Applications of MRI to AKI

Evidence to date

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associate professor

Notthingham, October, 2019, supported by PARENCHYMA COST Association

250 years of EXCELLENCE
in medical education,
research & innovation
and healthcare

Semmelweis University
http://semmelweis.hu

FACULTY OF MEDICINE
I. Department of Pediatrics

Diagnosis of AKI

Based on:

Serum creatinine and urine output

Increase in Serum Cr by 0.3 mg/dl within 48 hours

OR

Increase in Serum Cr to 1.5 times of baseline, within the prior 7 days

OR

Urine volume <0.5 ml/kg/h for 6 hours.

KDIGO Acute Kidney Injury Work Group. Kidney Int. 2012

250 years of EXCELLENCE in medical education, research & innovation and healthcare

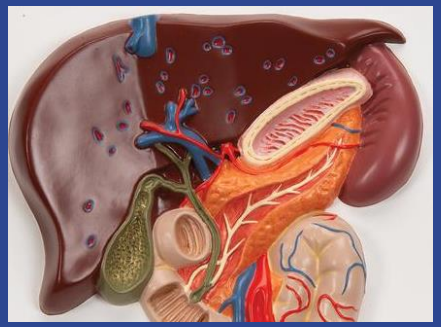
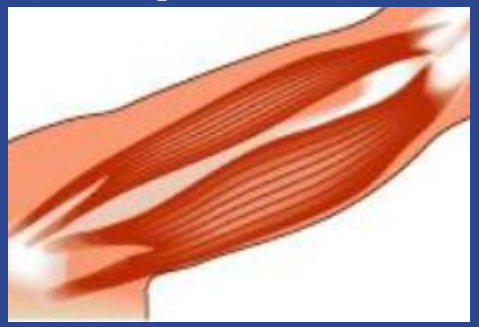
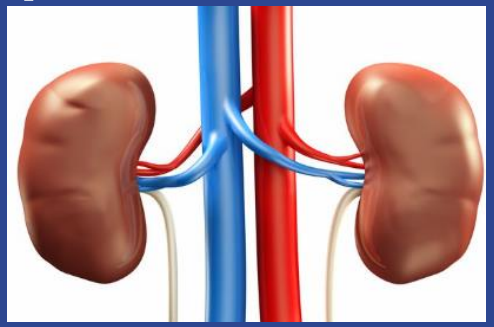
Diagnosis of AKI

Based on:

serum creatinine increase and/or decrease in urine output

BUT

NOT sensitive, specific, rapid ENOUGH

CONSTANT NEED

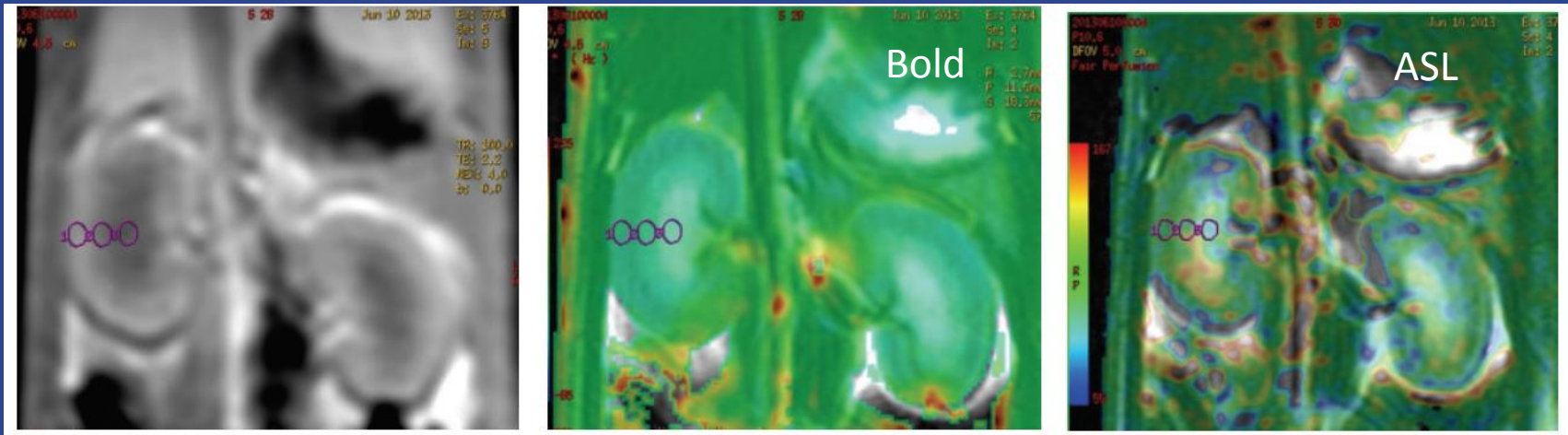
new biomarkers, non-invasive, imaging techniques

Contrast induced AKI (CIAKI)

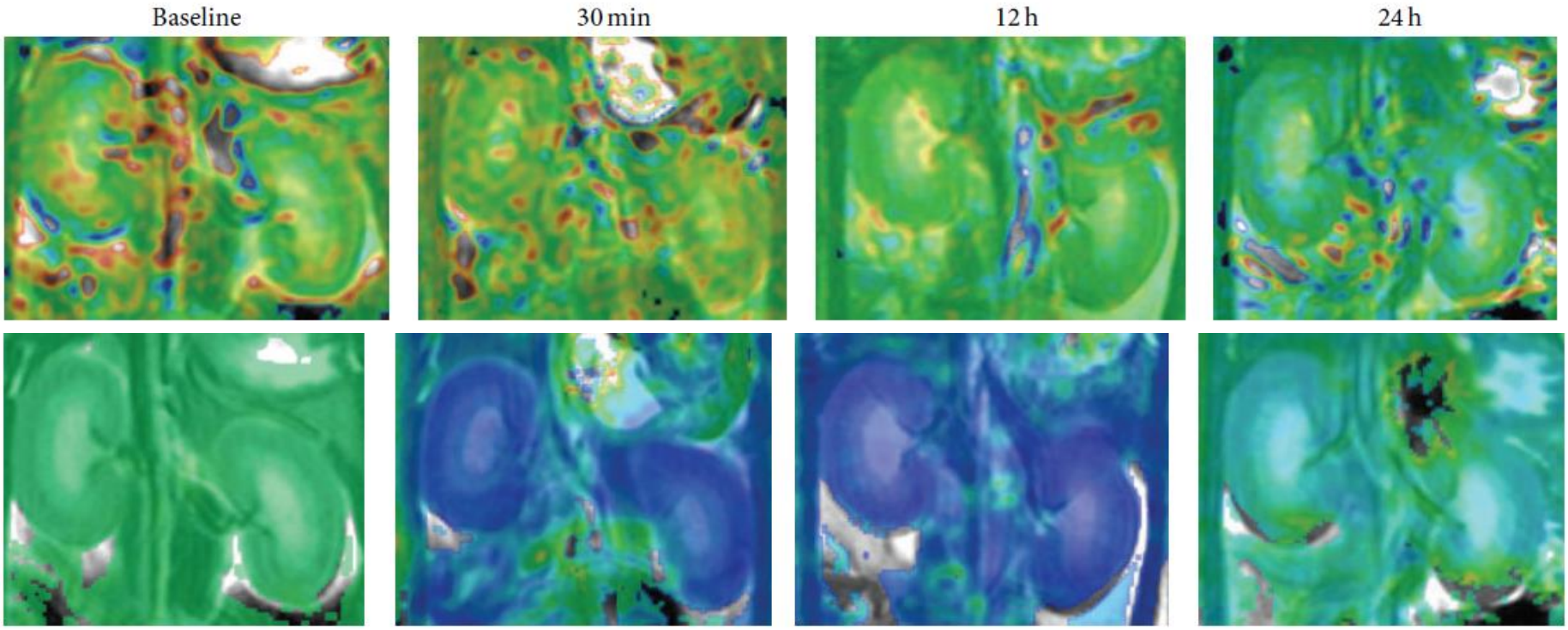
- 3rd leading cause of AKI in hospitalized patients (11% incidence)
- Long-term consequences, high mortality
- Underdiagnosed in many cases – no marker
- Risk factors:
  - dosage, frequency and route of administration
  - type of contrast agent
  - comorbidities, hydration status etc.

Why fMRI instead of SeCr?

