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Magnetisation Transfer (MT) and Chemical Exchange Saturation Transfer (CEST)

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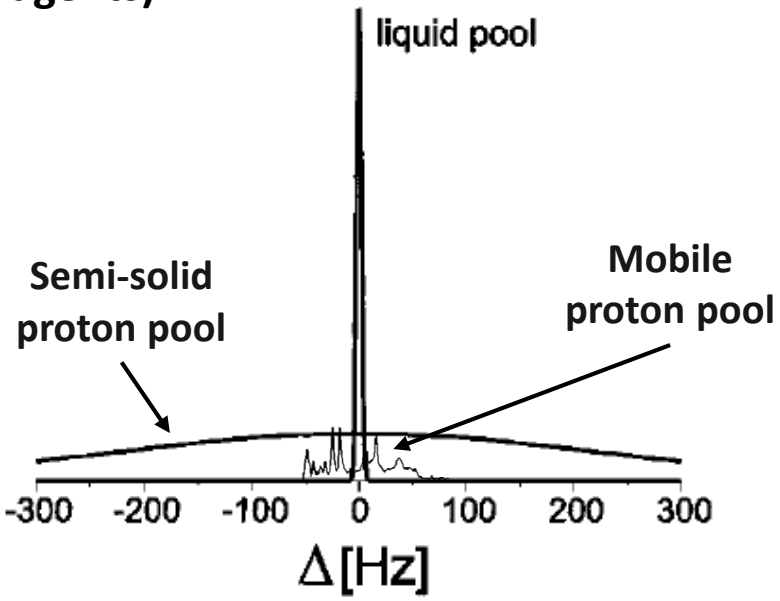
MAGNETIZATION TRANSFER: THEORY

In NMR, MT (magnetization transfer) is a general term that describes the process of magnetization transfer from one spin population to another

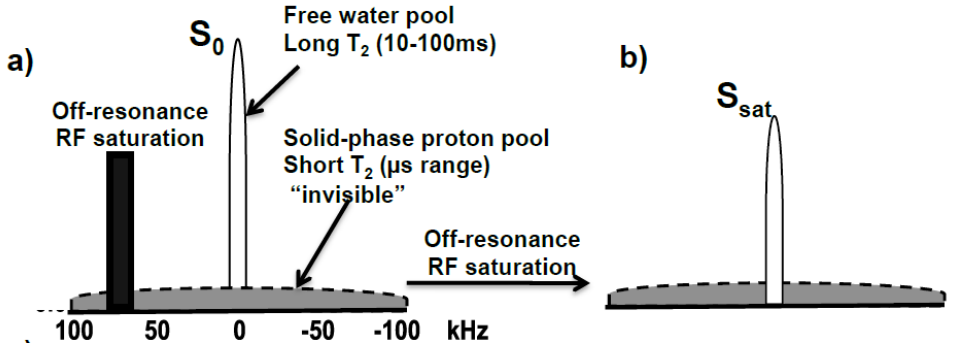
- **In MRI, MTC (Magnetization Transfer Contrast) denotes saturation transfer contrast originating from semi-solid macromolecules (large protein, collagen, myelin) or bound water protons with broad lineshapes (short T_2 10-100 µs)**

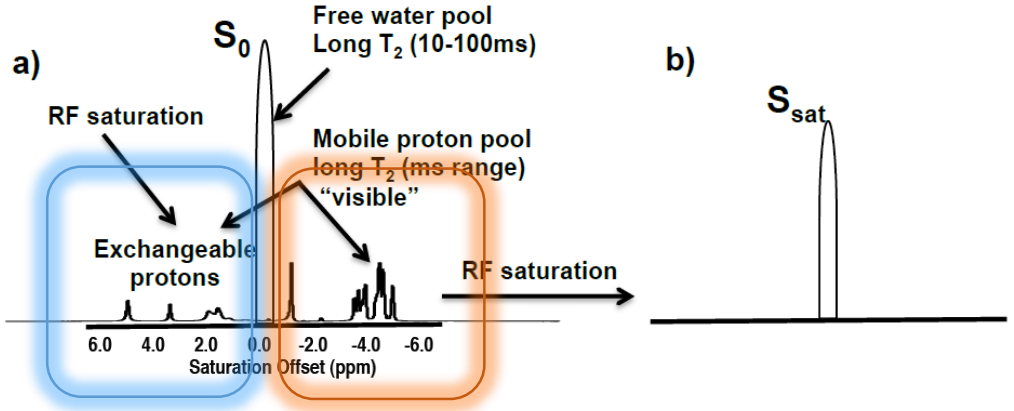
- **In MRI, CEST (Chemical Exchange Saturation Transfer) denotes saturation transfer by chemical exchange originating from mobile proteins (long T_2 > 10 ms) and metabolites (or exogeneous contrast agents)**

- Selective magnetic labeling of a proton pool that is stored as a change in longitudinal magnetization
- Transfer of this label to a water proton pool
- Accumulation of the label for the pupose of water signal reduction

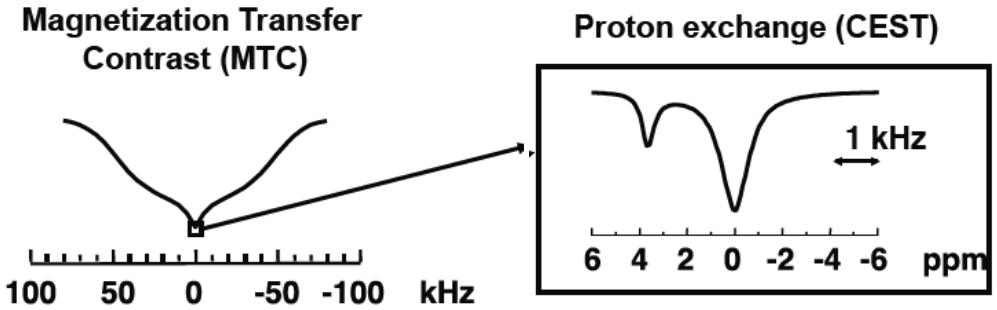


MTC AND CEST

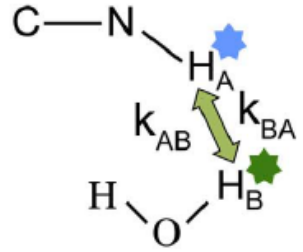




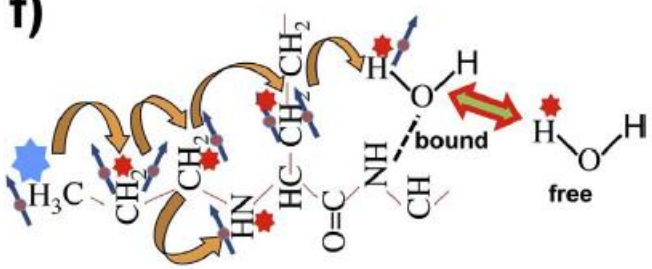
- **Labelling proton pools of the semisolid macromoleular component (spin-diffusion or cross-relaxation) followed by transfer to solvent water protons by means of bound water (dipolar coupling or chemical exchange)**



- **Labelling of mobile protons downfield from water (chemical exchange)**

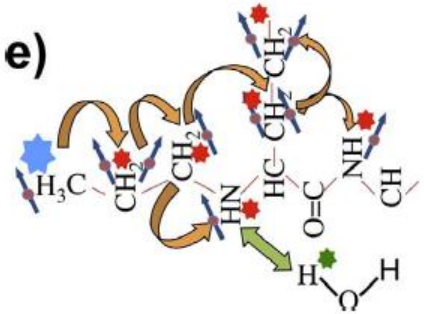


f)



- **Labelling of aliphatic proton in mobile proteins upfield from water (relayed NOE)**

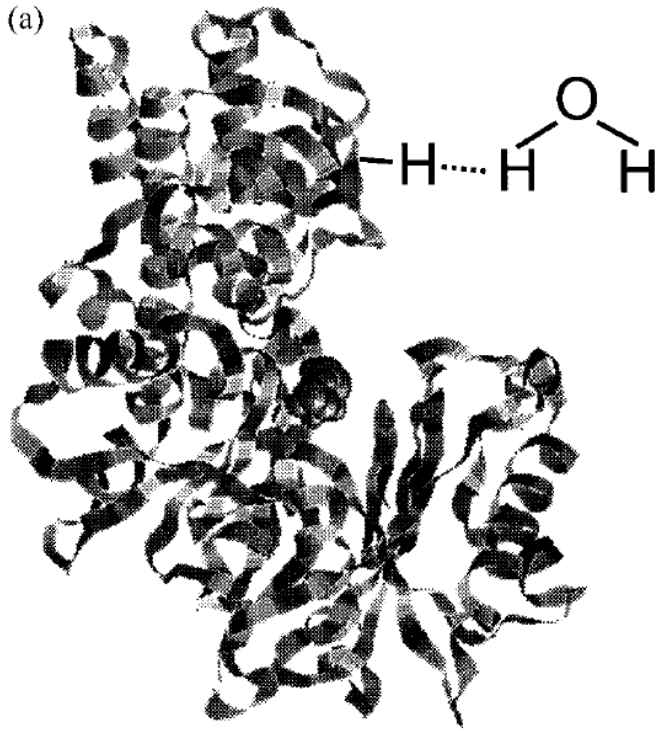
e)

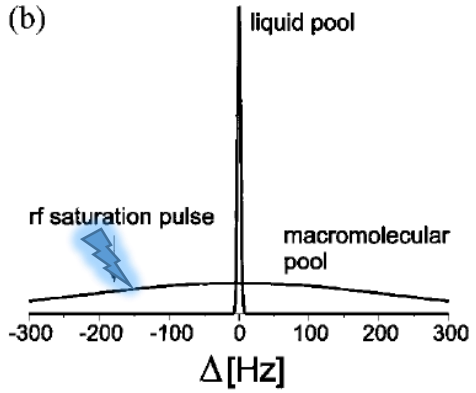


S. D. Wolff and R. S. Balaban, Magnetization transfer contrast (MTC) and tissue water proton relaxation in vivo. Magn Reson Med, 1989, 10, 135-144

