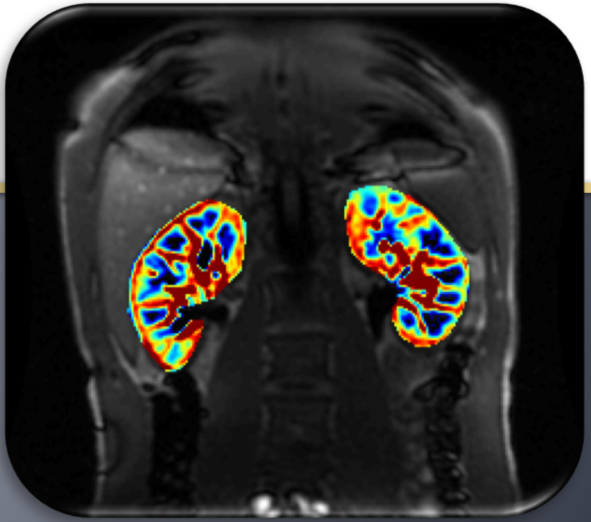


NIH/NIDDK Renal Imaging Workshop
Thursday, July 12th, 2018



Motivation: Improving Diagnostic Tools

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- Goal of assessing kidney function using *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[1] and Perfusion[2] MRI appear to differentiate ATN from rejection in renal transplants
  - ASL methods avoid toxicity of exogenous contrast agents

[1]Sadowski et al. Radiology, 2005

[2]Szolar et al. MRI, 1997

Background: Types of Arterial spin labeling (ASL) techniques

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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

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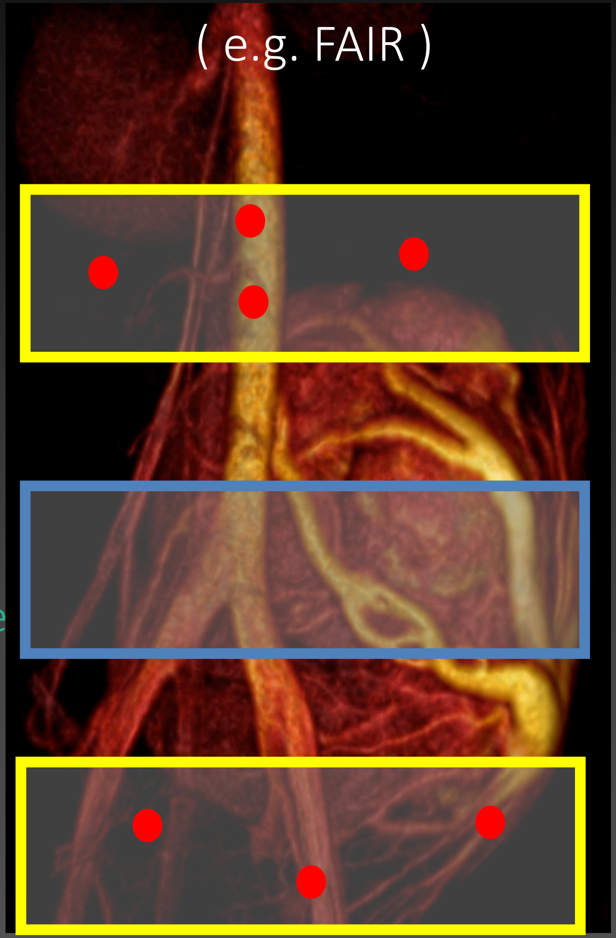
Labeling Plane/Slab

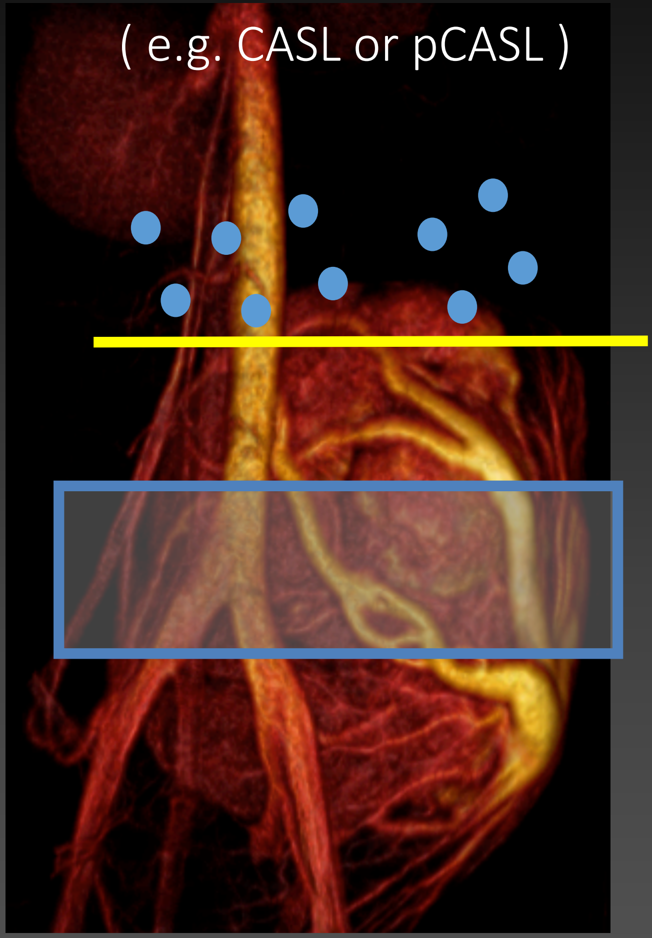
Image Volume/Slice

Selective Slab Based



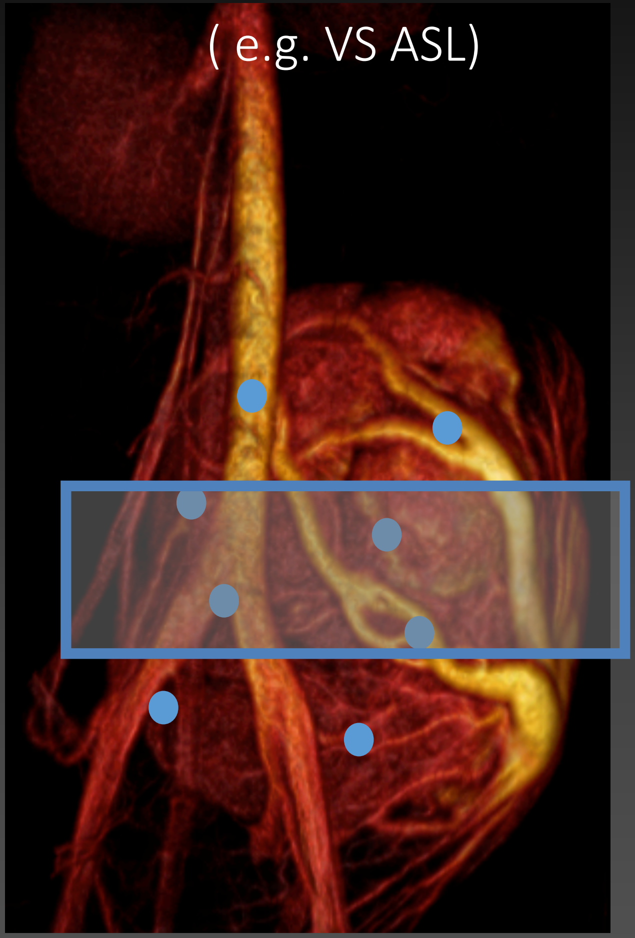
Blood in slab is inverted and moves into volume

Slice Based



Blood that passes through plane is inverted

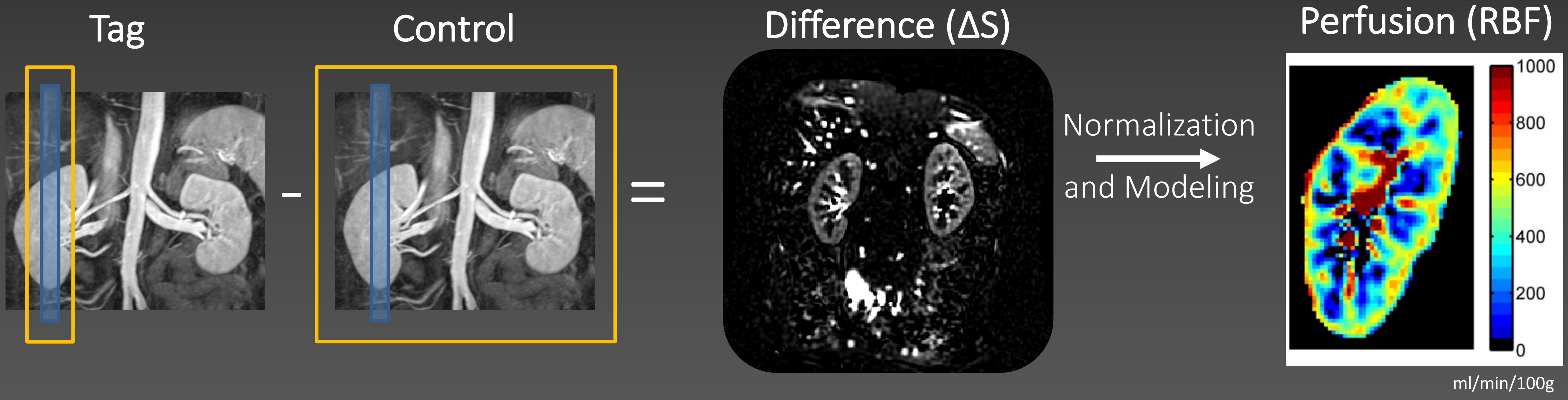
Motion Based



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



Background: ASL Signal Models

Reference Image Correction
Bulk decay of signal after labeling correction
Account for label time
Account for tagging efficiency