- Model: adult male Wistar rats,
  ionic iodinated CA (6 ml/bwkg, iv.)
- Time points: Baseline, 30 min, 12h, 24h, 48h, 72h,96h
- Methods: 3T GE BOLD, ASL, SeCrea



Chen et al, 2015

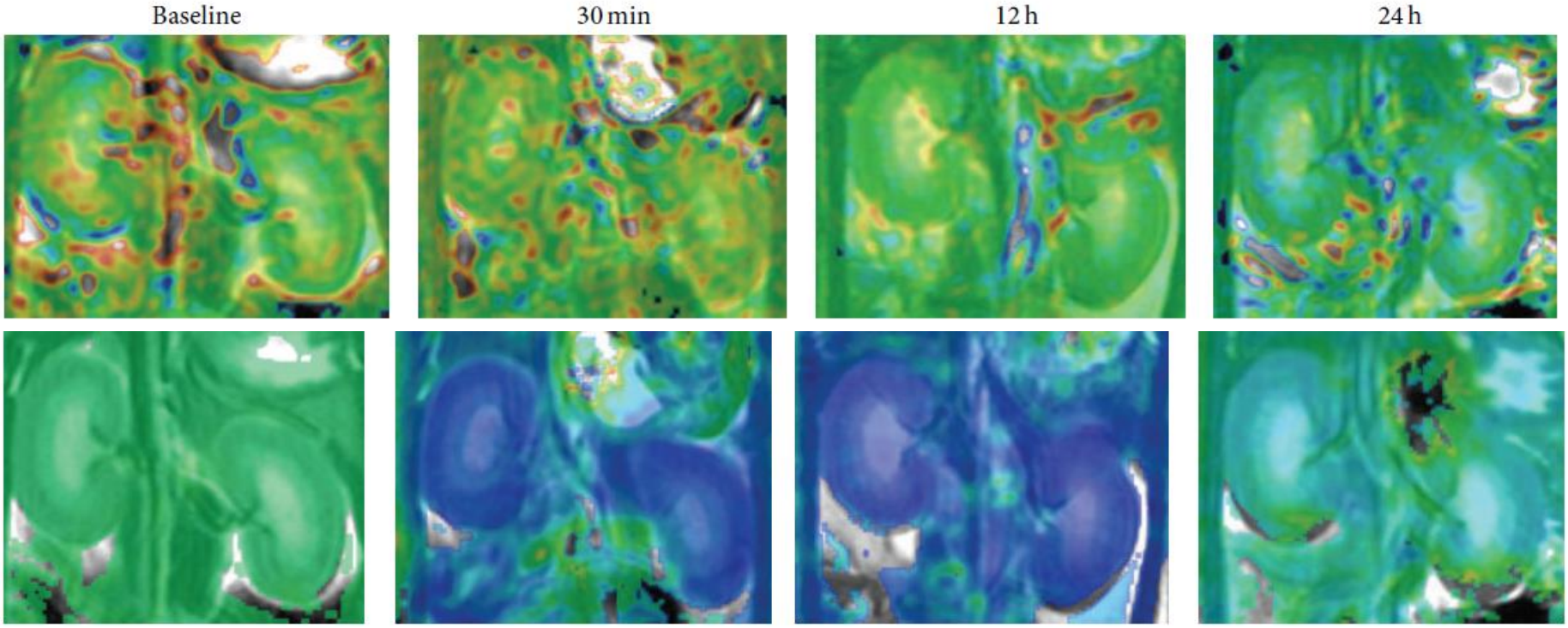


Group	Cortex	Outer-medulla	Inner-medulla
Baseline ($n = 6$)	120.84 ± 2.34	109.26 ± 4.17	111.36 ± 5.22
30 min ($n = 6$)	110.62 ± 18.78	99.84 ± 8.95	107.36 ± 18.13
12 h ($n = 6$)	97.89 ± 3.69*	95.37 ± 3.74*|	109.32 ± 20.41
24 h ($n = 6$)	97.35 ± 3.51*	93.62 ± 2.20*	108.56 ± 11.85
48 h ($n = 6$)	93.19 ± 2.64*	94.11 ± 6.31*	107.36 ± 8.39
72 h ($n = 6$)	105.83 ± 16.79	100.10 ± 17.29	91.66 ± 20.88
96 h ($n = 3$)	106.15 ± 16.1	103.41 ± 11.51	104.17 ± 5.55

$R2*$ value of pre- and postinjection of CM (mean ± SD; Hz). *vs. Baseline

RBF and oxygen level decrease in outer medulla and cortex.

Chen et al, 2015



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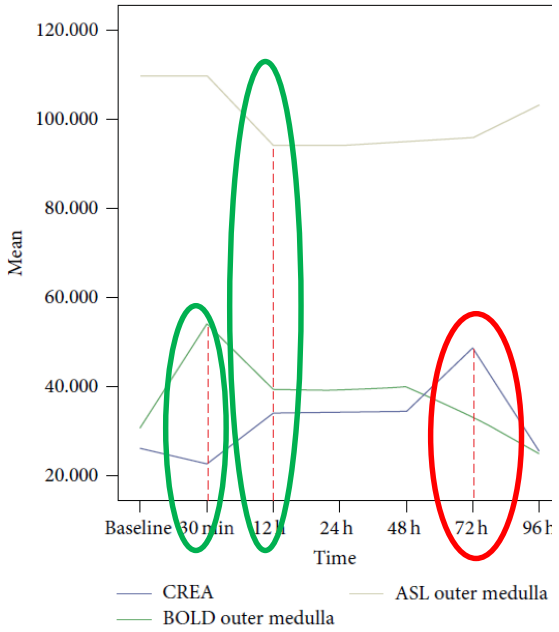


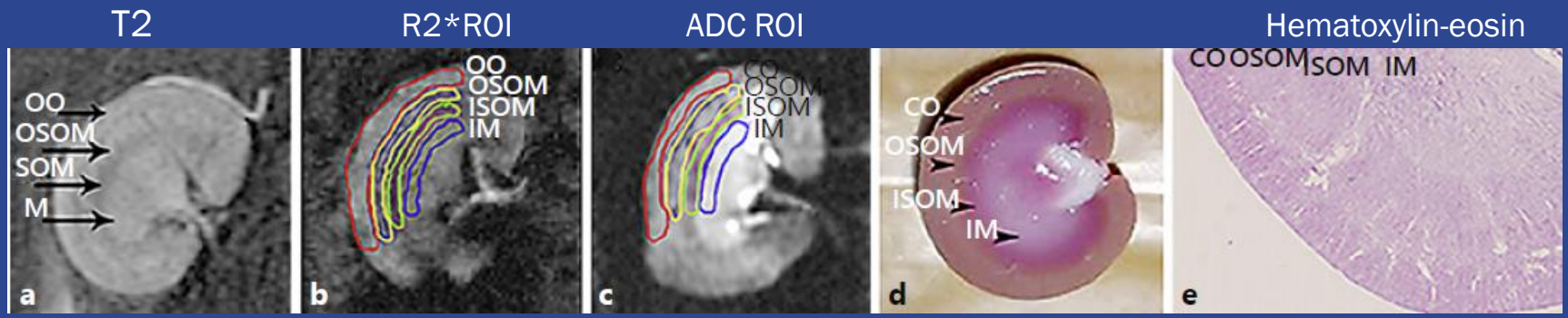
ASL and BOLD are more sensitive than Crea to renal injury.

Higher dose, higher incidence?

- Model: adult, male New Zealand rabbits

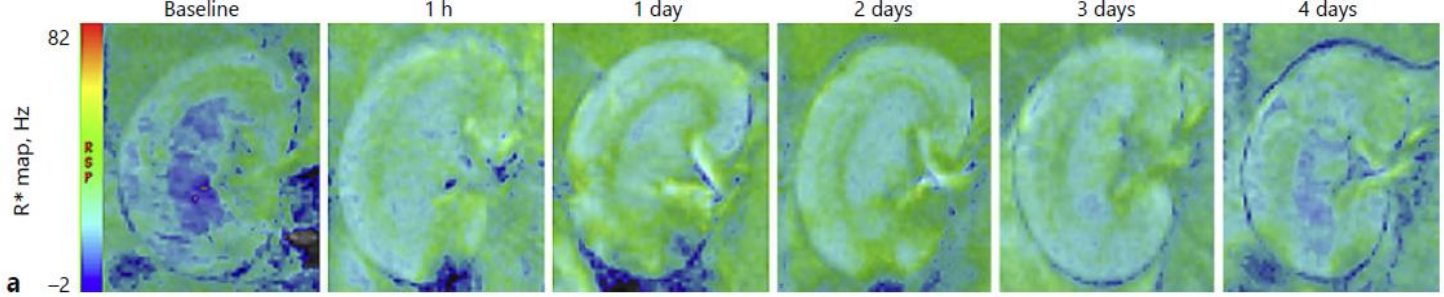
  iohexol (1, 2.5, 5.0 gL/bwkg, iv.)