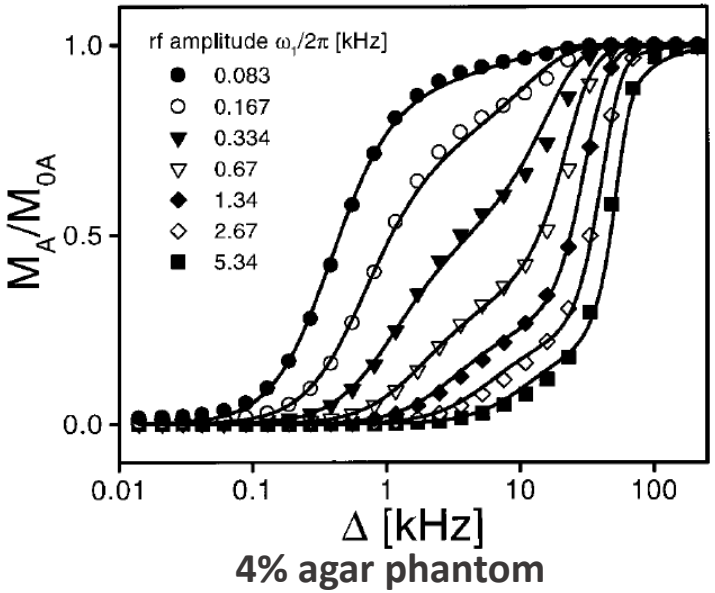
Forsen, S., Hoffman, R.A., 1963. Study of moderately rapid chemical exchange reactions by means of nuclear magnetic double resonance. J. Chem. Phys. 39, 2892–2901.
S. D. Wolff and R. S. Balaban, NMR Imaging of Labile Proton Exchange. J. Magn. Reson., 1990, 86, 164-169

MAGNETIZATION TRANSFER CONTRAST





$$MTR = 1 - S_{sat}/S_0$$



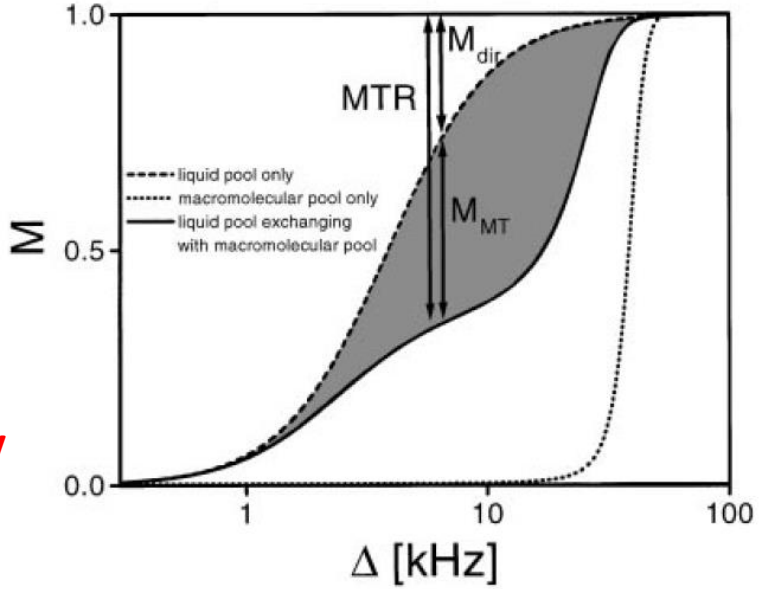
4% agar phantom

Applications:

- magnetic resonance angiography (MRA) to enhance signal contrast between the blood and other tissue
- Characterization of white matter disease in the brain, principally demyelination disease (multiple sclerosis) or for assessing knee cartilage

Limitations:

- sensitivity, specificity, and reproducibility of MTR measures can be influenced by various experimental parameters and field strength
- MTR measures tend to reflect a complex combination of sequence details and relaxation parameters

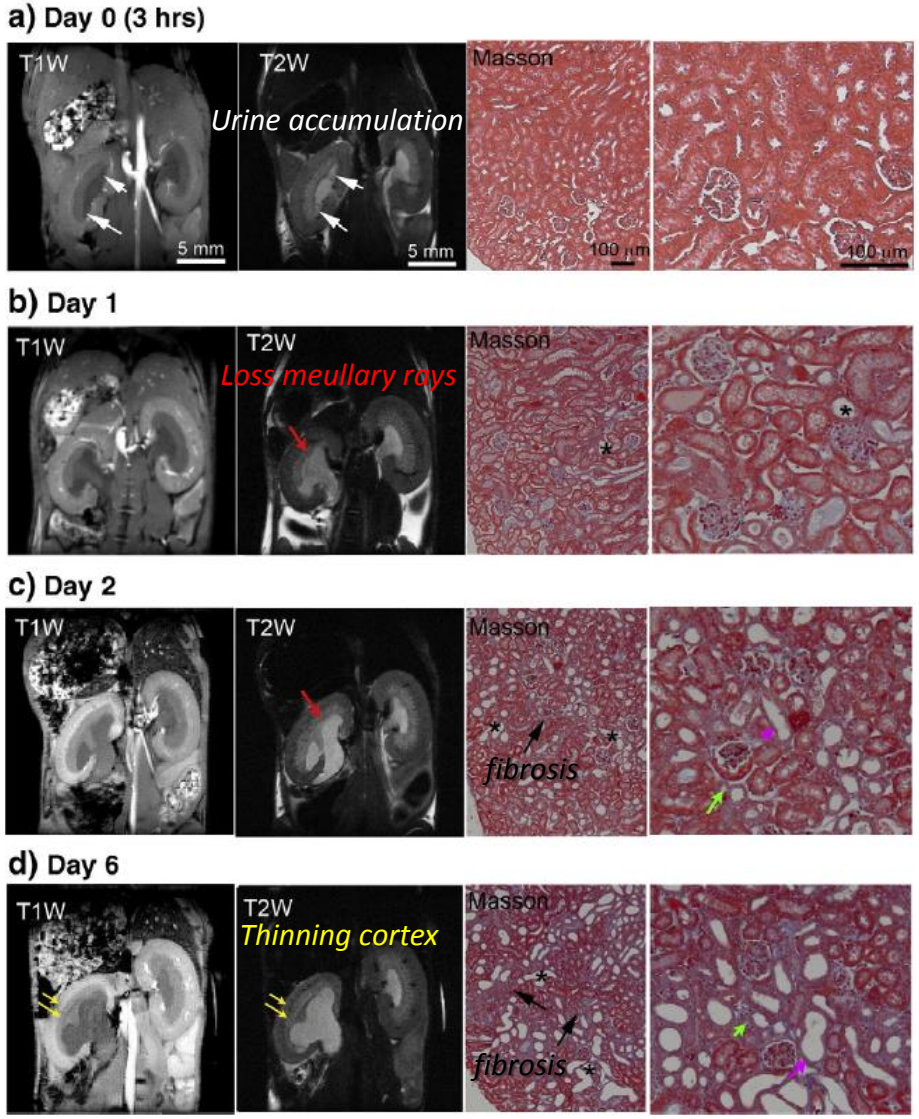


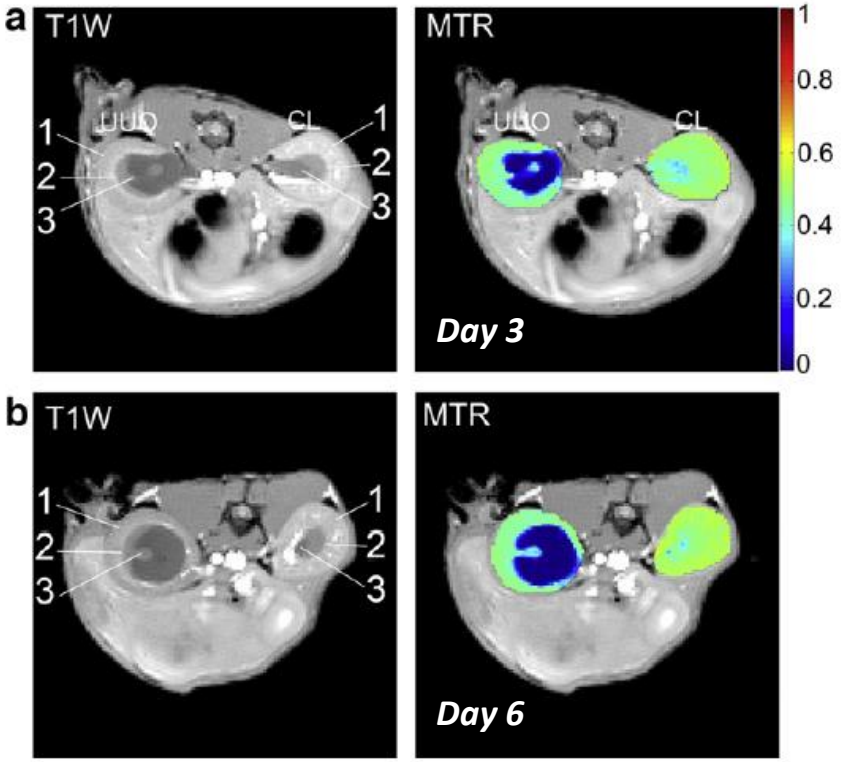
Magnetic Resonance Imaging 32 (2014) 1125–1132

Longitudinal assessment of mouse renal injury using high-resolution anatomic and magnetization transfer MR imaging ☆