RBF is renal blood flow [ml/100g/min]
λ 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)
α is the tagging efficiently

FAIR
(pulsed ASL)

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

- 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
- Excellent ASL review can be found here: https://www.ncbi.nlm.nih.gov/pubmed/?term=10.1002%2Fmrm.25197

Methods: FAIR-bSSFP ASL for Kidney Perfusion

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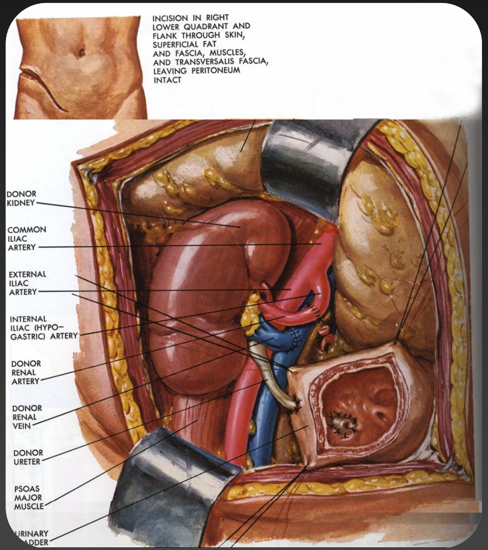
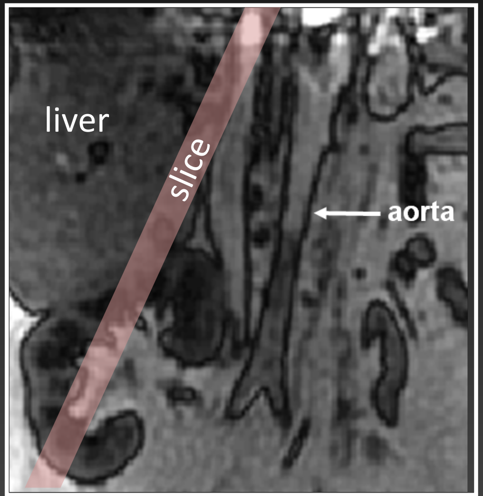
- Preliminary Results in Healthy Native Kidneys
  - Martirosian et al. *Magn Reson Med*. Feb 2004; 51(2): 353-361.
- Correlated with Renal Artery Stenosis Grade
  - Fenchel et al. *Radiology*. Mar 2006; 238(3): 1013-1021.
- Feasibility in Diseased Native and Transplanted Kidneys
  - Artz et al. *Magn Reson Imaging*. 2011 Jan;29(1):74-82.
  - Li et al., Kidney International Reports. 2017; 2:36-43.
  - Cai et al., *J Magn Reson Imaging*. 2017; 46:589-594.
- Reproducibility in Diseased Native and Transplanted Kidneys
  - Artz et al. *J Magn Reson Imaging*. 2011 Jun;33(6):1414-21.
- Accuracy using an Interventional Swine Study
  - Artz et al. *Investigative Radiology.* 2011 Feb;46(2):124-31.
  - Wentland et al. *Nephrol Dial Transplant*. 2012 Jan;27(1):128-35.
- Demonstration of longitudinal change in renal transplant living donor-recipient pairs
  - Niles et al. *Investigative Radiology.* 2016 Feb;51(2):113-20.

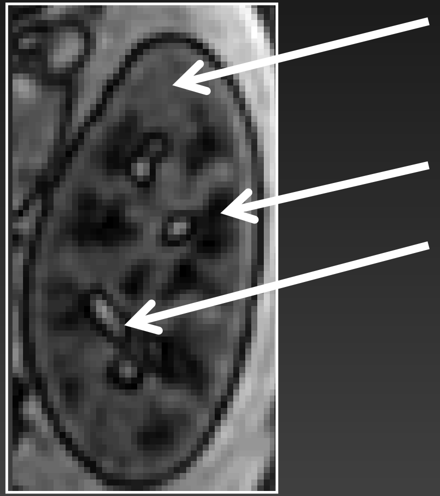
- Review of ASL use for renal perfusion can be found here:
  - Nery et al., *Diagnostics* 2018; 8:2-15.

Methods: ASL MRI uses a FAIR tagging scheme and balanced SSFP readout





Imaged in sagittal plane



Sagittal view

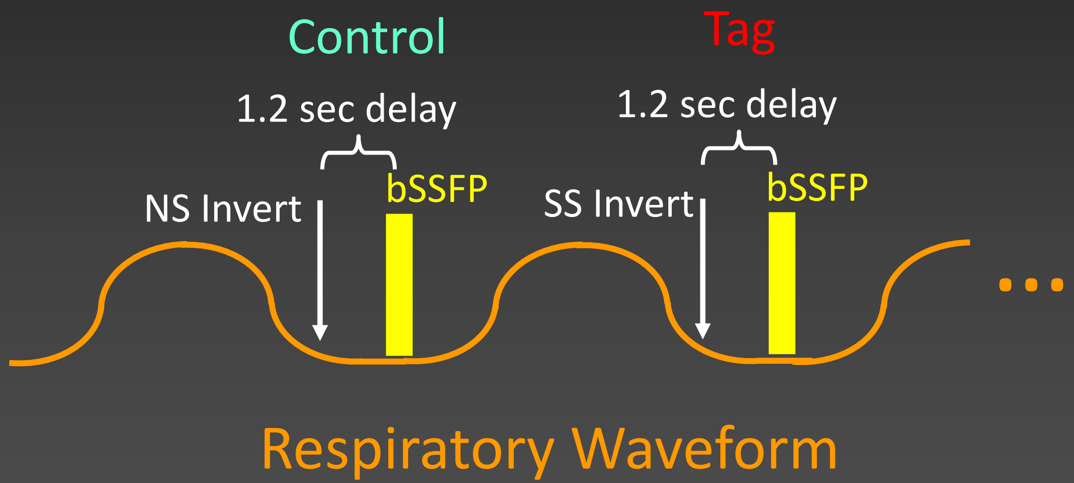
Acquisition parameters:

- 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.