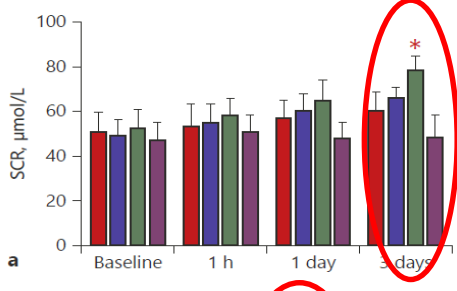
- Time points: Baseline, 1h, 24h, 48h, 72h,96h
- Methods: 3T GE , SeCrea, uNGAL, histology, VEGF, HIF-1 IHC

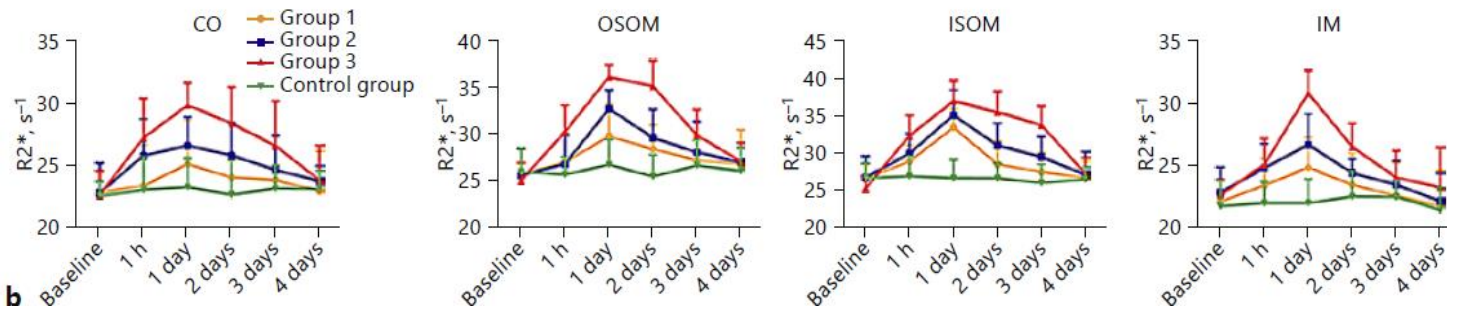


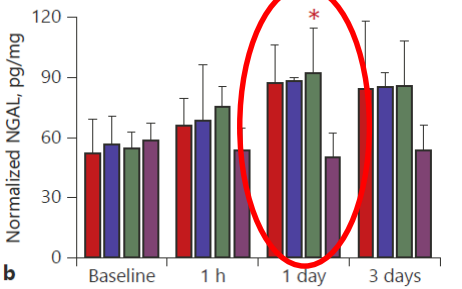
cortex (CO), outer stripe of outer medulla (OSOM), inner stripe of outer medulla (ISOM), and inner medulla(IM)

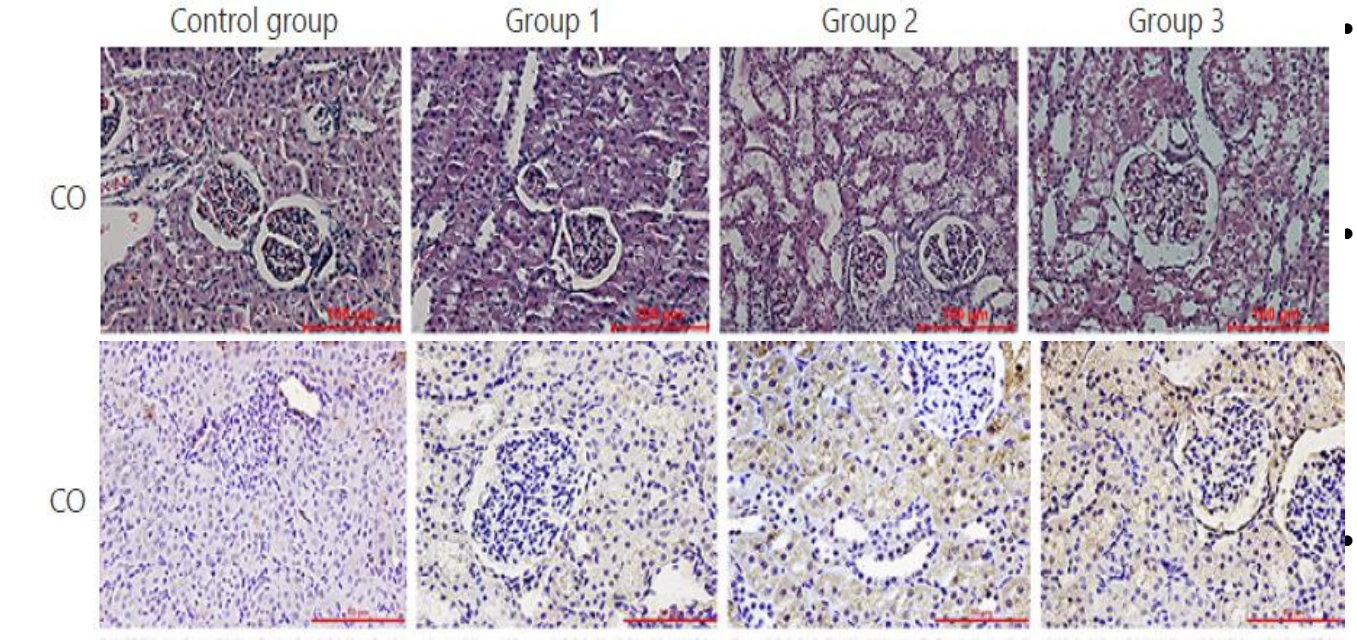
Wang al, 2019





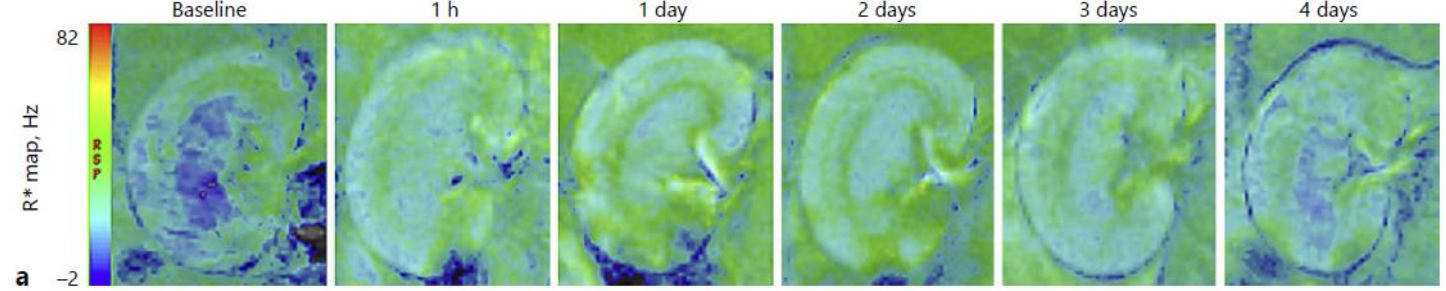


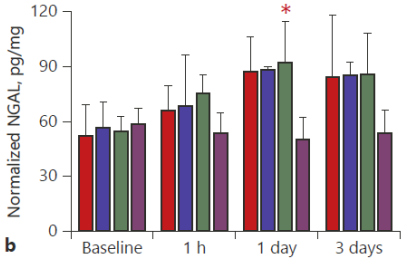


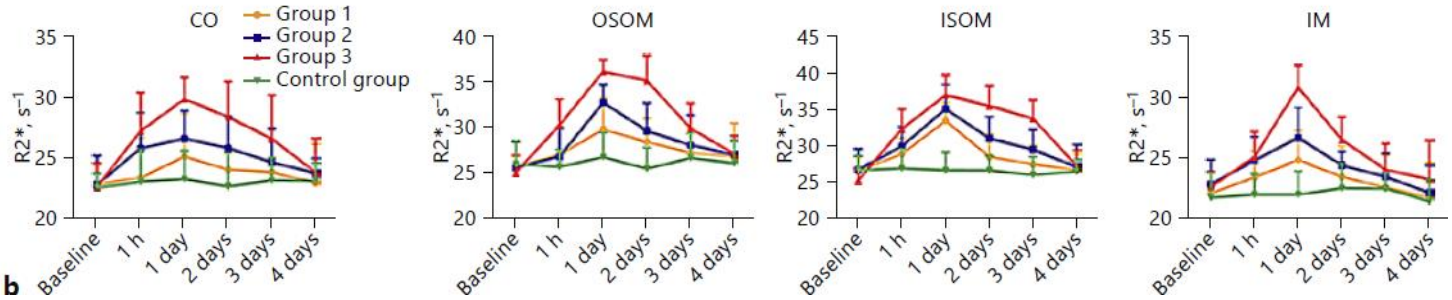


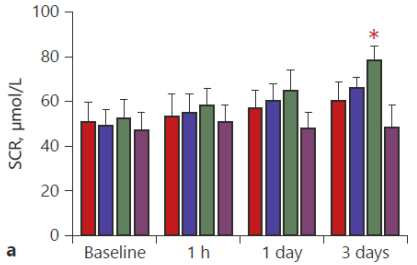
- CA iohexol cause a dose and time-dependent response in renal hypoxia.
- Cortical BOLD and ASL values correlates with NGAL, HIF-1, VEGF expression indicating massive tubular injury.
- Medullary hypoxia is typical in CIAKI.