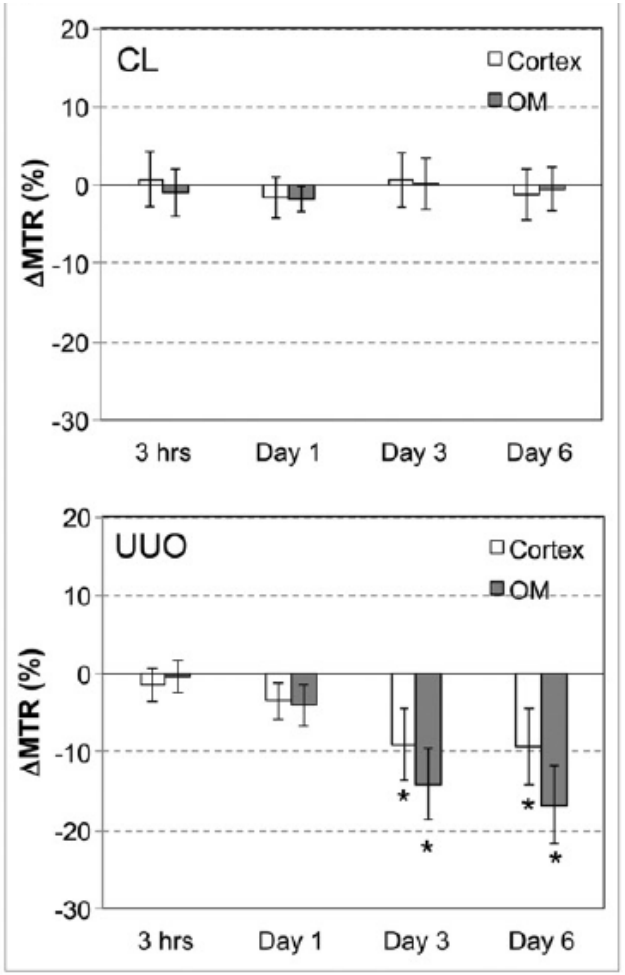
Feng Wang [a,b], Rosie Jiang [e], Keiko Takahashi [e], John Gore [a,b,c,d], Raymond C. Harris [e], Takamune Takahashi [d,e,*], C. Chad Quarles [a,b,c,d,**]

- **Obstructive nephropathy is a primary source of renal impairment in infants and children**
- **The Unilateral Ureteral Obstruction (UUO) model in mice induces serial changes in renal structure and recapitulates key features of tubular damage, apoptosis, and renal fibrosis**
- **The decreased MTR values suggest reduced macromolecular content, which could be related to apoptosis, tubular atrophy and urine retention**





7T, RF @20 ppm, 820° x 12ms



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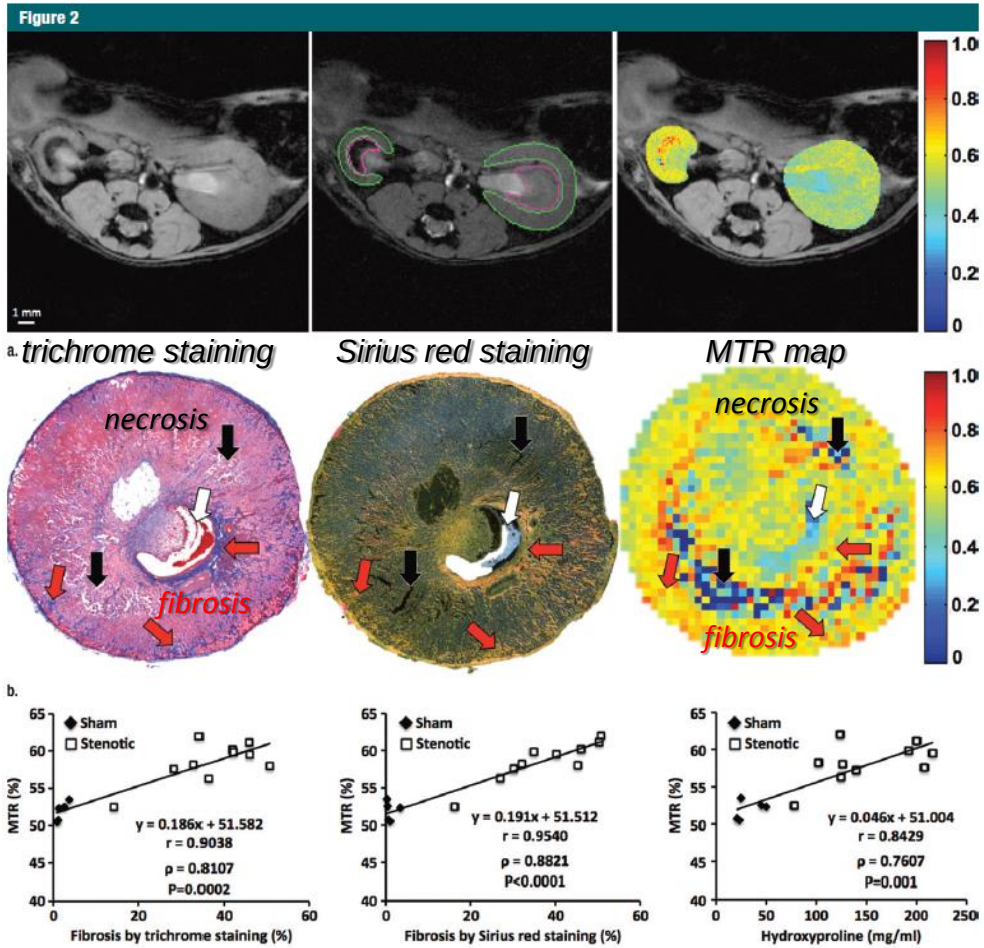
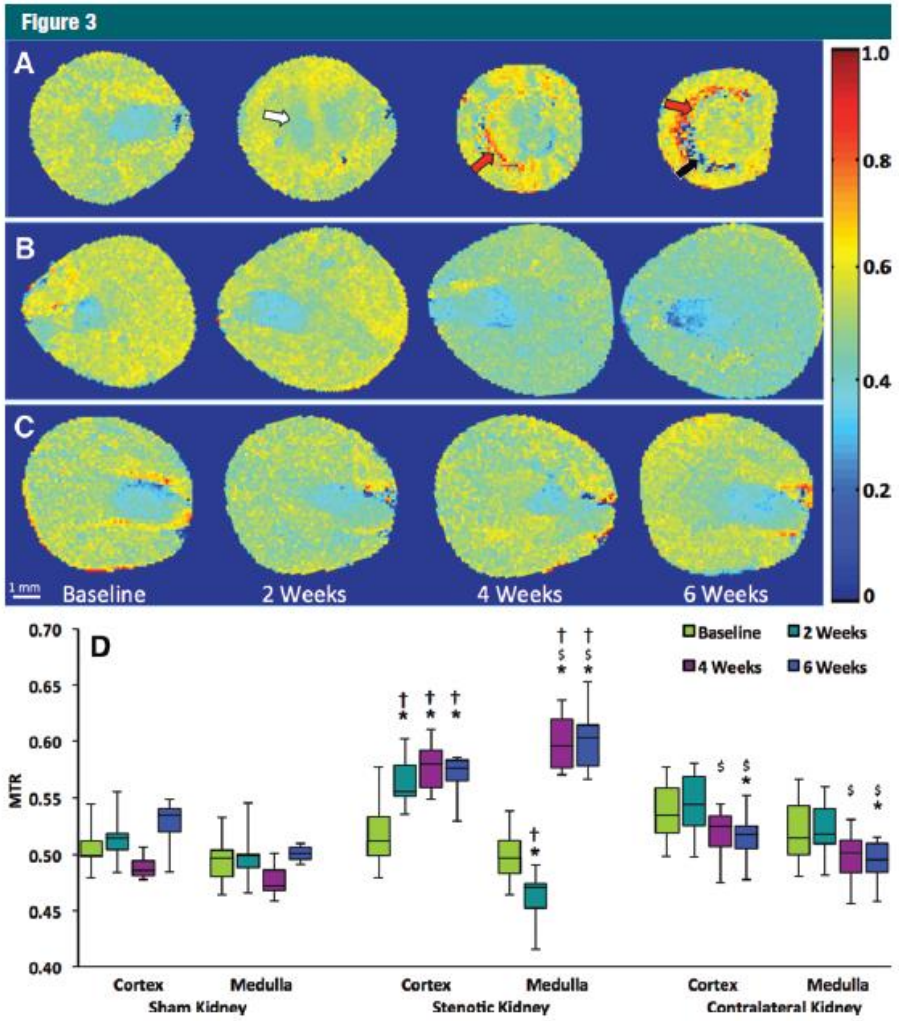
Radiology: Volume 283: Number 1—April 2017

Kai Jiang, PhD
Christopher M. Ferguson, MS
Behzad Ebrahimi, PhD
Hui Tang, PhD
Timothy L. Kline, PhD
Tyson A. Burningham, BS
Prassana K. Mishra, PhD
Joseph P. Grande, MD, PhD
Slobodan I. Macura, PhD
Lilach O. Lerman, MD, PhD

Noninvasive Assessment of Renal Fibrosis with Magnetization Transfer MR Imaging: Validation and Evaluation in Murine Renal Artery Stenosis[1]



- **Renal artery stenosis (RAS) decreases renal blood flow (RBF) and causes a progressive loss of renal mass and function.**
- **Kidney undergoes a progressive deposition of extracellular matrix components (fibronectin and collagen type I, III, and IV) which may evolve into tubulointerstitial fibrosis.**