1. Artz NS, et al. JMRI 2011.

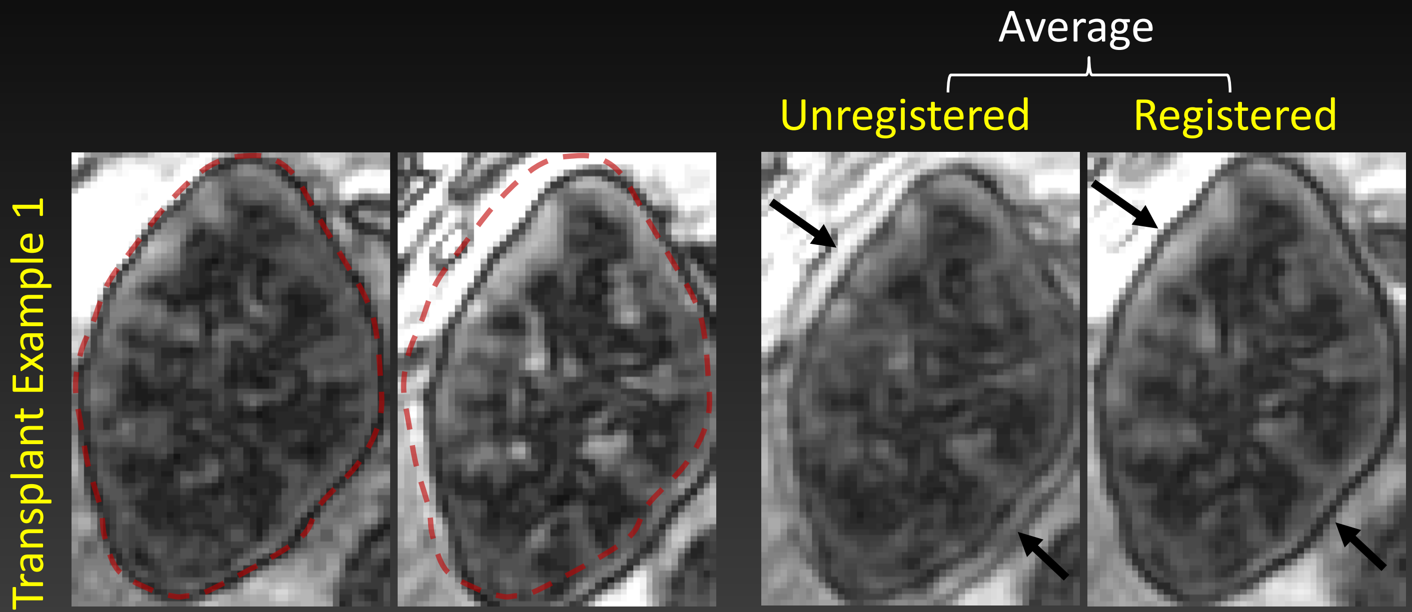
Methods: Motion Compensation

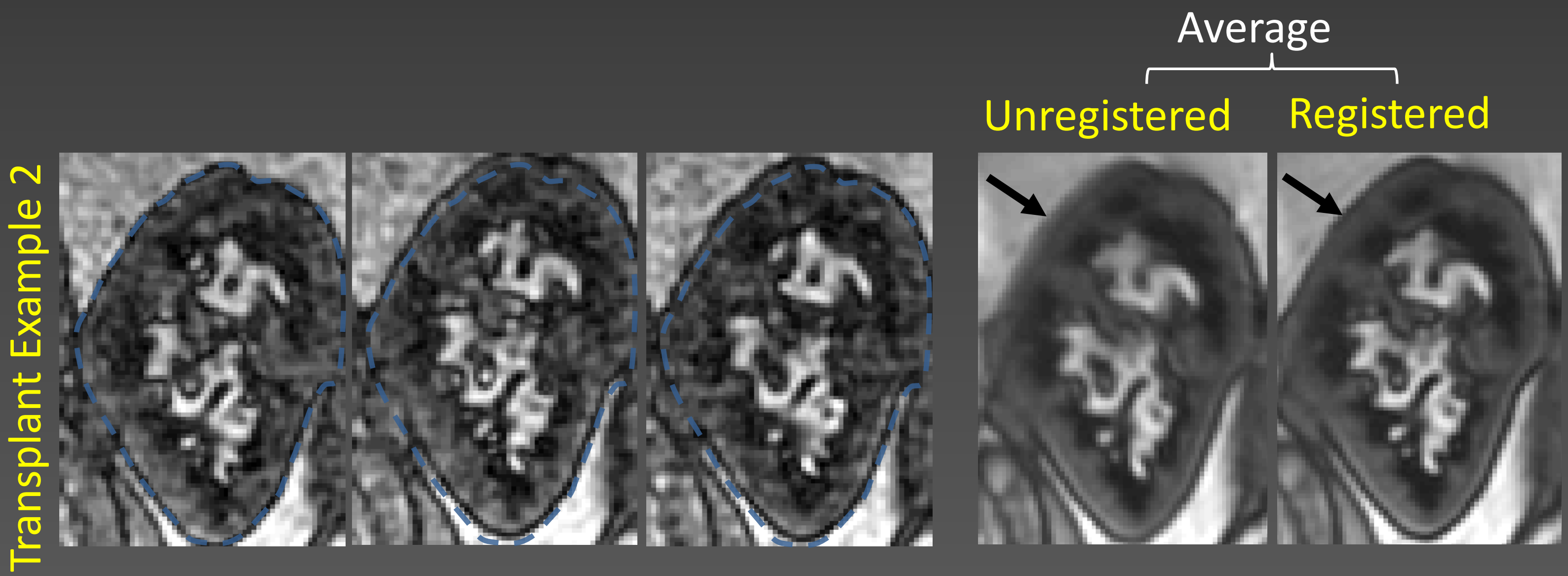
- Respiratory triggering and coaching
- Retrospective Image Registration
  - Images aligned for each kidney separately using Normalized Mutual Information (NMI)



- Magnetization Compensation
  - Respiratory Rate $\leq$ 12 breaths/min

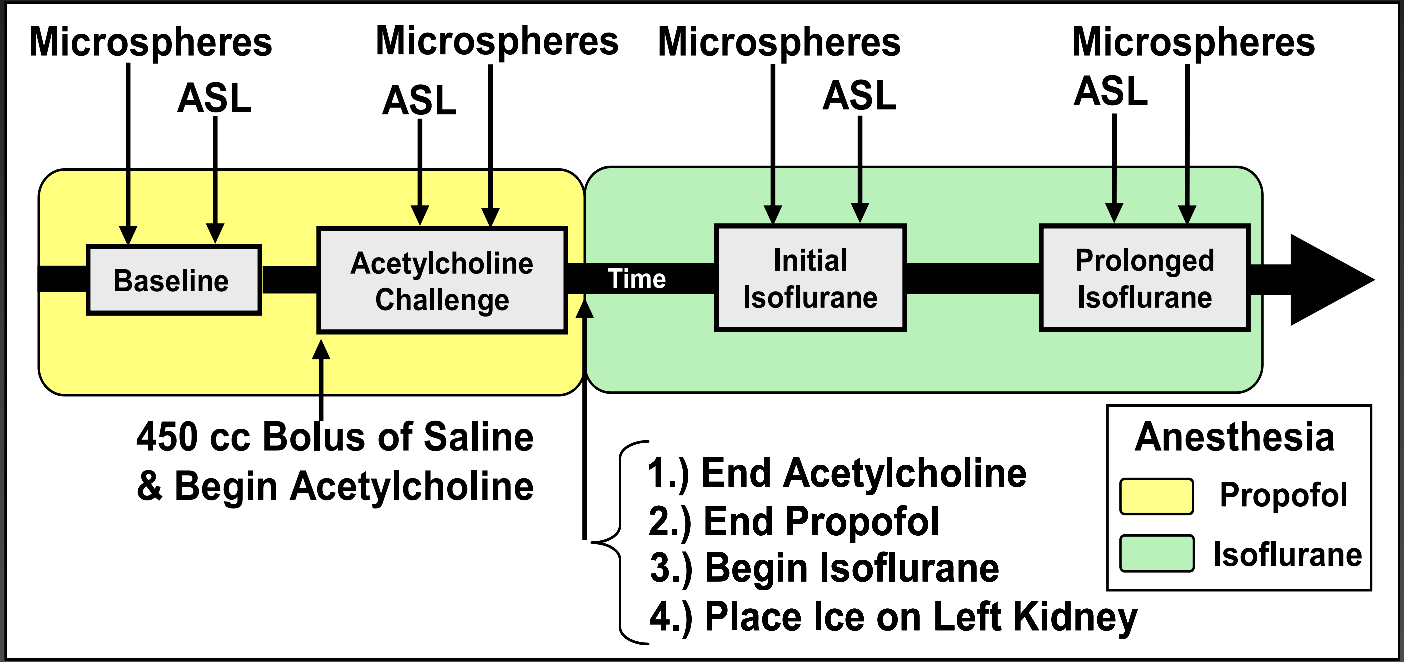
Methods: Retrospective Image Registration





Results: ASL vs. Fluorescent Microspheres

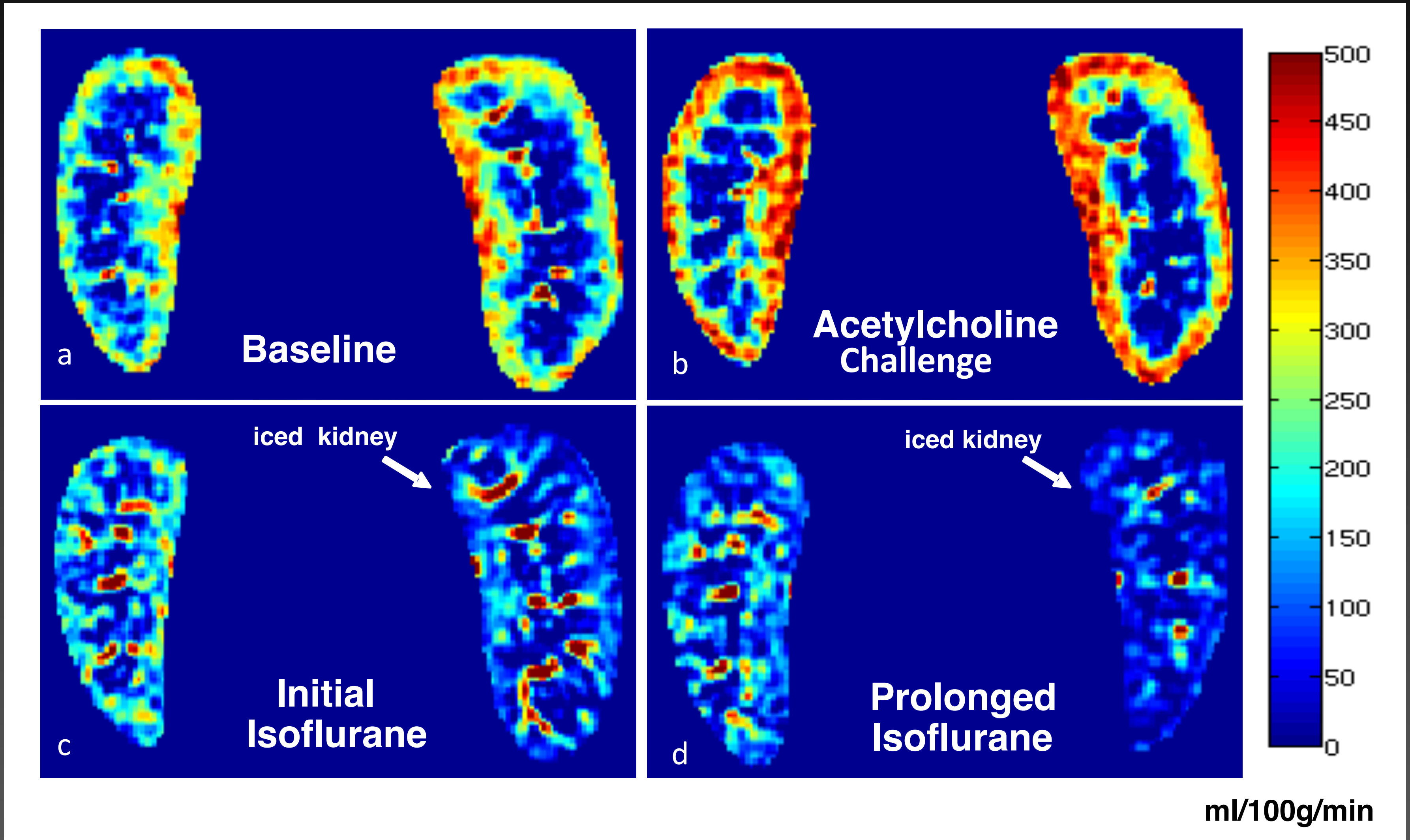
- Interventional Swine Study
  - 11 female swine (34-38 kg)
  - Microsphere and ASL perfusion (cortex only) measured at four time points