Wang al, 2019

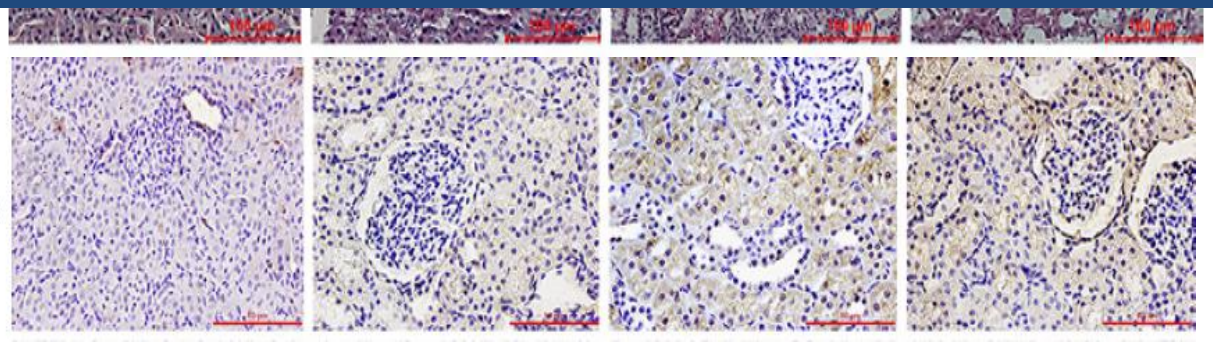








uNGAL combined with fMRI is the earliest indicator of renal hypoxic injury casued by CIAKI in a CA dose-dependent manner.



values correlates with NGAL, HIF-1, VEGF expression indicating massive tubular injury.

3. Medullary hypoxia is typical in

Wang al, 2019

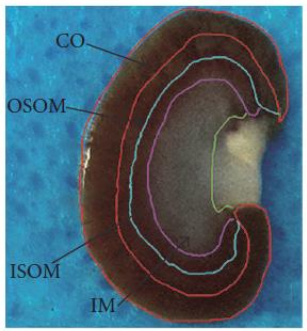
Higher frequency, higher incidence?

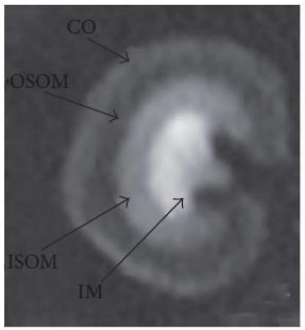
- Model: adult, male Wistar rats

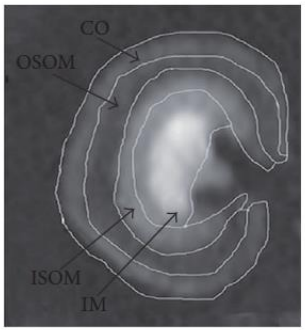
  iodine (4.0 gL/bwkg, iv. 1x, 2x, 1-3-5d)

- Time points: Baseline, 1h, 1d, 3d, 5d, 10d
- Methods: 3T GE , SeCrea, uNGAL, histology, HIF-1 IHC

Native T2 R2*ROI







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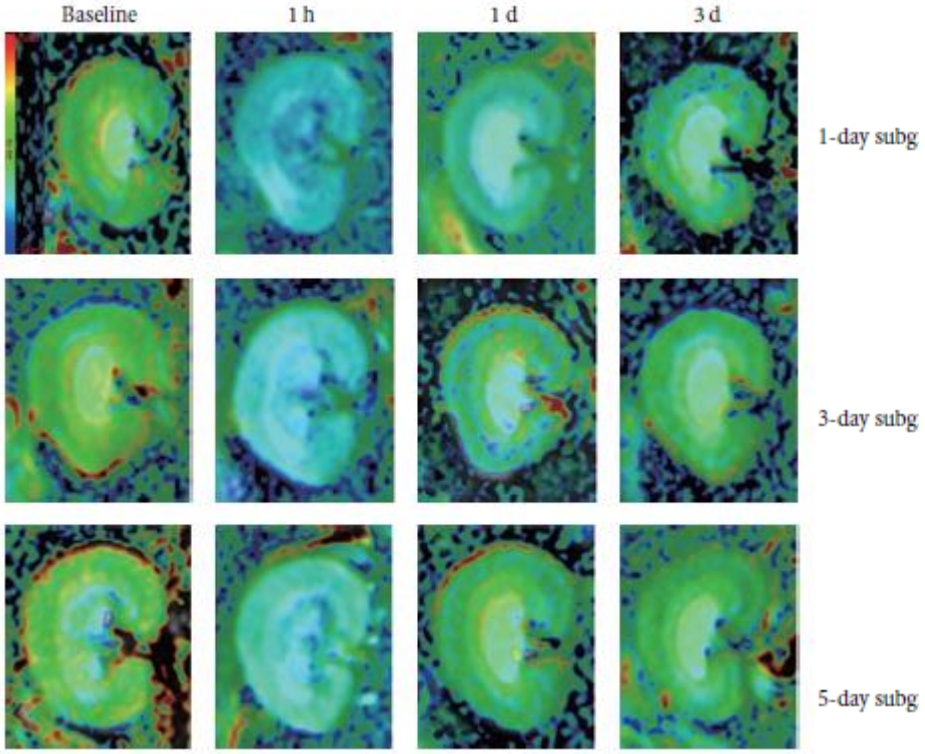
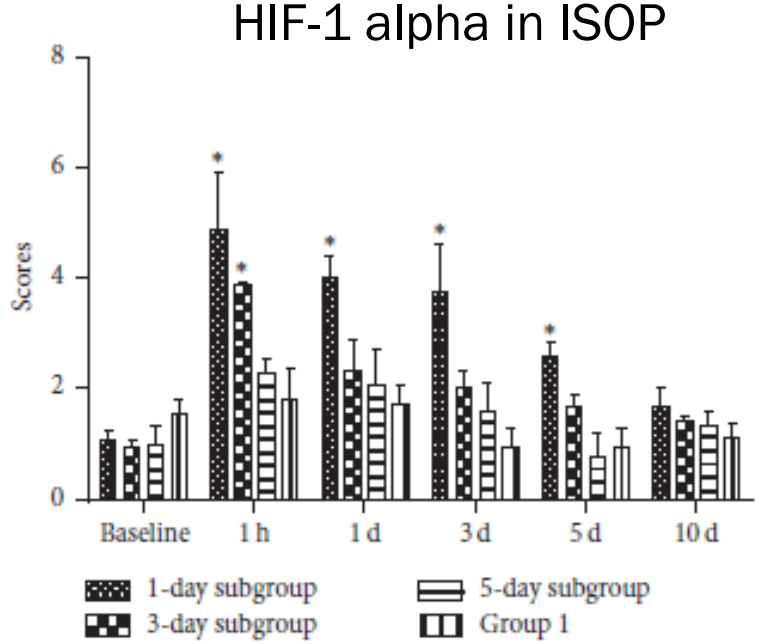
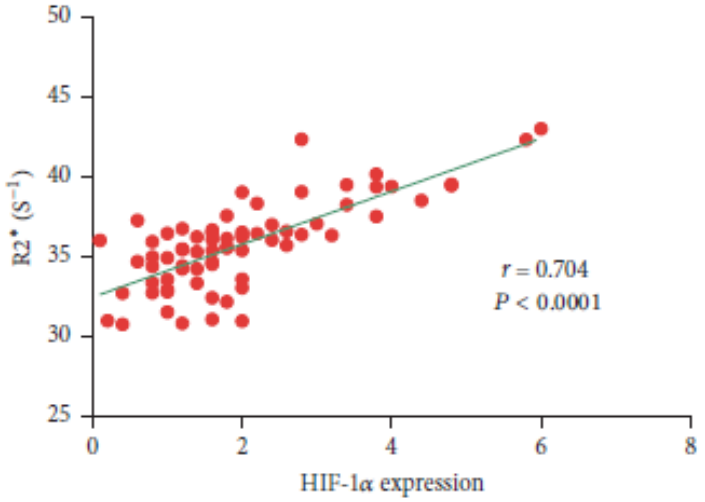
Wang al, 2018