Stenotic kidney

Contralateral kidney

Sham kidney

16.4T, RF @2.1 ppm, 10 µTx80ms

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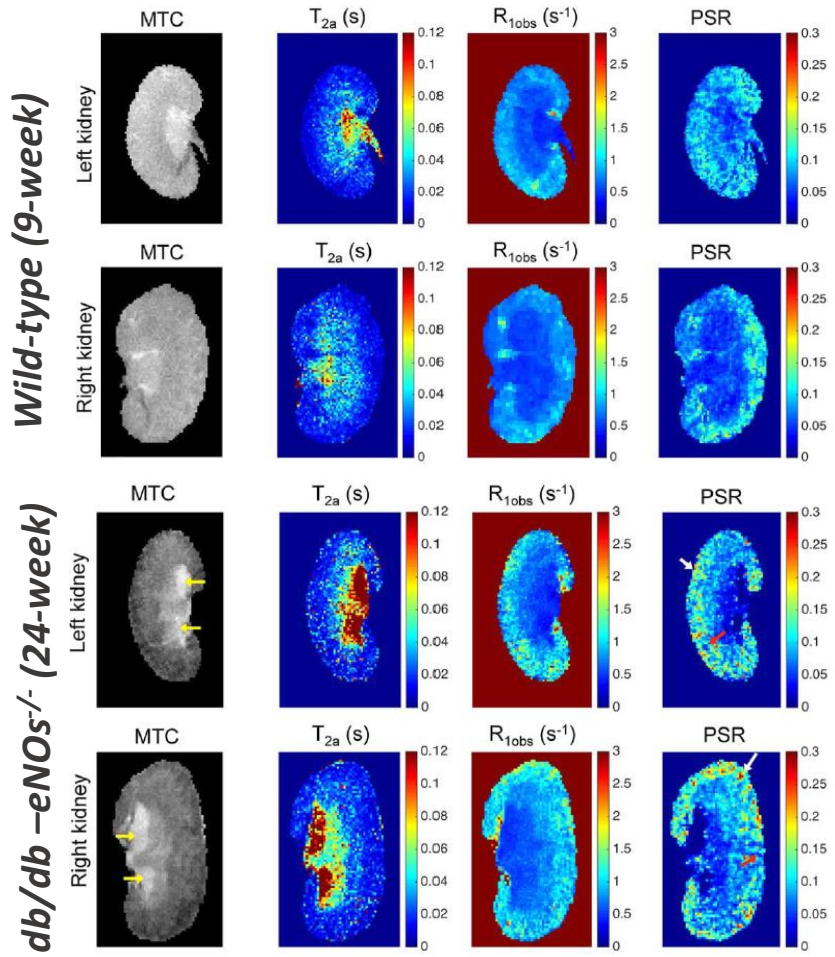
FULL PAPER

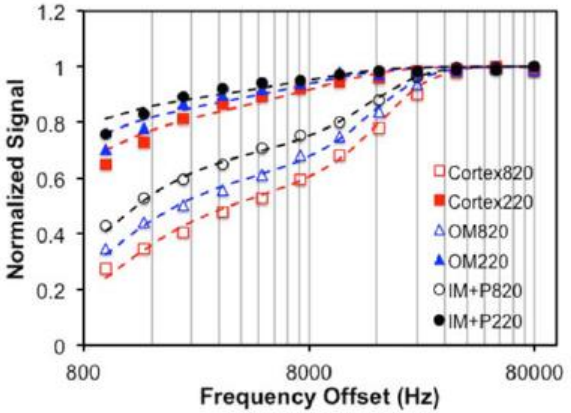
Magn Reson Med. 2018;2655–2669.

Assessment of renal fibrosis in murine diabetic nephropathy using quantitative magnetization transfer MRI

Feng Wang[1,2]* | Daisuke Katagiri[3]* | Ke Li[1] | Keiko Takahashi[3] | Suwan Wang[3] | Shinya Nagasaka[3,4] | Hua Li[1,2] | C. Chad Quarles[1,2] | Ming-Zhi Zhang[3] | Akira Shimizu[4] | John C. Gore[1,2] | Raymond C. Harris[3] | Takamune Takahashi[3]

- **Diabetic nephropathy (DN) is a major diabetic complication**
- **Renal fibrosis is a hallmark of progressive kidney disease, including DN**
- **db/db mice that lack the eNOS gene exhibit advanced DN similar to that found in human DN**

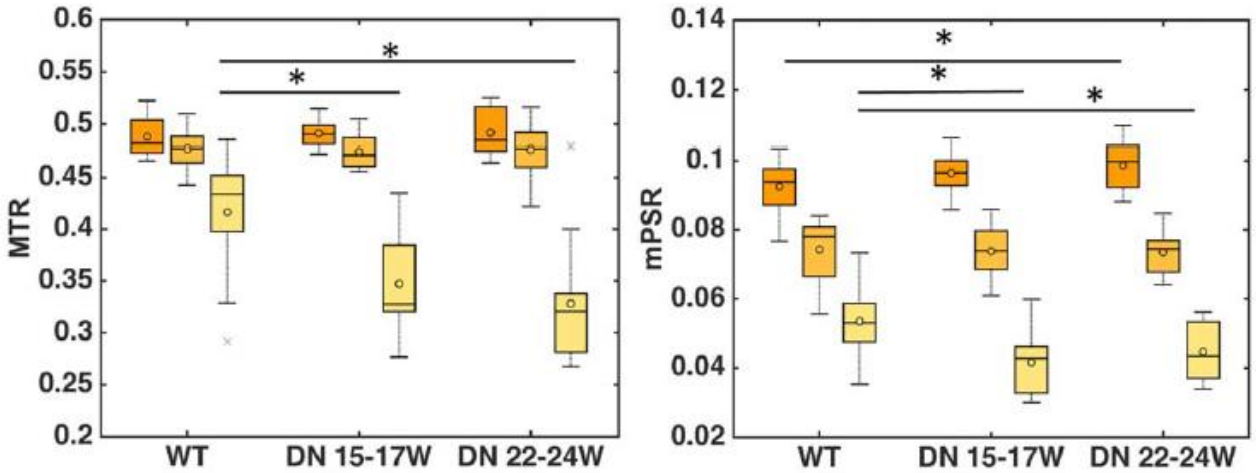




Henkelman-Ramani's model:

$$SI(\omega_1,\Delta f)=\frac{M_0\left(R_b\left[\frac{RM_{0b}}{R_a}\right]+R_{RFB}(\omega_{1CWPE},\Delta f,T_{2b})+R_b+\frac{RM_{0b}}{F}\right)}{\left[\frac{RM_{0b}}{R_a}\right]\left(R_b+R_{RFB}(\omega_{1CWPE},\Delta f,T_{2b})\right)+\left(1+\left[\frac{\omega_{1CWPE}}{2\pi\Delta f}\right]^2\left[\frac{1}{T_{2a}R_a}\right]\right)\left(R_{RFB}(\omega_{1CWPE},\Delta f,T_{2b})+R_b+\frac{RM_{0b}}{F}\right)}$$

F = relative size of the macromolecular pool (PSR)



7T, RF @3-266 ppm, 820°x20ms

Cortex: increased fibrosis

OM , IM+P: urine retention

Cortex (dark orange)
OM (light orange)
IM+P (yellow)

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Abdominal Radiology

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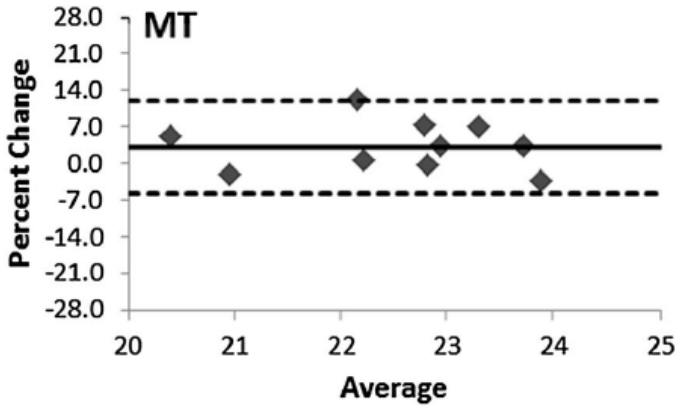
Abdom Radiol (2018) 43:629–638
https://doi.org/10.1007/s00261-017-1236-y

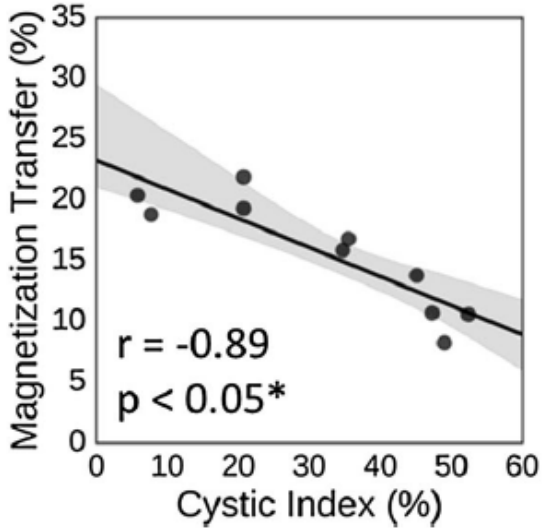
CrossMark

Quantitative MRI of kidneys in renal disease

Timothy L. Kline,[1] Marie E. Edwards,[2] Ishan Garg,[1] Maria V. Irazabal,[2] Panagiotis Korfiatis,[1] Peter C. Harris,[2] Bernard F. King,[1] Vicente E. Torres,[2] Sudhakar K. Venkatesh,[1] Bradley J. Erickson[1]