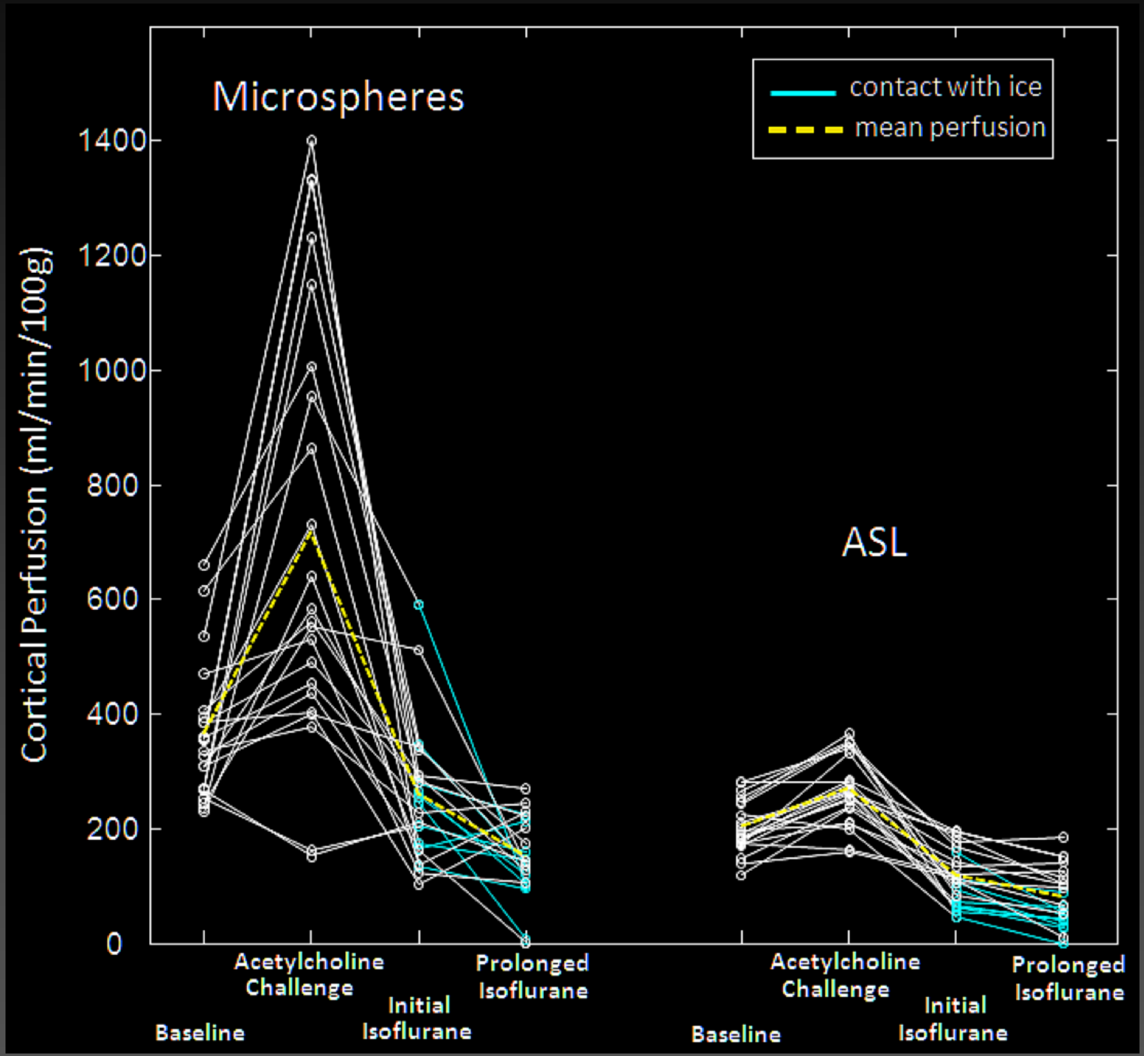
  - 2 back-to-back injections of microspheres at each time point
  - ASL scanning and processing: same as previous studies

Artz et al. *Investigative Radiology.* 2011 Feb;46(2):124-31.
Wentland et al. *Nephrol Dial Transplant*. 2012 Jan;27(1):128-35.

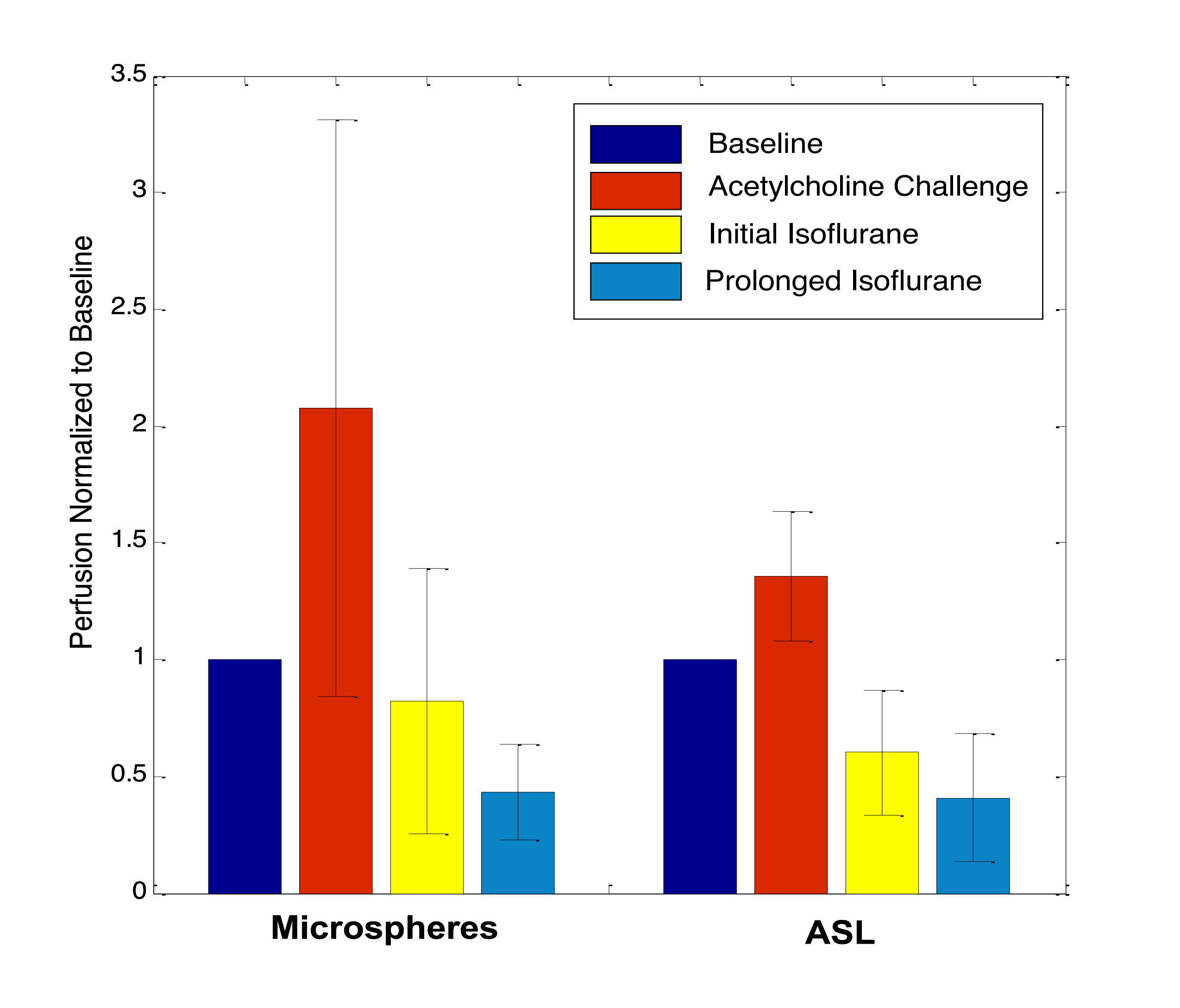
Results: ASL Perfusion Maps



Results: Individual RBF Responses



Results: Normalized Perfusion vs Intervention



Averaged for 11 Swine (22 kidneys)