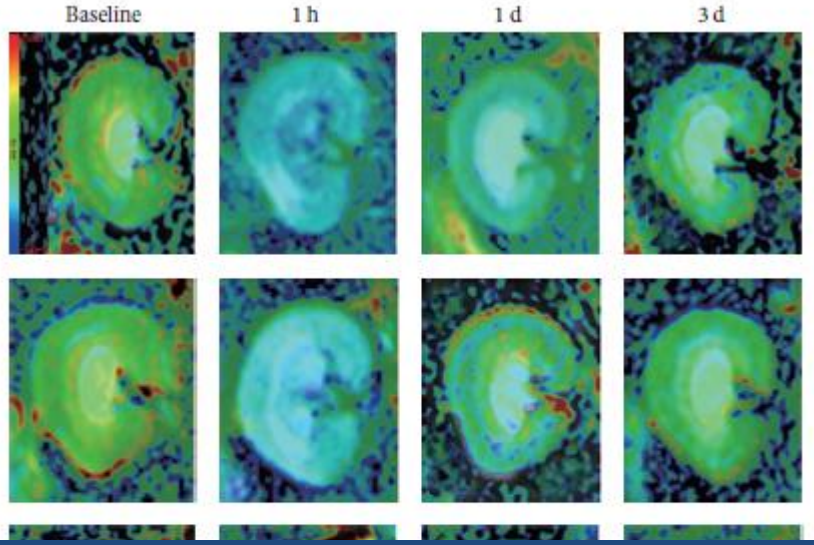


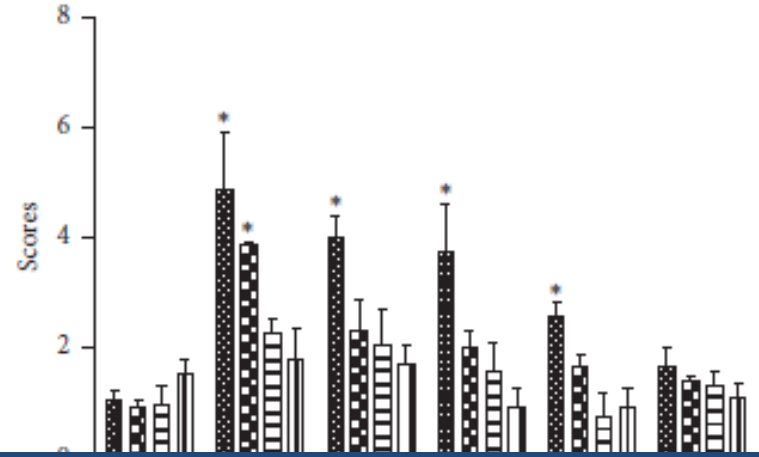




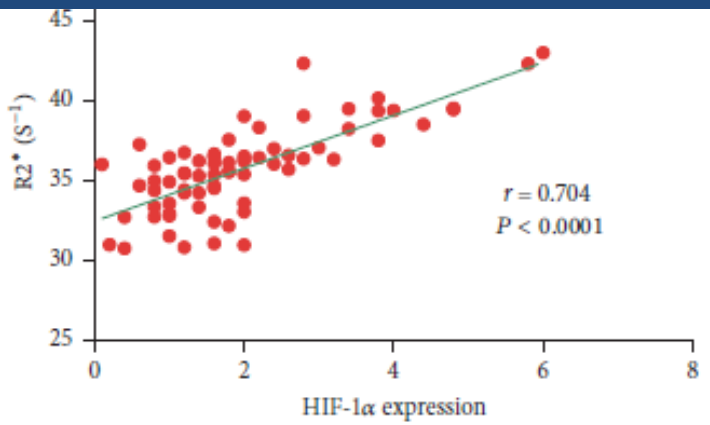
1. Inner stripe of the outer medulla is the most sensitive to renal hypoxia.
2. Repeated iodaxol treament results in increased reduction of oxygen tension and hypoperfusion.

Wang al, 2018





Repetitive CA injections within a short-term face higher-risk of CIAKI and a long-term loss of kidney function.

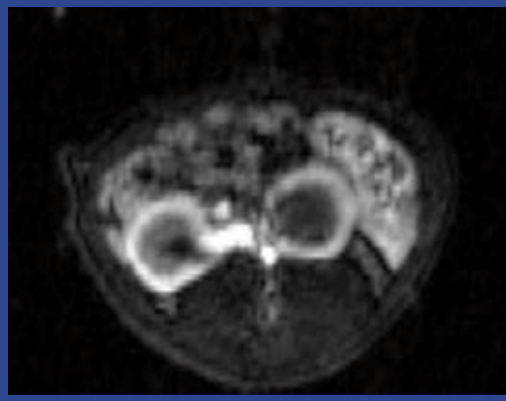


2. Repeated iodaxol treament results in increased reduction of oxygen tension and hypoperfusion.

Wang al, 2018

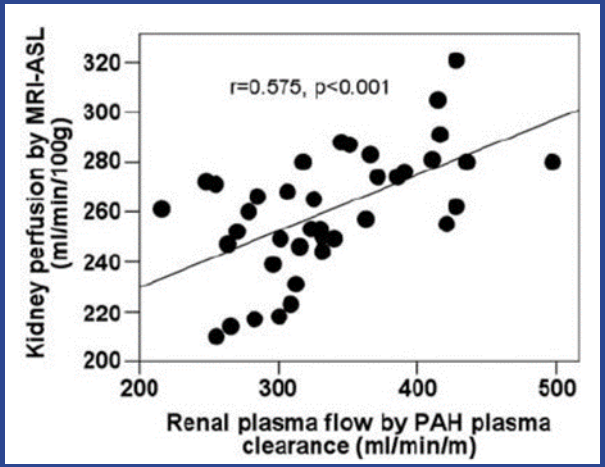
fMRI for perfusion in AKI?

- Model: adult, male Wistar rats,
  - 50 min warm ischemia
- Time points: contralateral baseline, 5d
- Methods: 3T GE ASL , DCE, histology



	left (AKI)	right (healthy)
1*	(295)[1]	304
2	456	634
3	191	344
4	289	504
5	374	462
6	269	371
Mean	*316±102*	*416±124*

Nr.	Rat 2	
	left (AKI)	right (healthy)
1	456	634
2	425	615
3	430	651
4	433	650
Mean	*436±12*	*638±15*



Ritt, et al 2009; Zimmer et al, 2013

fMRI for perfusion in AKI?

- Model: adult, male Wistar rats,
  - 50 min warm ischemia
- Time points: contralateral baseline, 5d

ASL is a sensitive and reproducible marker of renal perfusion in AKI.