test–retest reproducibility





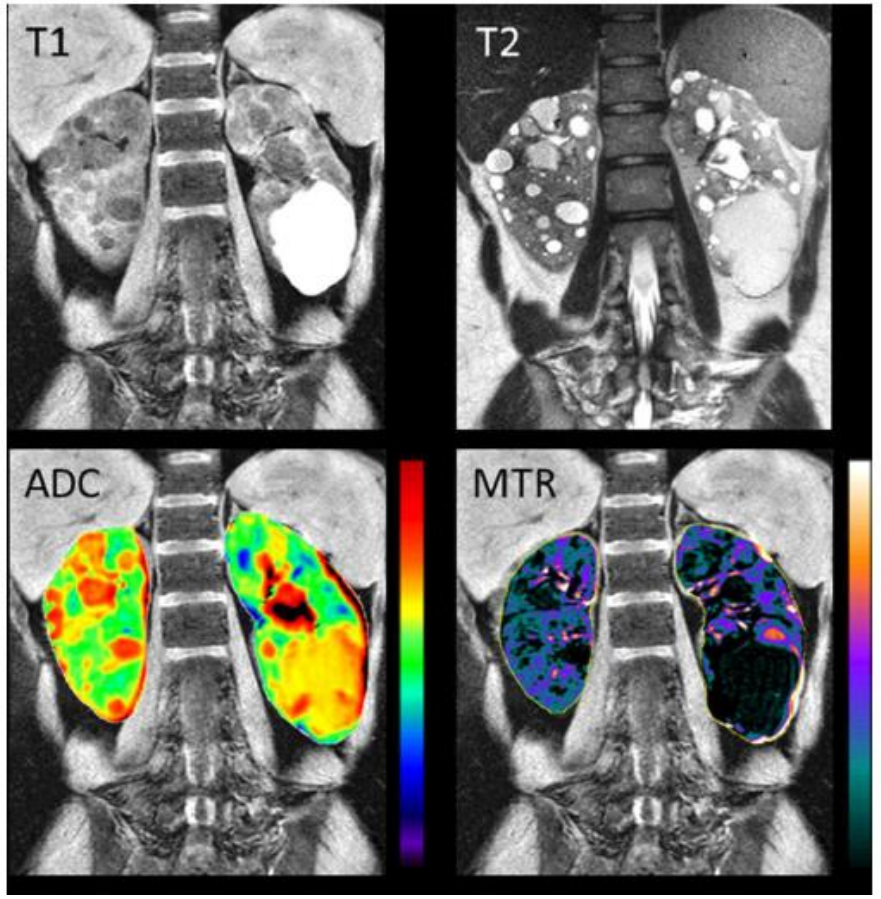


Table 3. Characteristics of the 20 patients in this study comparing the controls to the ADPKD patients for quantitative MR measurements

Scan	Parameter	Control	ADPKD	*p* value
BOLD	R2* (s^{-1})	18.1 ± 1.6	14.9 ± 1.7	0.002*
DWI	ADC ($\times 10^{-3}$ mm^2/s)	2.18 ± 0.10	2.46 ± 0.20	0.013*
DWI	PF (%)	15.05 ± 3.97	12.48 ± 3.39	0.121
DWI	D ($\times 10^{-3}$ mm^2/s)	2.08 ± 0.21	3.04 ± 1.86	0.005*
DWI	D* ($\times 10^{-3}$ mm^2/s)	32.44 ± 17.25	27.65 ± 12.20	0.734
MT	MTR (%)	23.8 ± 1.2	16.3 ± 4.4	<0.001*
MRE	Tissue Stiffness (kPa)	3.8 ± 0.5	3.2 ± 0.3	0.016*

3T, RF @12 ppm

NCRP: non-cystic renal parenchyma patients (18-30 years old)

ADPKD: autosomal dominant polycystic kidney disease patients with normal renal function

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CEST (CHEMICAL EXCHANGE SATURATION TRANSFER)

Journal of Magnetic Resonance **143,** 79–87 (2000)

A New Class of Contrast Agents for MRI Based on Proton Chemical Exchange Dependent Saturation Transfer (CEST)

K. M. Ward,[1] A. H. Aletras, and R. S. Balaban[2]

TABLE 1

Chemical-Exchange-Dependent Saturation Transfer Data from All Compounds Evaluated in this Study

Compound[a]	Conc (mM)	Functional group	ppm[b]	pH[c]	M_S/M_O	$M_O - M_S$ (%)
Sugars[d]		Hydroxyl protons (–OH)				
Mannitol	250 mM	–OH	1.000	7.0	0.89	9.0
Sorbitol	250 mM	–OH	1.000	7.0	0.88	7.3
Fructose	250 mM	–OH	1.333	7.0	0.88	9.3
Dextrose	250 mM	–OH	1.500	7.0	0.89	8.7
Galactose	250 mM	–OH	1.167	7.0	0.85	10.3
Sucrose	250 mM	–OH	1.333	7.0	0.86	10.2
Maltose	250 mM	–OH	1.500	7.0	0.79	14.8
Lactose	250 mM	–OH	1.333	7.0	0.68	20.9
Dextran[e]						
1.75 gm/100 ml	0.25 mM	–OH	1.167	7.0	0.91	8.1
3.50 gm/100 ml	0.5 mM	–OH	1.333	7.0	0.88	10.2
7.00 gm/100 ml	1.0 mM	–OH	1.333	7.0	0.81	13.6
14.0 gm/100 ml	2.0 mM	–OH	1.500	7.0	0.76	18.9
Amino acids[f]		Amino protons ($–NH_2$)				
L-Alanine	125 mM	$–NH_2$	3.000	4.0	0.36	67.4
L-Arginine	125 mM	$–NH_2$	3.000	4.0	0.36	65.8
L-Arginine	125 mM	Guanidinium protons	2.000	5.0	0.33	57.7
L-Lysine	125 mM	$–NH_2$	3.000	4.0	0.34	66.2
L-Glutamine[g]	125 mM	$–NH_2$	2.000	5.2	0.70	27.6
L-Tryptophan[g]	35 mM	$–NH_2$	2.000	6.5	0.89	12.2
5-Hydroxytryptophan[h]	62.5 mM	$–NH_2$	2.833	4.0	0.57	41.6

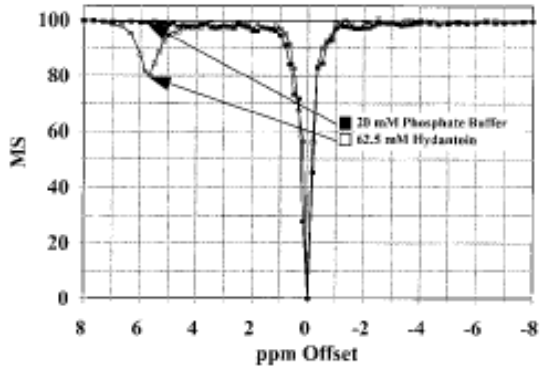
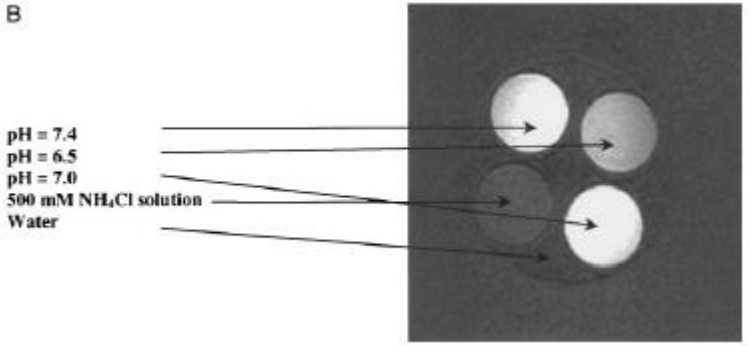


FIG. 1. Representative chemical exchange dependent saturation transfer (CEST) spectra of phosphate buffer (20 mM, pH 4.0) and hydantoin (62.5 mM, 20 mM phosphate buffer, pH 4.0) solutions at T = 37°C.