Results: Test/Retest and Reproducibility Study Design

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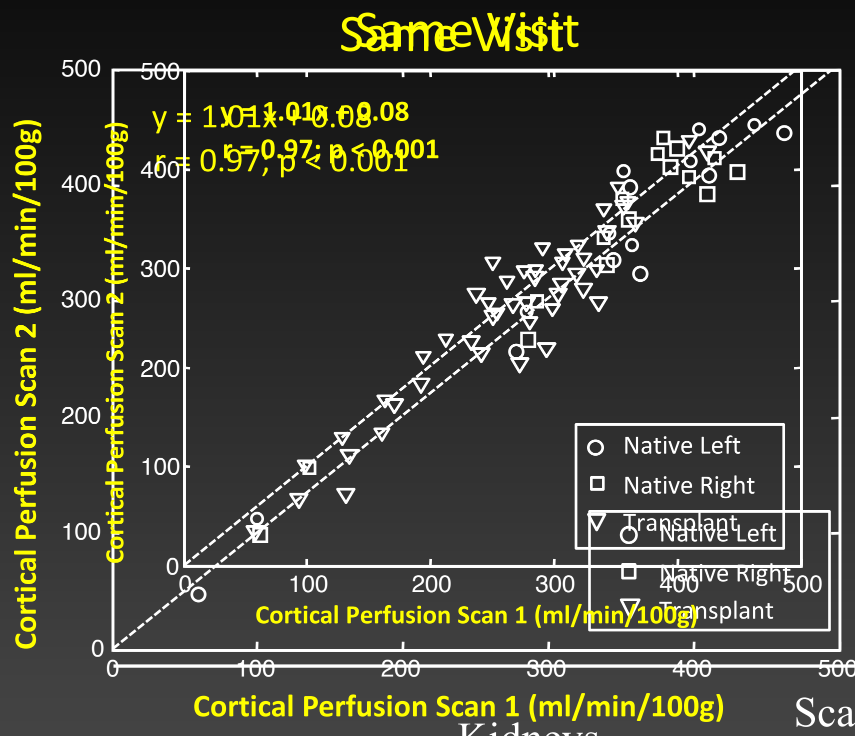
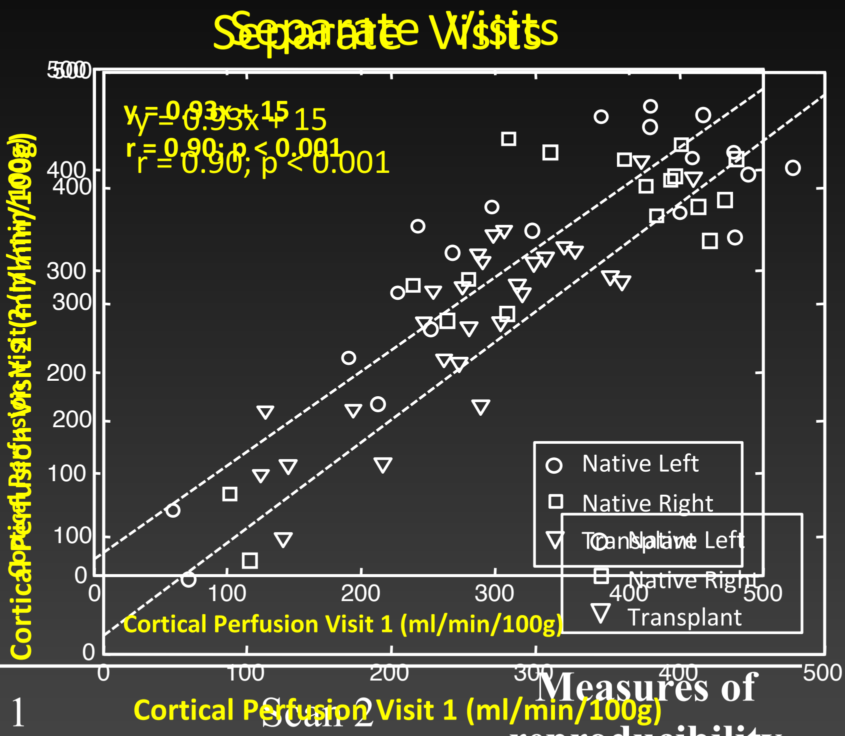
- Human Subjects (n = 24 subjects)
  - 10 with native kidneys, 14 with transplanted kidneys
    - Broad range of renal function
    - All subjects were stable
      - serum creatinine levels varied < 0.3 mg/dL between visits
      - no events changed their clinical status during the interim
    - Refrained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

Artz et al. *J Magn Reson Imaging*. 2011 Jun;33(6):1414-21.

Reproducibility – Cortical Perfusion

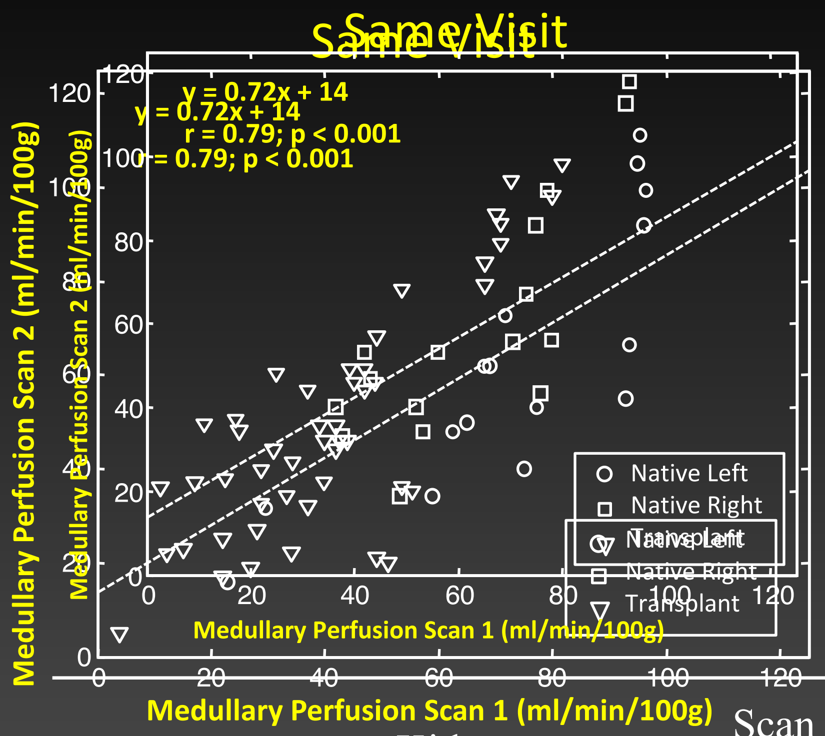


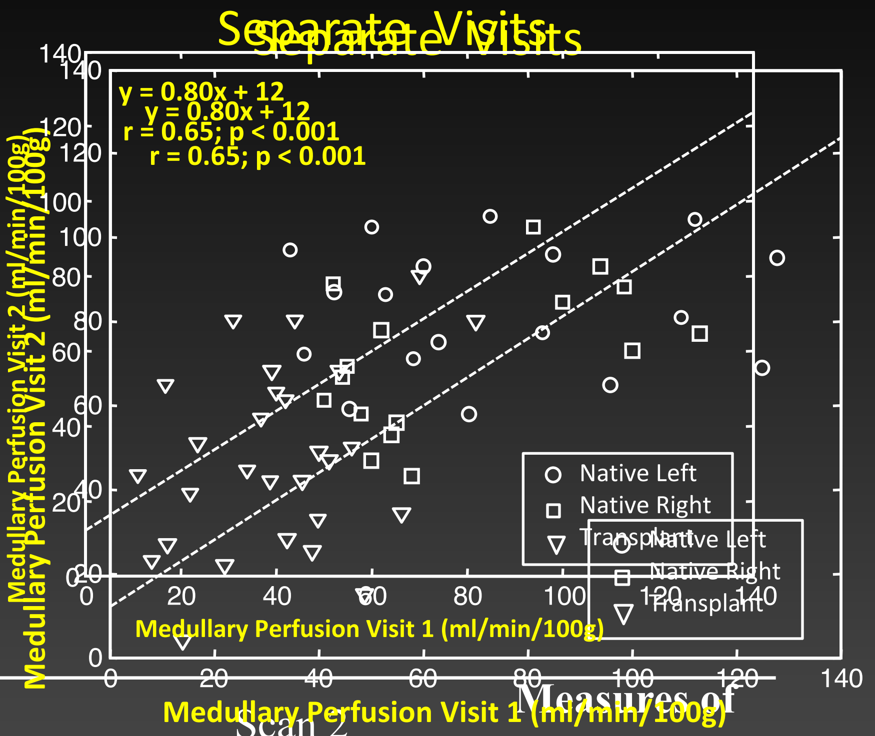


	Kidneys	Scan 1 Mean Perfusion*	Scan 2 Mean Perfusion*	Measures of reproducibility: ICC	CV(%)
Same Visit	Native Right	337	340	0.98	4.8
	Native Left	337	332	0.98	5.2
	Transplant	269	275	0.96	6.0
Separate Visits	Native Right	337	339	0.89	11.0
	Native Left	318	336	0.89	13.1
	Transplant	271	272	0.94	7.6