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Mean	*316±102*	*416±124*

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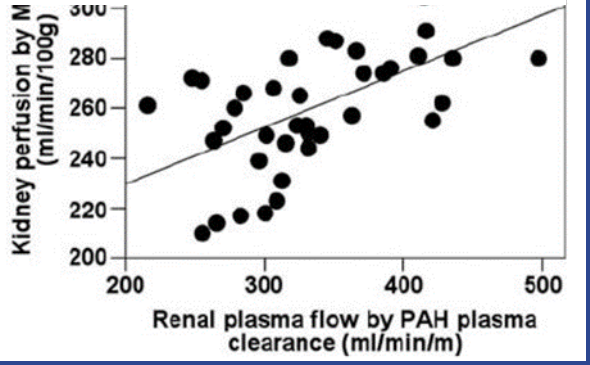
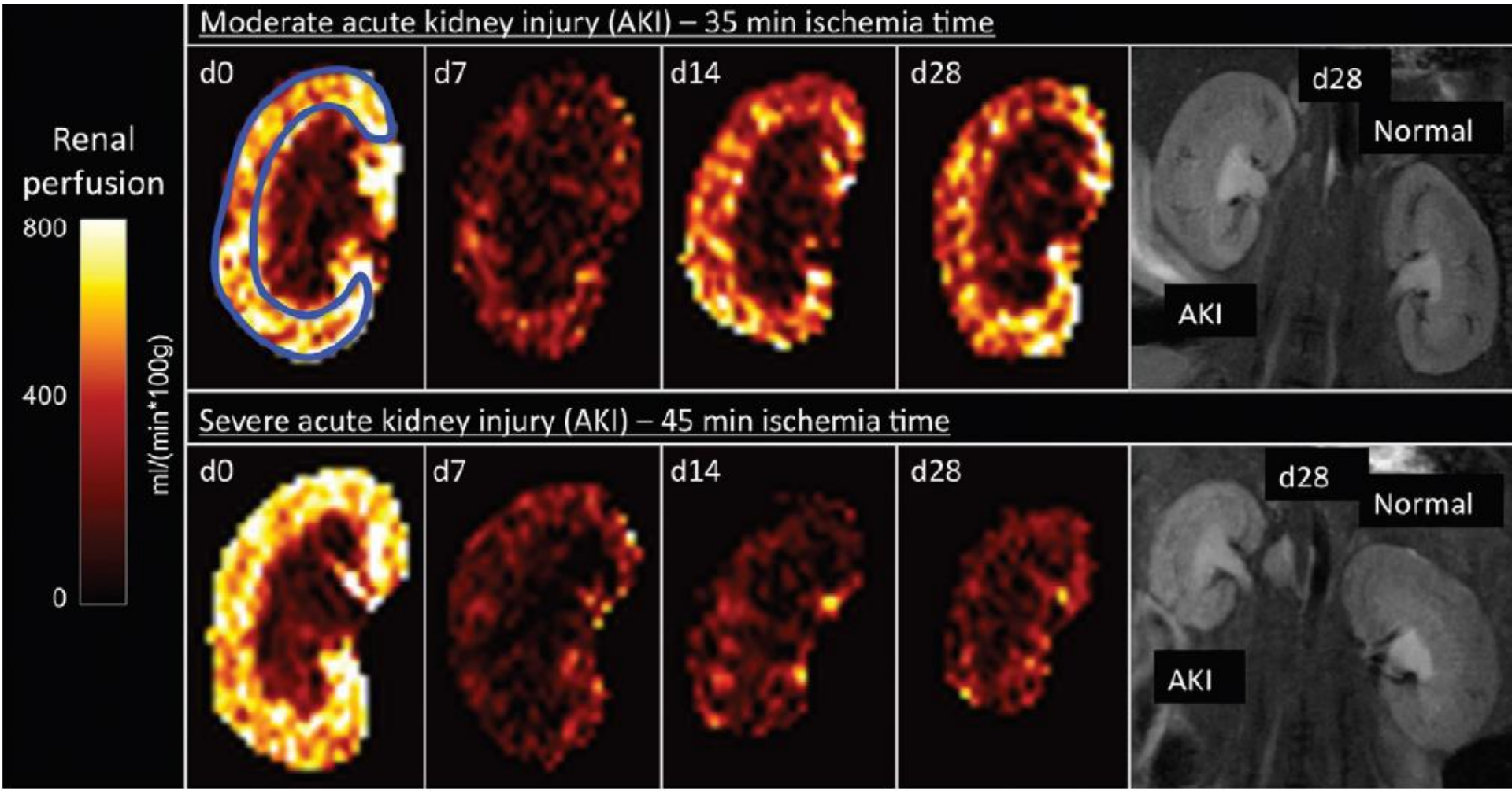


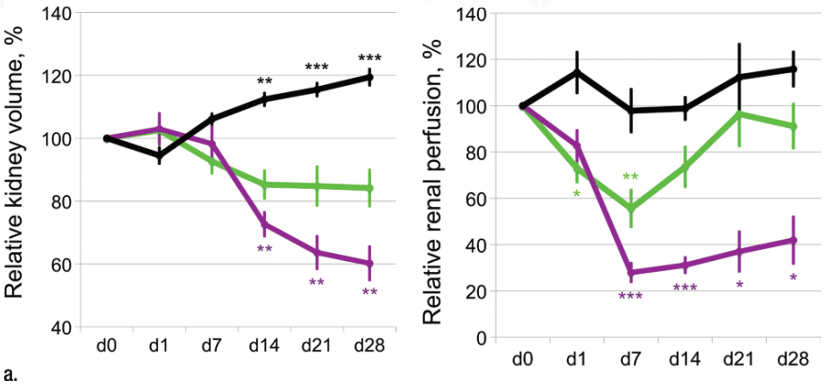
Zimmer et al, 2013

fMRI for perfusion in AKI?

- Model: adult, male mice,
  - mild (35min) or severe (45 min) unilateral ischemia
  - Different strains C57/B6 vs. Sv
- Time points: Baseline, 1d, 7d, 28d
- Methods: 7T GE ASL, PAH- renal plasma flow, inulin- GFR, histology (Masson), collagen- expression

Hueper et al, 2013, Tewes et al, 2017

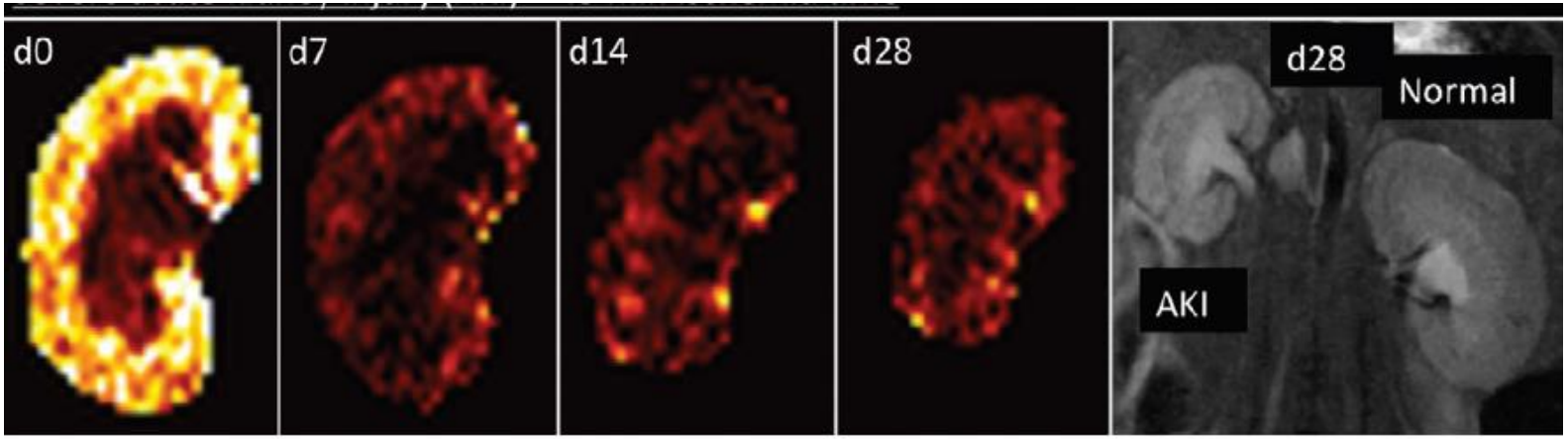


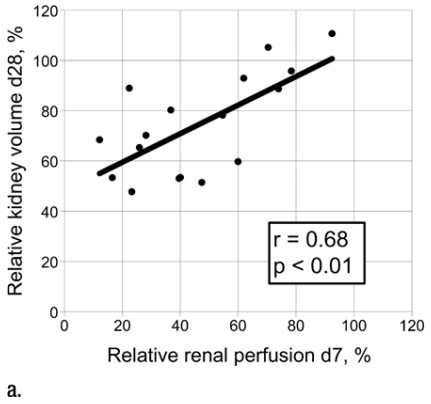


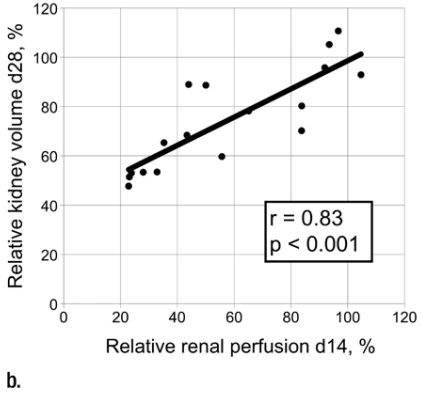
a.