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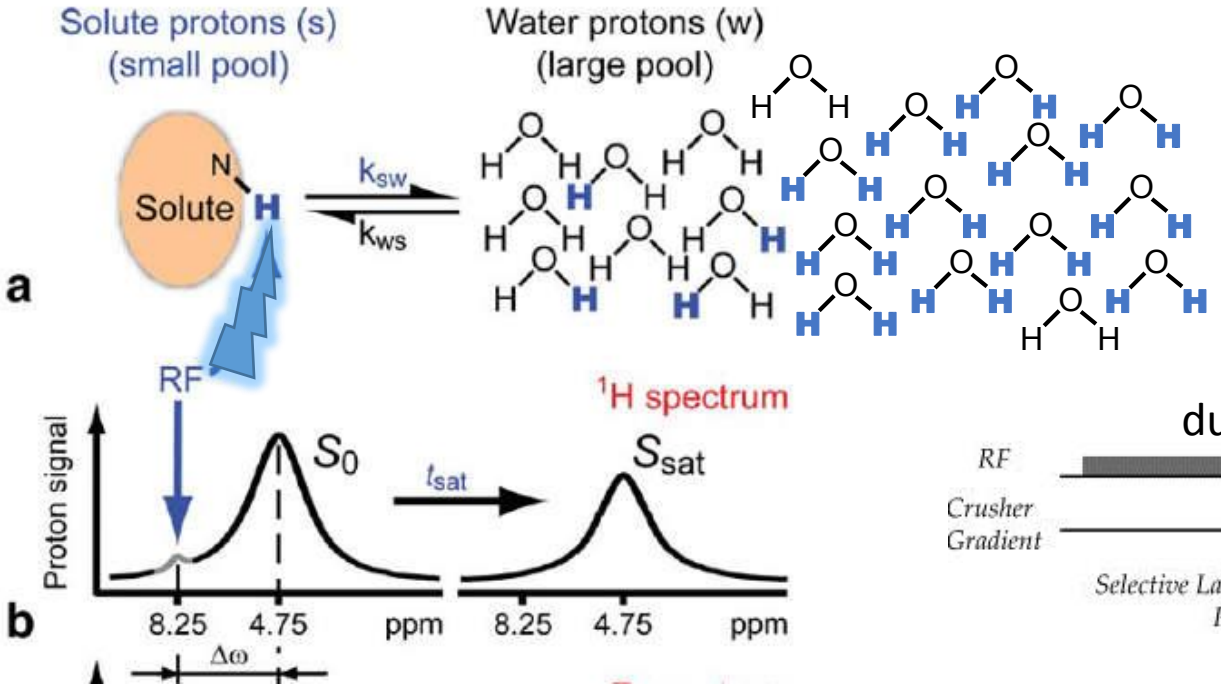
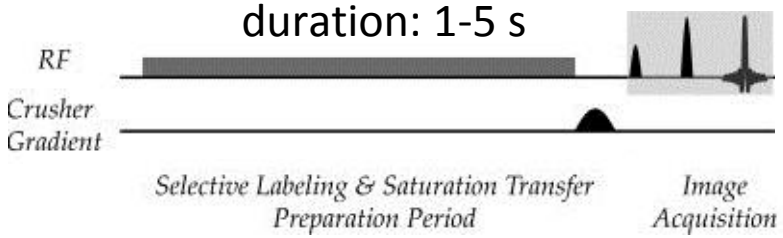
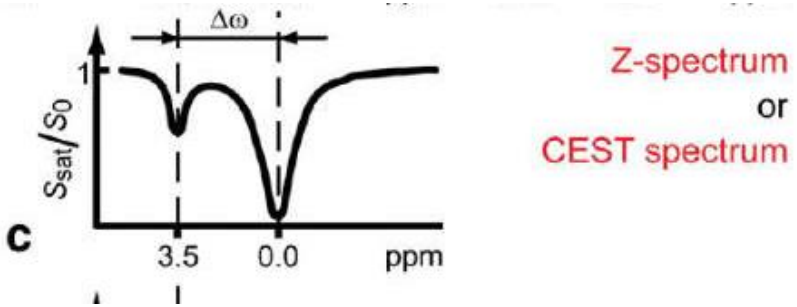
CEST: HOW IT WORKS

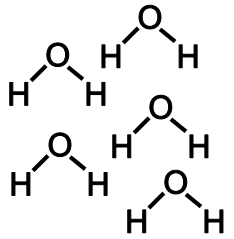
NMR

MRI

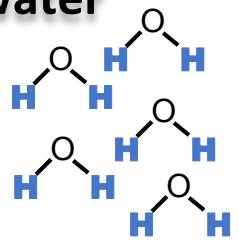








Bulk water



HIGH MRI signal

LOW MRI signal

$$MTR_{asym}(\Delta\omega) = \{S_{sat}(-\Delta\omega) - S_{sat}(\Delta\omega)\} / S_0$$

Adapted from Magn Reson Med 2011, 65, 927

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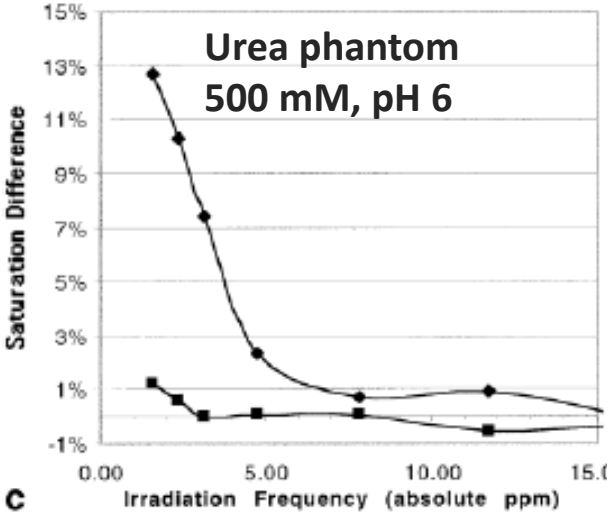
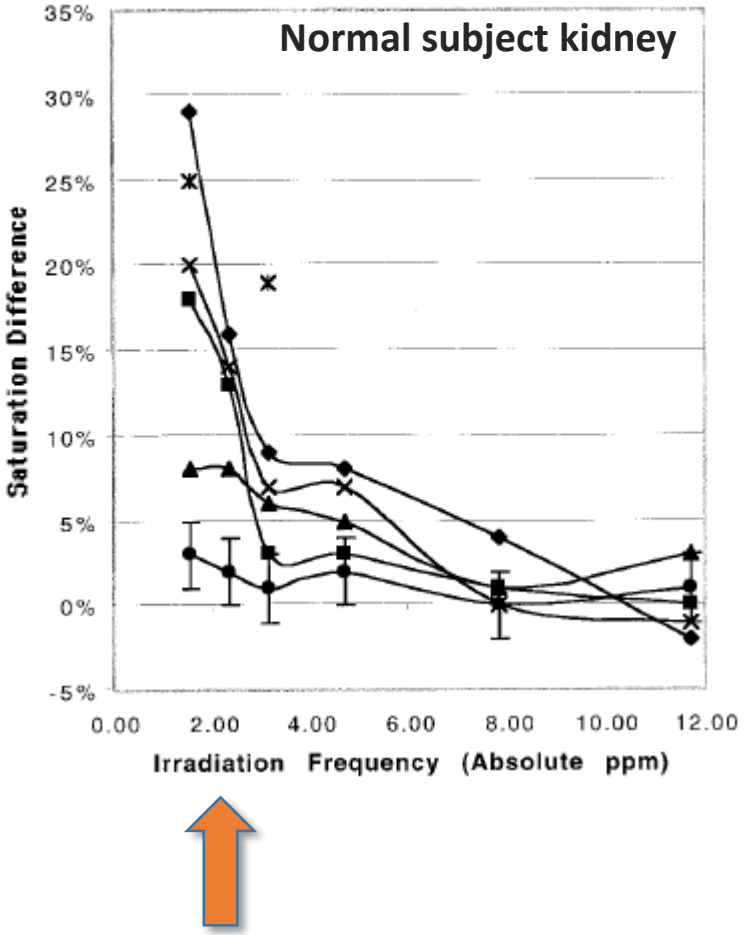
JOURNAL OF MAGNETIC RESONANCE IMAGING 12:745–748 (2000)

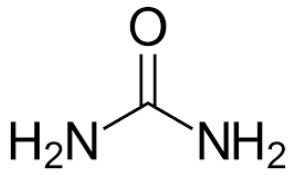
Original Research

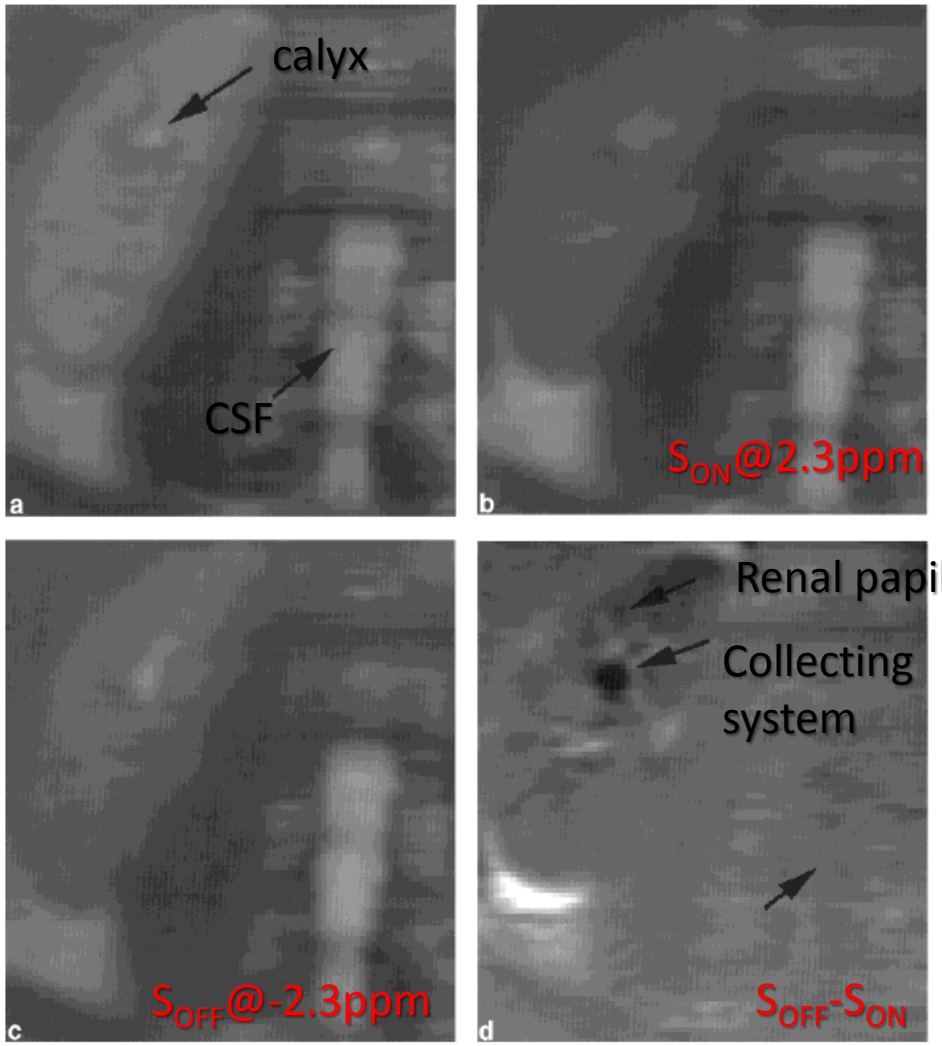
Imaging of Urea Using Chemical Exchange-Dependent Saturation Transfer at 1.5 T