* Perfusion listed in ml/min/100g

Reproducibility – Medullary Perfusion

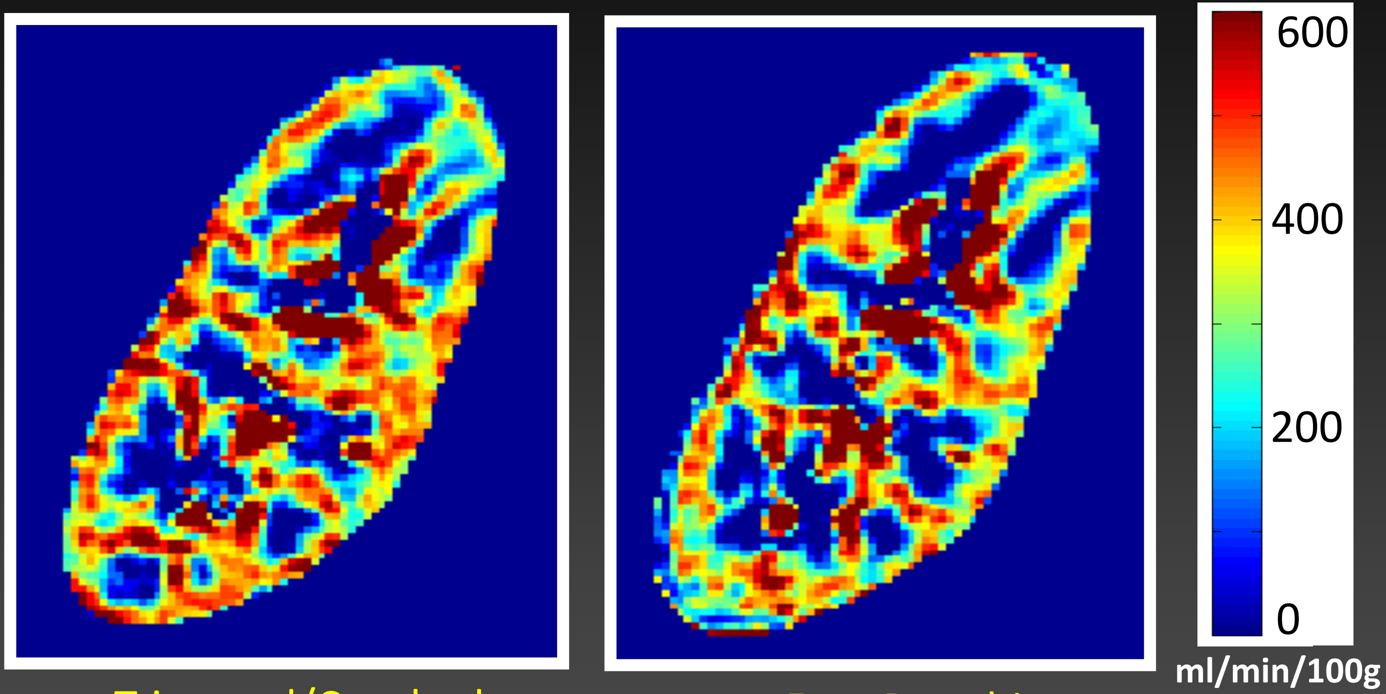




	Kidneys	Scan 1 Mean Perfusion*	Scan 2 Mean Perfusion*	Measures of reproducibility: ICC	Measures of reproducibility: CV(%)
Same Visit	Native Right	64	65	0.78	16.7
	Native Left	72	57	0.72	23.8
	Transplant	38	43	0.77	26.7
Separate Visits	Native Right	72	65	0.63	19.8
	Native Left	79	77	0.13	28.1
	Transplant	36	40	0.46	37.0

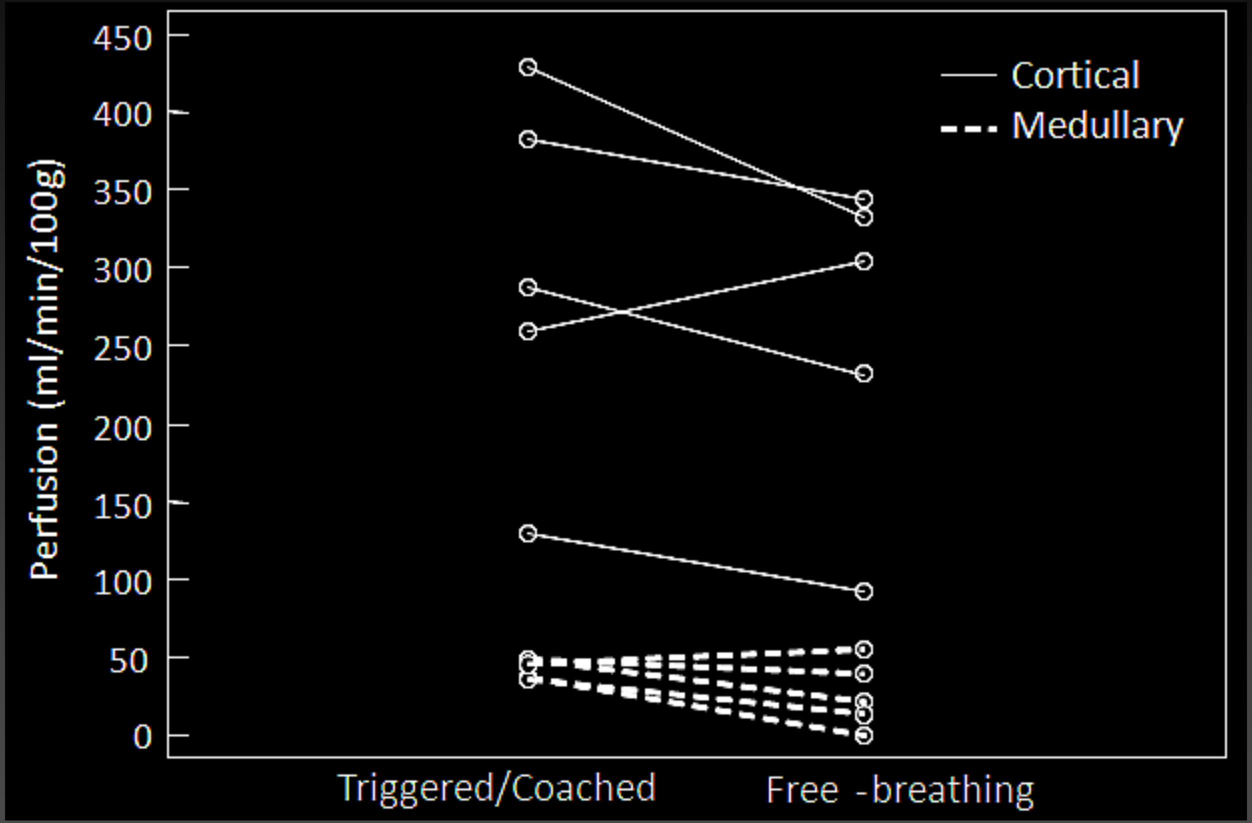
* Perfusion listed in ml/min/100g

Results: Coached/Triggered vs Free Breathing



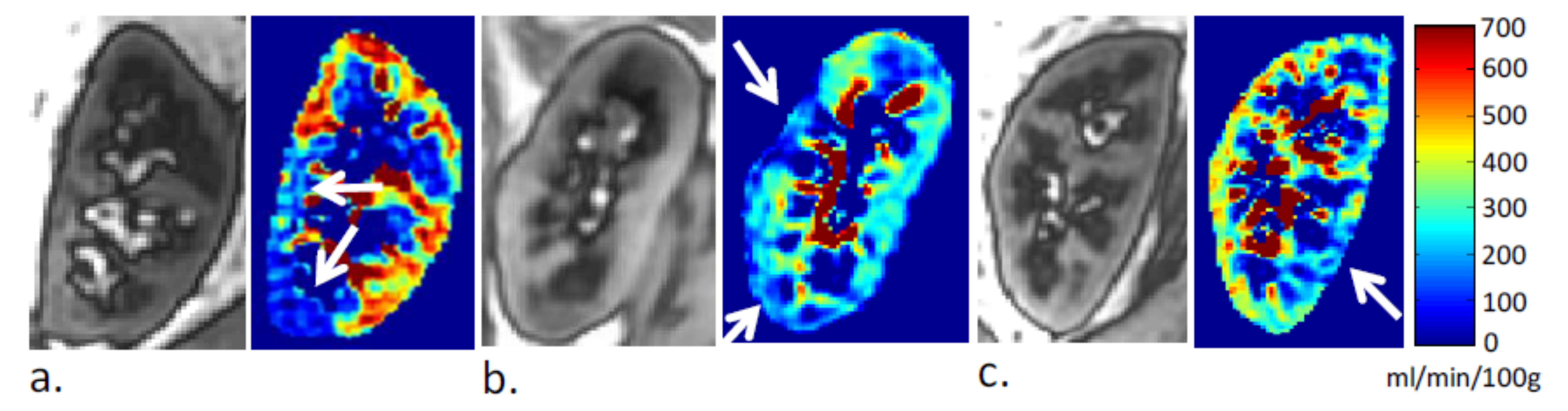
Average Perfusion	Triggered/Coached	Free Breathing
Cortical	382 ml/min/100g	344 ml/min/100g
Medullary	36 ml/min/100g	13 ml/min/100g