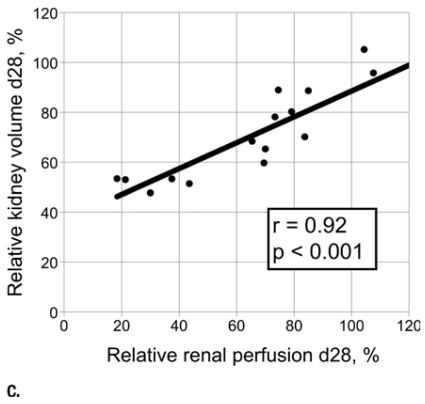
Hueper et al, 2013, Tewes et al, 2017

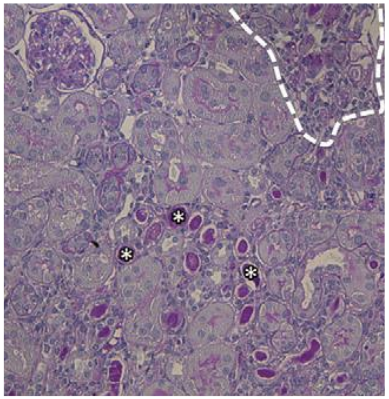
- Kidney volume and renal perfusion were decreased after AKI (measured by T2-weighted and ASL resp).
- Contralateral kidney-size increased and hyperfiltration were observed as a compensatory mechanism.





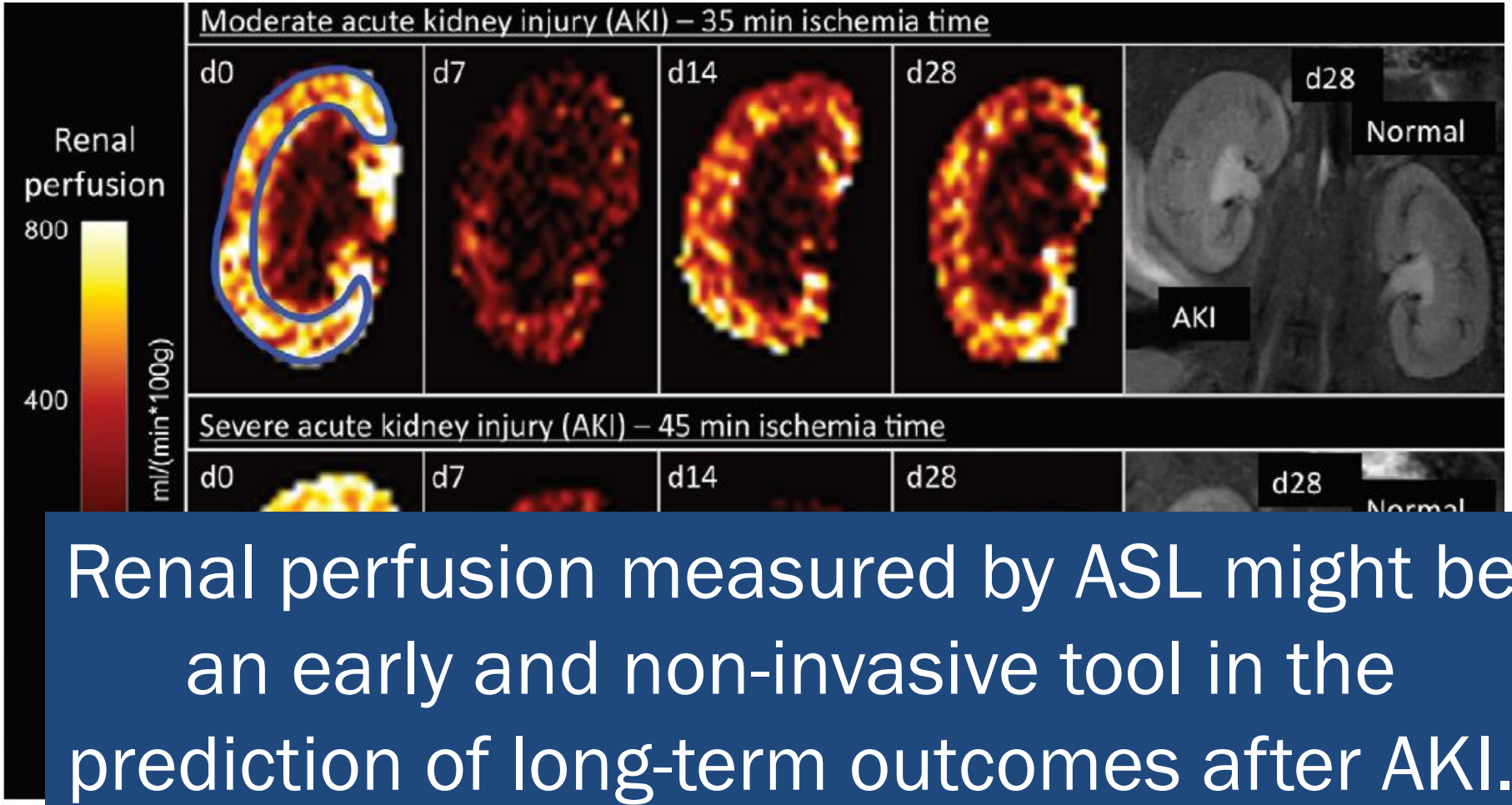




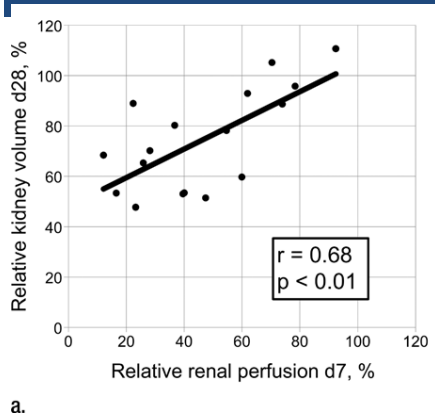


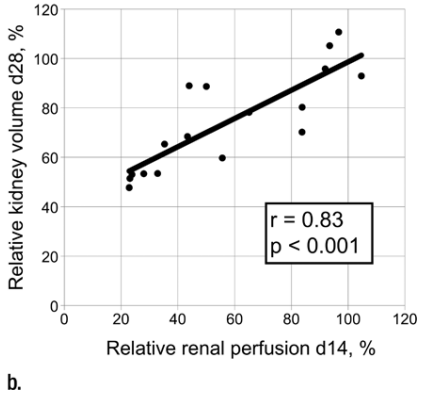
- Perfusion measured by ASL at d7, d14 is significantly correlated to kidney volume and structural renal damage at d28.

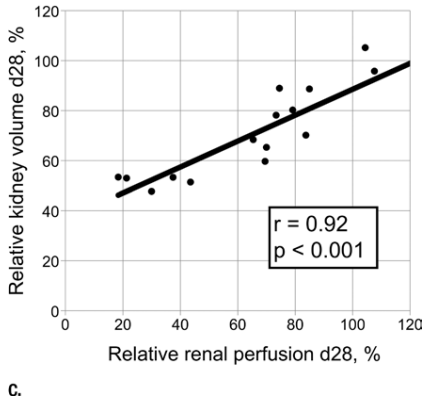
Hueper et al, 2013, Tewes et al, 2017

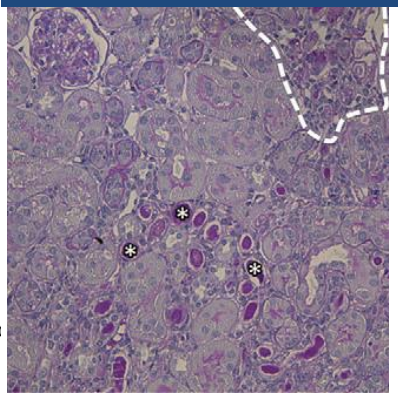


Renal perfusion measured by ASL might be an early and non-invasive tool in the prediction of long-term outcomes after AKI.









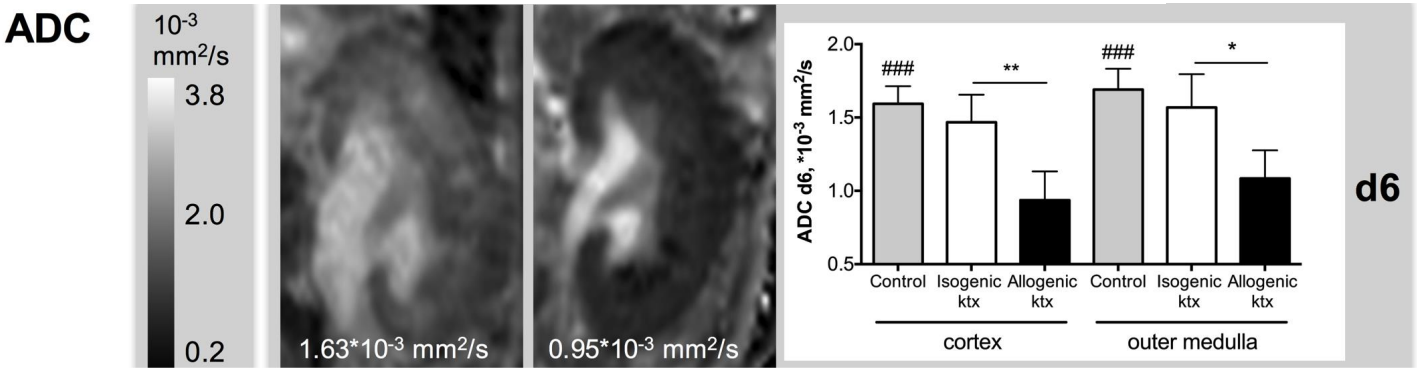
Hueper et al, 2013, Tewes et al, 2017

fMRI for inflammation in AKI?