Azar P. Dagher, MD,* Anthony Aletras, PhD, Peter Choyke, MD, and Robert S. Balaban, PhD









1.5T, RF @2.3 ppm, 240W, 20x175ms

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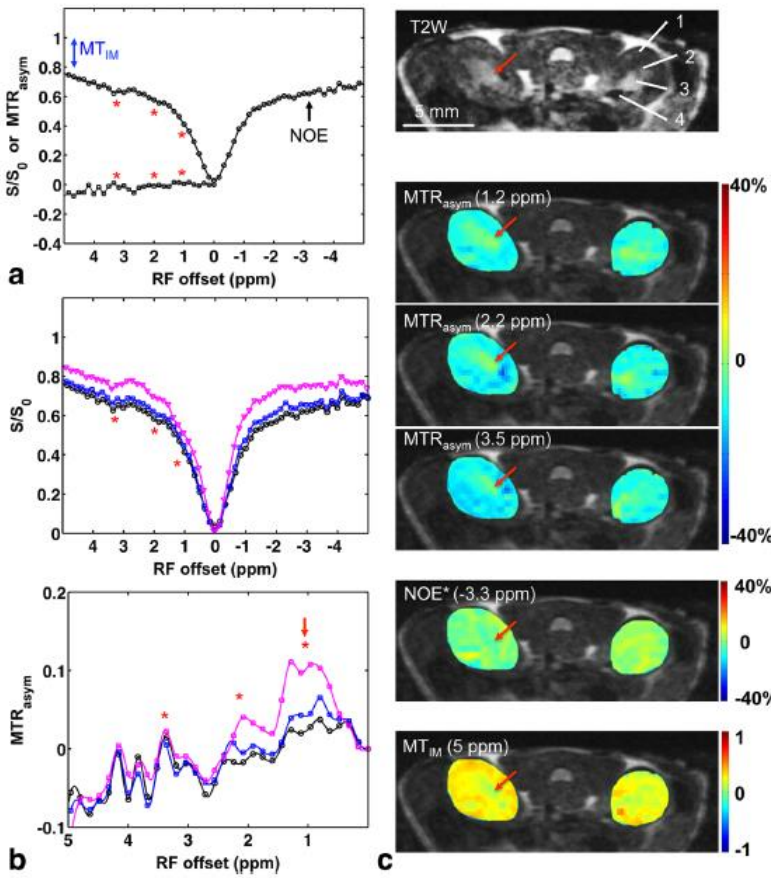
PRECLINICAL AND CLINICAL IMAGING – Full Papers

Magnetic Resonance in Medicine 76:1531–1541 (2016)

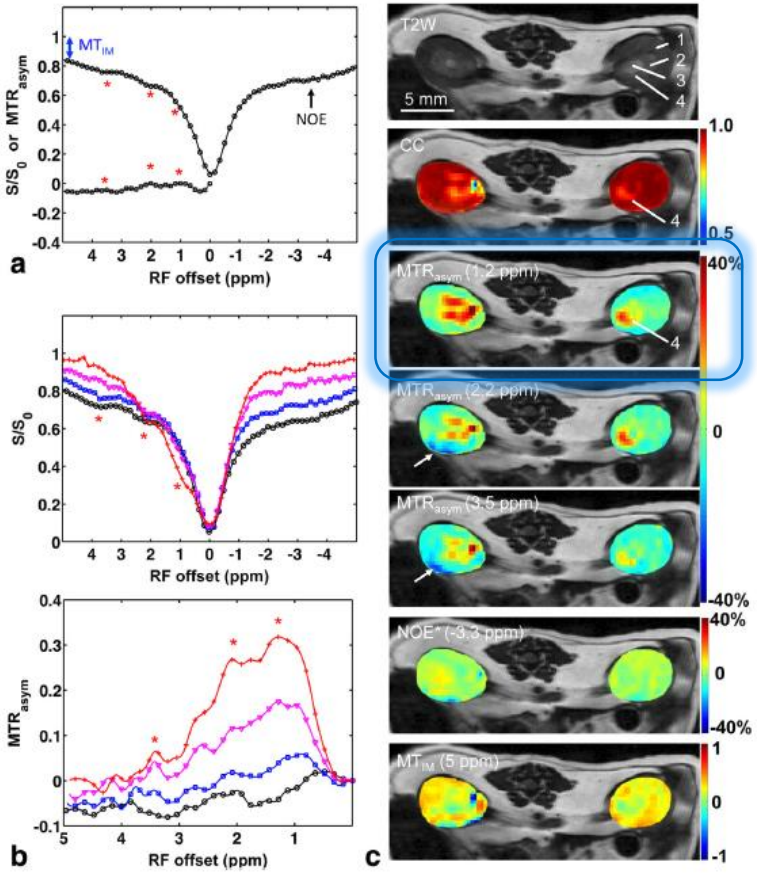
- **Diabetic kidney disease is associated with changes in tissue metabolites (glucose, glycogen)**
- **Db/db mice (carry leptin receptor deficiency for type 2 diabetes) and db/db eNOS$^{-/-}$ show advanced nephropathy**

Mapping Murine Diabetic Kidney Disease Using Chemical Exchange Saturation Transfer MRI

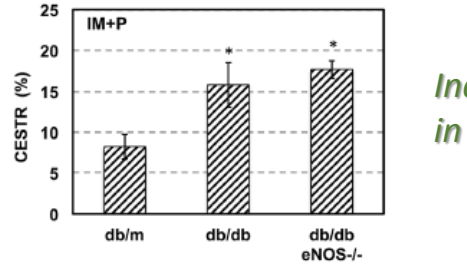
Feng Wang,[1,2]* David Kopylov,[3] Zhongliang Zu,[1,2] Keiko Takahashi,[4] Suwan Wang,[4] C. Chad Quarles,[1,2] John C. Gore,[1,2,5] Raymond C. Harris,[4] and Takamune Takahashi[4]



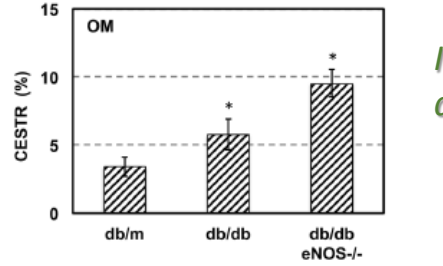
Nondiabetic db/m mouse (16 weeks)



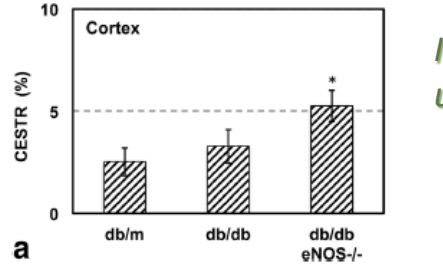
diabetic db/db mouse (16 weeks)



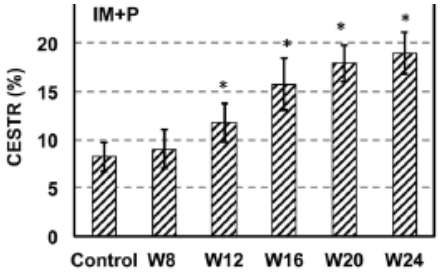
Increased glucose in urine



Increased glycogen deposition



Increased glucose uptake



db/db mice

7T, RF @1.2 ppm, 1 µTx5s

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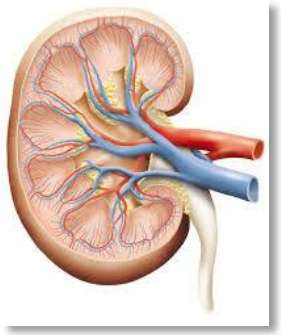
KIDNEY REGULATION OF ACID-BASE HOMEOSTASIS

- The kidneys play a major role in the regulation of acid-base balance by reabsorbing bicarbonate filtered by the glomeruli and excreting titratable acids and ammonia into the urine
- Decline in kidney function will result in derangements in acid-base homeostasis with reduced ammonia excretion, inability to reabsorb bicarbonate and failure of acid excretion when kidney function is severely impaired
- In chronic kidney disease (CKD), with declining kidney function, acid retention and metabolic acidosis occur
- Degree of acidosis approximately correlates with severity of renal failure and usually is more severe at a lower GFR
- Several adverse consequences have been associated with metabolic acidosis, including muscle wasting, bone disease and progression of renal failure

reabsorption of HCO_3^- in blood



Secretion of H^+ in tubules and excretion

Renal pH mapping may represent a novel biomarker for detecting (early) renal damage

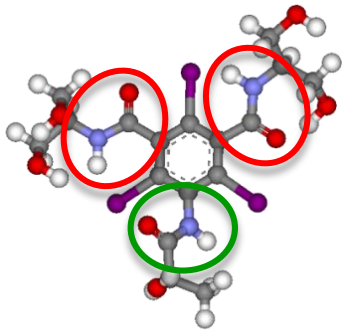
Italian National Research Council

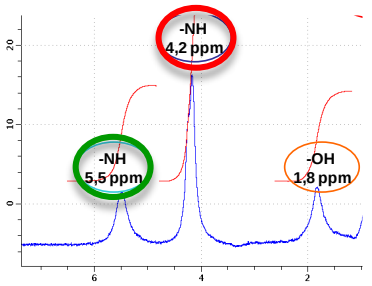
PRECLINICAL AND CLINICAL IMAGING - Full Papers

Magnetic Resonance in Medicine 65:202–211 (2011)

Iopamidol as a Responsive MRI-Chemical Exchange Saturation Transfer Contrast Agent for pH Mapping of Kidneys: In Vivo Studies in Mice at 7 T