Results: Coached/Triggered vs Free Breathing



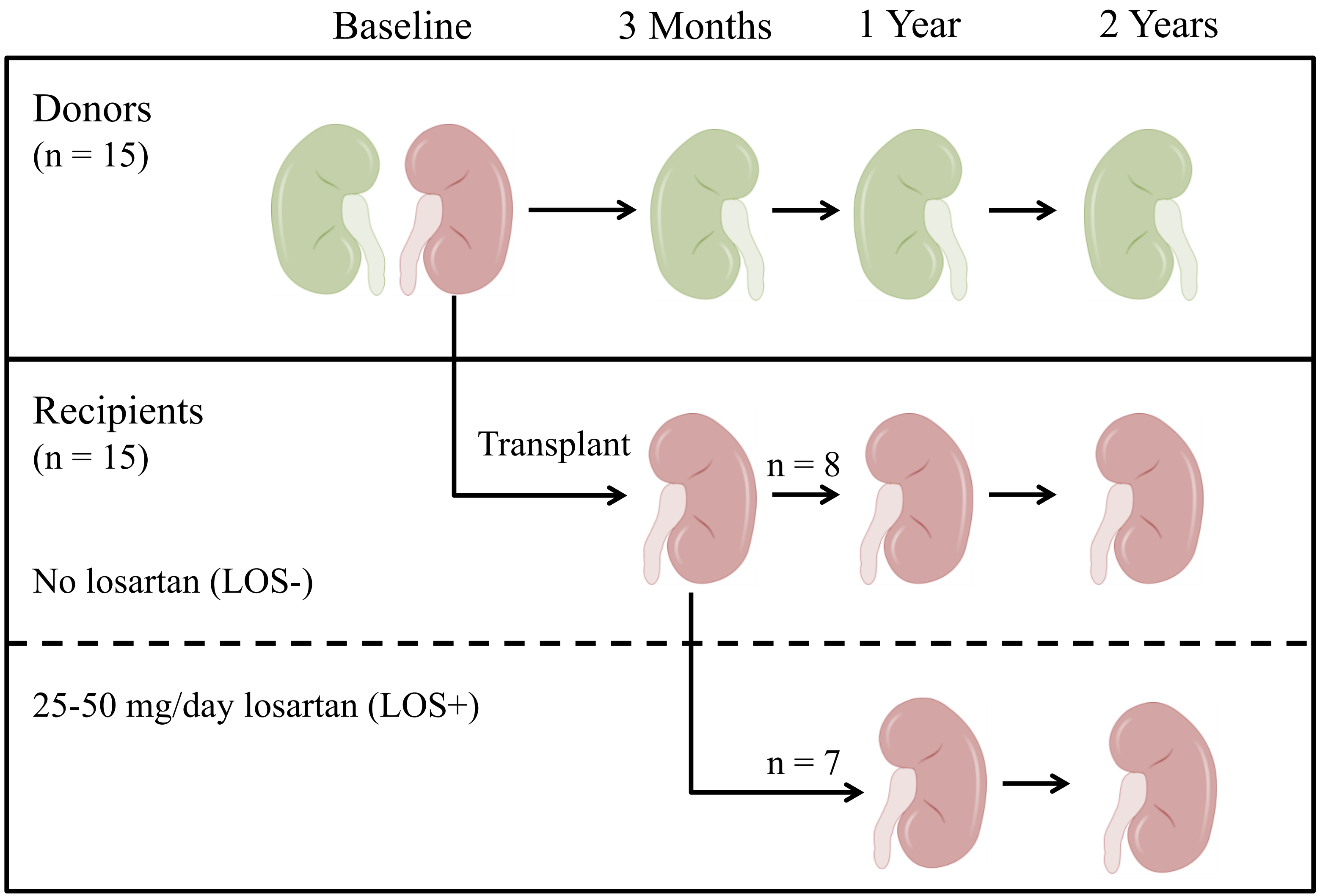
- Data trend toward lower perfusion values under free-breathing.
- The trend was not statistically significant but N = 5.

Regional Perfusion Information



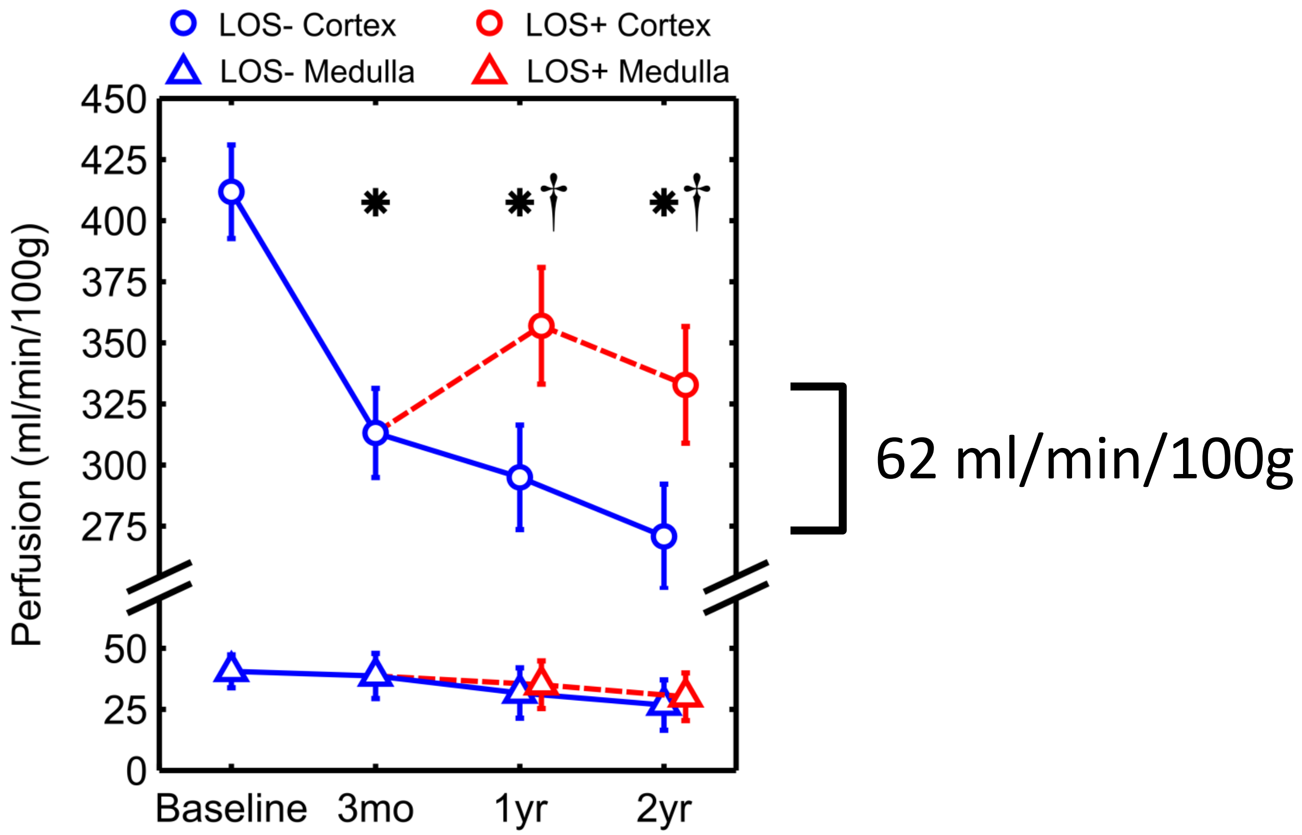
Regional perfusion heterogeneity observed in 3 transplant subjects

Results: Longitudinal Study in Transplant Living Donor-Recipient Pairs



Niles et al. *Investigative Radiology.* 2016 Feb;51(2):113-20.