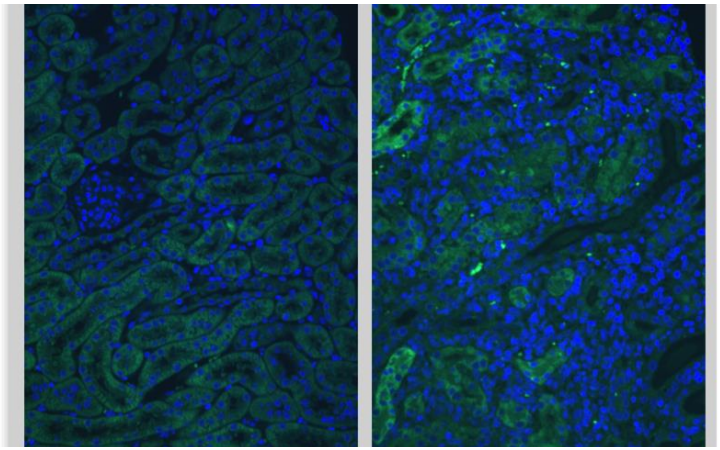
- **Model:** C57BL/6JHan-ztm (H2b) (B6) and female BALB/c JHan-ztm (H2d) (BALB/c) mice
  - Fully mismatched allogenic kidney transplantation
  - Isogenic kidney transplantation
- **Time points:** Baseline, 1d, 7d
- **Methods:** 7T GE DWI, histology (Banff-criteria), IHC, FACS

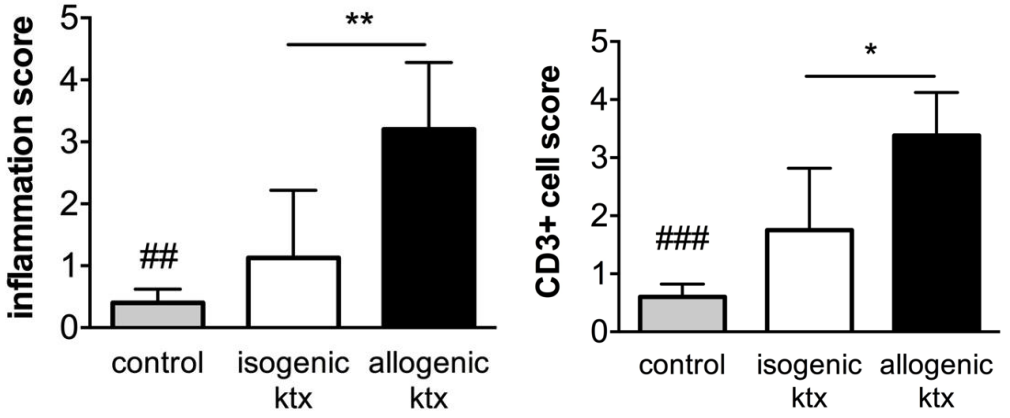
Hueper et al, 2016

	Control	Isogenic	Allogenic
		d6	d6
ADC cortex, $*10^{-3}$ mm²/s	1.593 ± 0.120	1.468 ± 0.189	0.936 ± 0.197**
ADC medulla, $*10^{-3}$ mm²/s	1.690 ± 0.142	1.567 ± 0.229	1.083 ± 0.192**
T2 cortex, ms	38.3 ± 2.0	49.2 ± 7.4***	46.0 ± 3.1***
T2 OSOM, ms	36.2 ± 2.1	49.0 ± 8.5***	48.7 ± 5.6***
T2 ISOM, ms	47.0 ± 5.1	58.4 ± 12.0*	46.7 ± 7.7#
T2 difference, ms	8.7 ± 3.4	9.1 ± 5.3	0.6 ± 6.7**,#

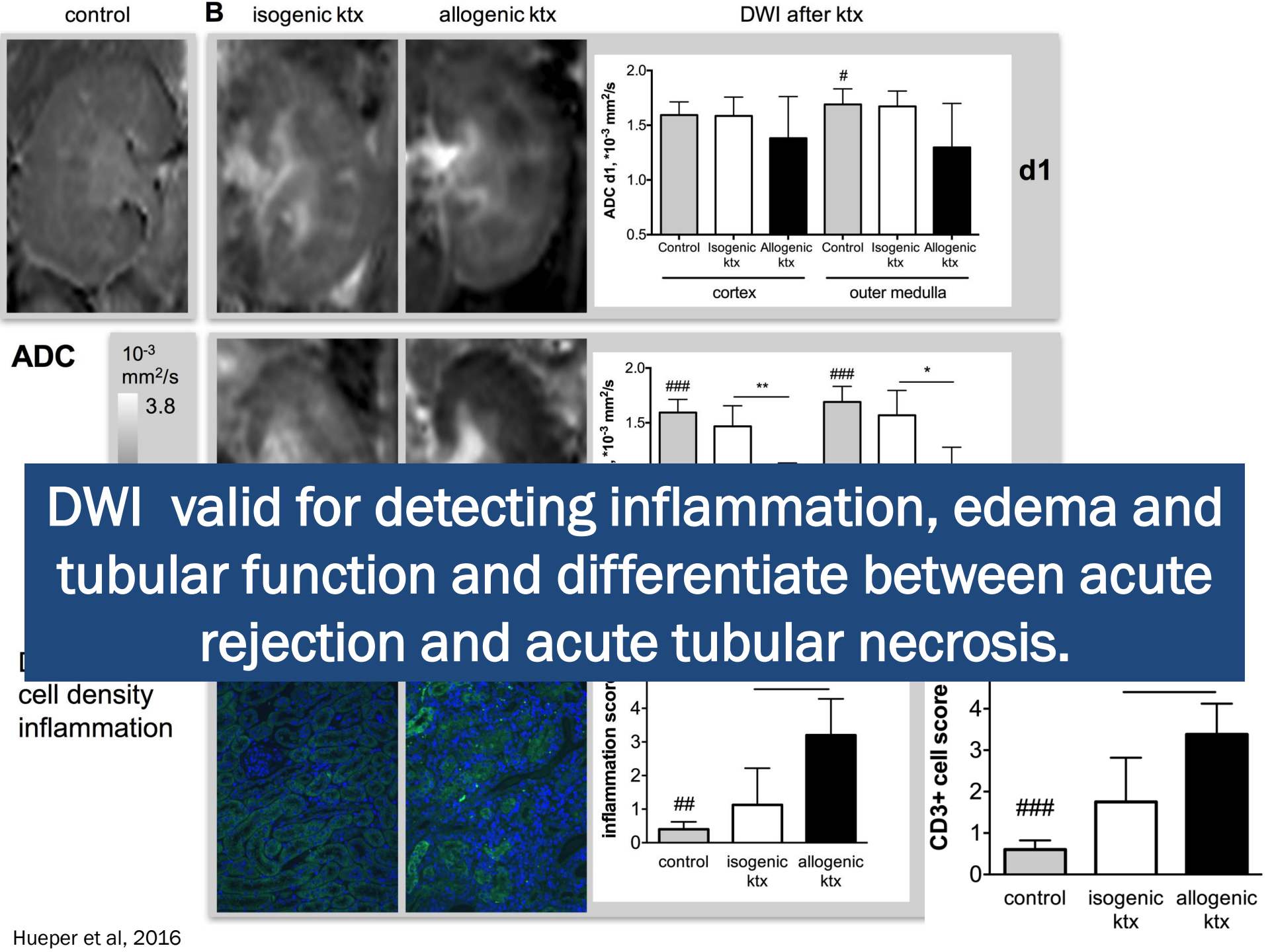


ADC was decreased only in isogenic group reflecting inflammation, while T2-increase, indicating tissue edema, was present in both Tx groups.





Hueper et al, 2016



DWI valid for detecting inflammation, edema and tubular function and differentiate between acute rejection and acute tubular necrosis.

Hueper et al, 2016

Conclusion

- Preclin fMRI can answer some questions that clinical studies can not .
- BOLD, ASL and DWI are promising tools in the diagnosis and follow-up of AKI.
- Improvement in the hardware, postprocessing and validation is essential for clinical use.

fMRI combined with existing biomarkers is the most optimal at the moment.