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



† $P < 0.05$ LOS- vs. LOS+

* $P < 0.05$ vs. baseline

Results: Changes in Estimated GFR and FE_{Na}

	Baseline (B)	Δ(B → 3 mo)	Δ(B → 1 y)	Δ(B → 2 y)	Δ(LOS− → LOS+)
Perfusion, cortex, mL/min per 100 g	412 ± 19	−99 ± 18*	−117 ± 21*	−141 ± 21*	62 ± 24 †
Perfusion, medulla, mL/min per 100 g	41 ± 7	−2 ± 9	−9 ± 10	−14 ± 10	3 ± 10
R_2*, cortex, s^{-1}	11.6 ± 0.3	0.2 ± 0.3	0.2 ± 0.4	0.4 ± 0.4	0.1 ± 0.4
R_2*, medulla, s^{-1}	18.1 ± 0.6	−1.4 ± 0.6‡	−1.7 ± 0.7‡	−1.5 ± 0.8	0.3 ± 0.8
eGFR, mL/min per 1.73 m^2§	43.9 ± 3.1	11.6 ± 3.6‖	9.4 ± 4.2‡	14.6 ± 4.3‖	1.6 ± 4.5
FE_{Na}, %	0.6 ± 0.2	0.4 ± 0.2‡	0.6 ± 0.2‡	0.2 ± 0.2	−0.2 ± 0.2

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 × (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_{Na} % *also* increases overall 50-100% initially but stabilized at 2 years

Summary/Conclusions

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- 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
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- Donna McGrew

Technologists:

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- Sara John RT
- Jenelle Fuller RT

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Extra Slides

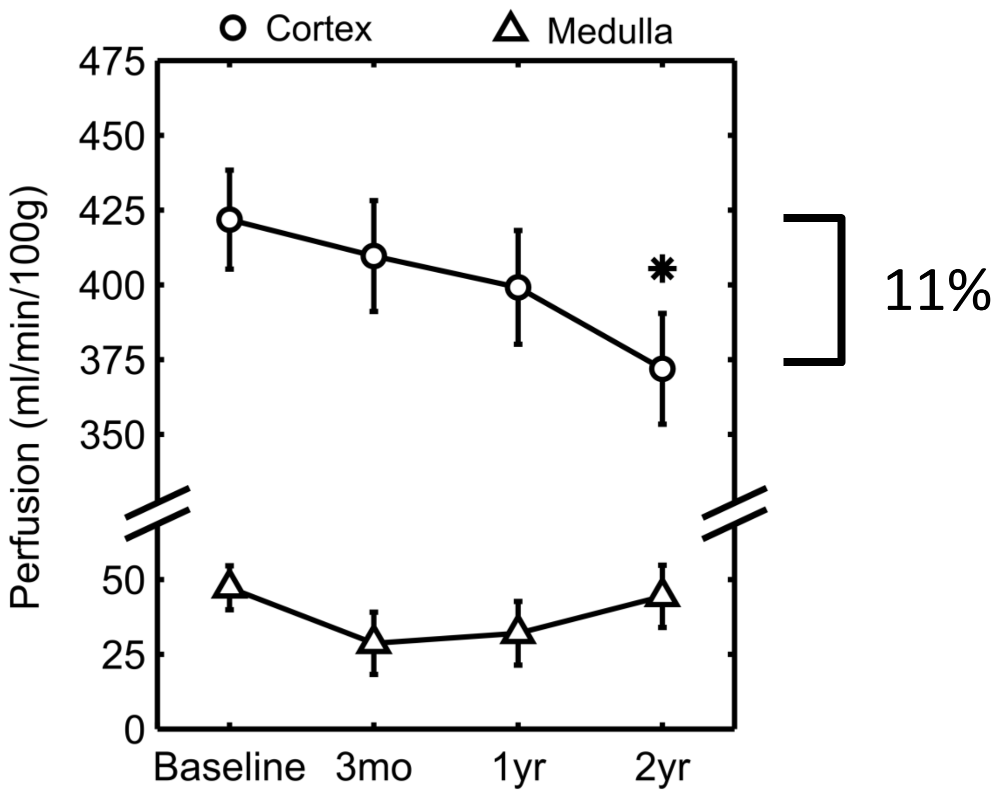
Main messages

- 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

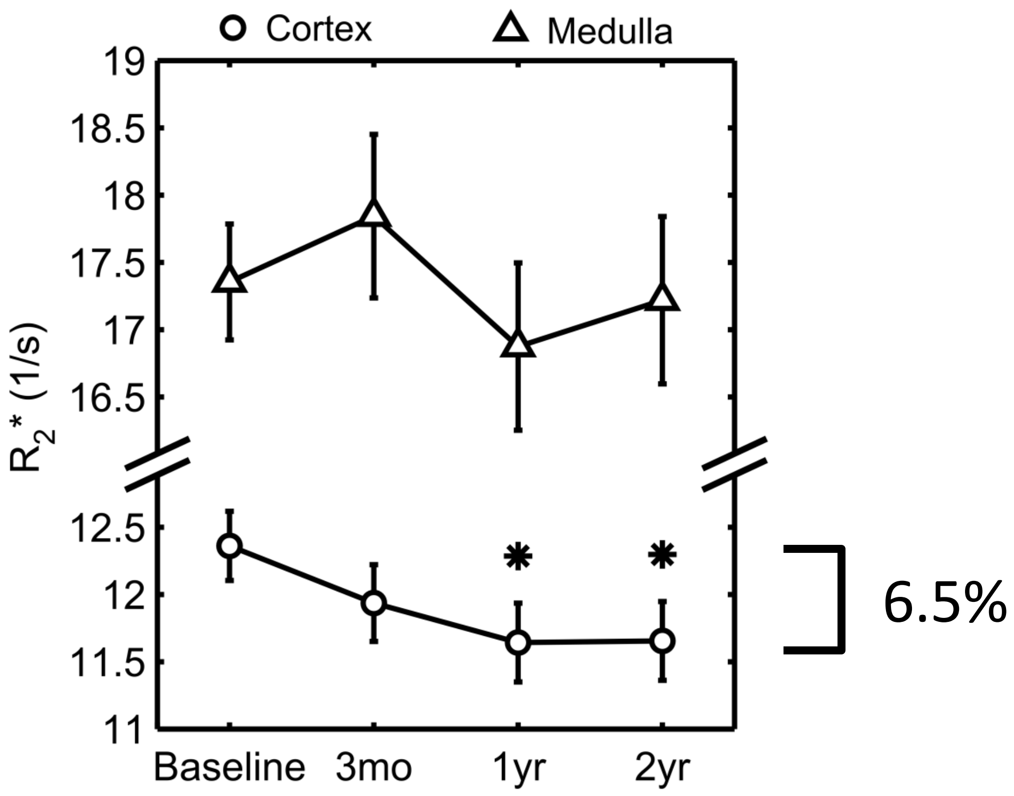
- Motivation
  - Oxygen delivery paradigm
  - Cortical/medullary perfusion anatomy
  - Benefits of endogenous contrast
    - risks of contrast agents in renal insufficiency
    - longitudinal assessment
- Background review
  - ASL methodology and prior work
  - Limitations
    - Signal to noise ratio
    - 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.



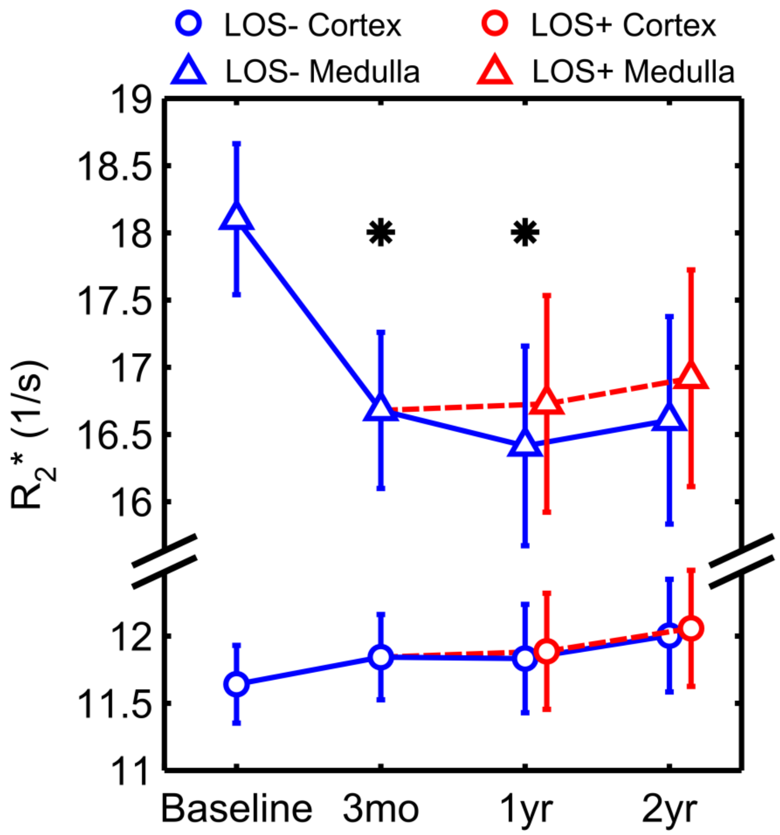
* $P < 0.05$ vs. baseline

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