Dario Livio Longo,[1] Walter Dastrù,[1] Giuseppe Digilio,[2] Jochen Keupp,[3] Sander Langereis,[3] Stefania Lanzardo,[4] Simone Prestigio,[4] Oliver Steinbach,[3] Enzo Terreno,[1] Fulvio Uggeri,[5] and Silvio Aime[1]*

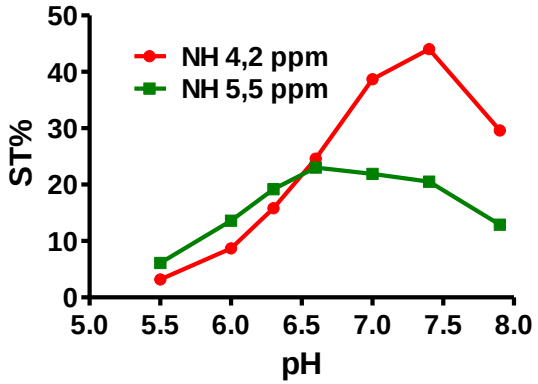


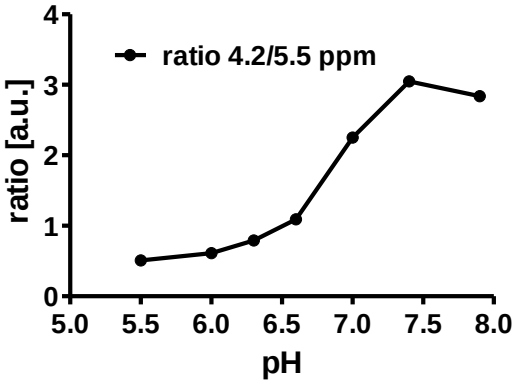


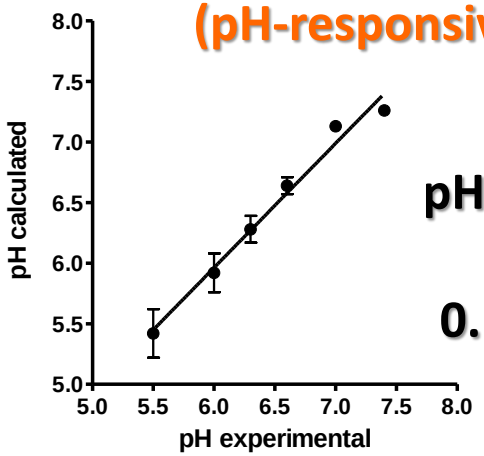
1H-NMR spectrum

Iopamidol

(pH-responsive contrast agent)







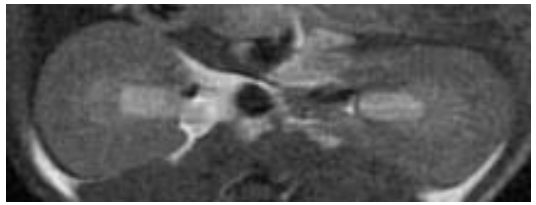
pH accuracy

≅

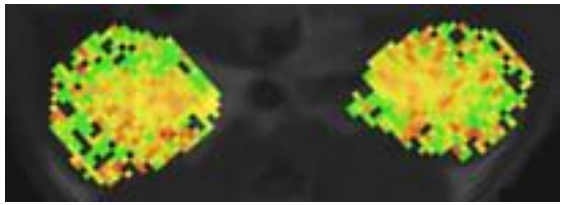
0.1 pH unit

Ratiometric approach:

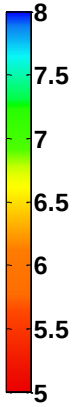
rule out the concentration term

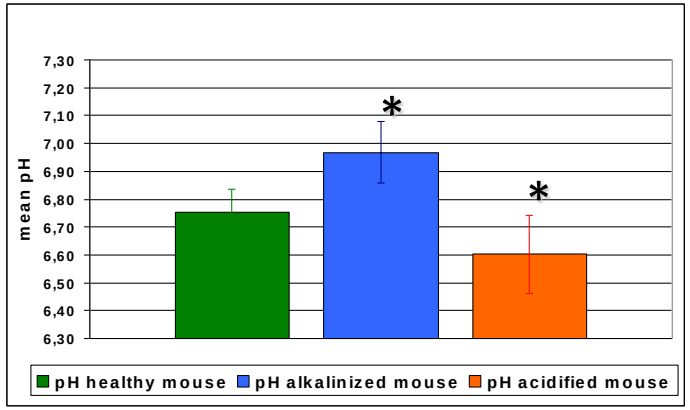


T_{2w} **anatomical image**



pH map





Magn Reson Med **2011**, 65, 202
Magn Reson Med **2013**, 70, 859
Phys Med Biol. **2014**, 59, 4493

Italian National Research Council

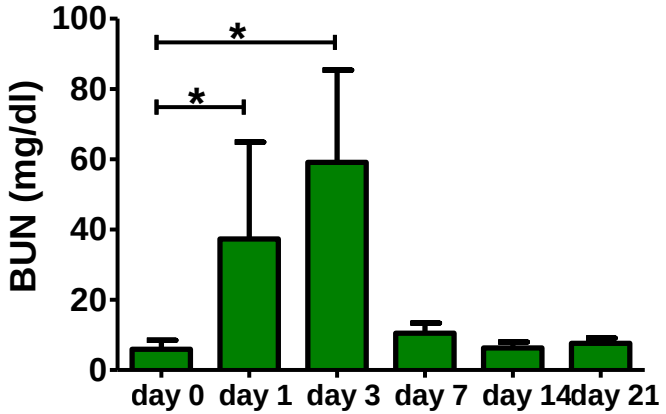
PRECLINICAL AND CLINICAL IMAGING - Note

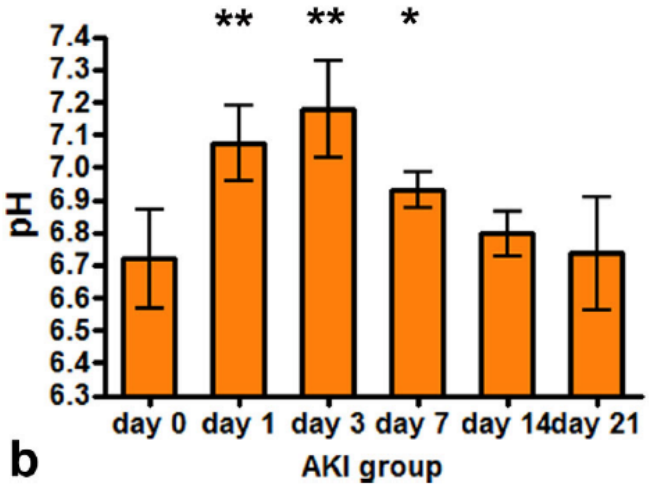
Magnetic Resonance in Medicine 70:859–864 (2013)

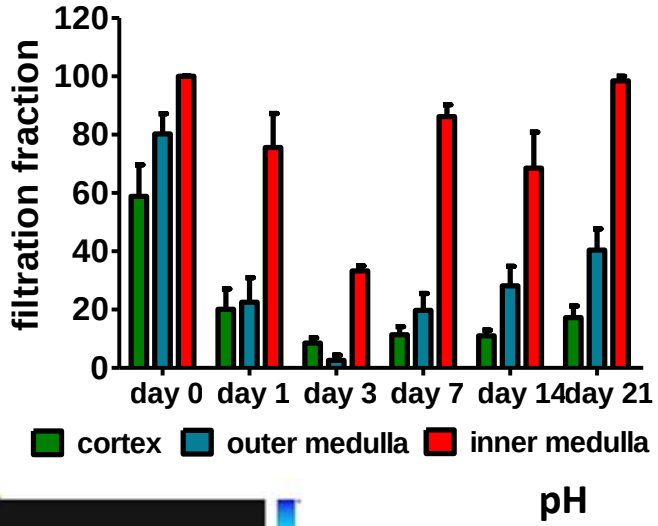
Imaging the pH Evolution of an Acute Kidney Injury Model by Means of Iopamidol, a MRI-CEST pH-Responsive Contrast Agent

Dario Livio Longo,[1] Alice Busato,[1] Stefania Lanzardo,[2] Federica Antico,[3] and Silvio Aime[1*]

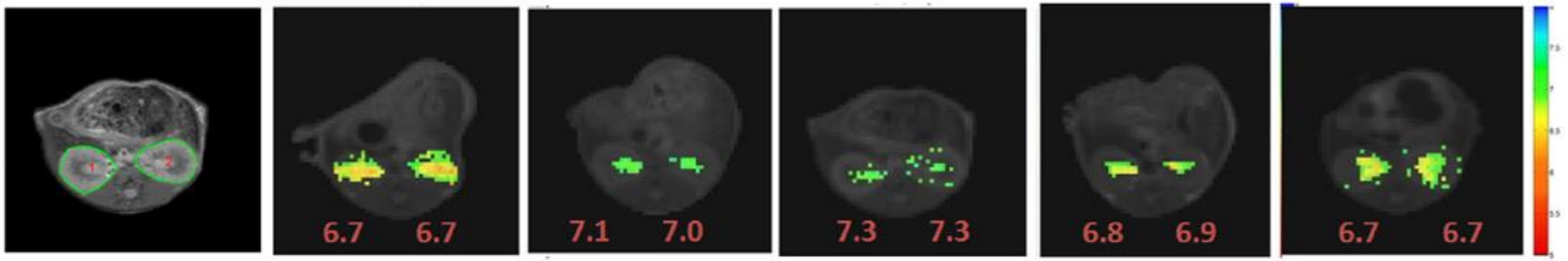
- **rhabdomyolysis is one of the leading causes of acute renal failure, initiated by acute disruption of skeletal muscle due to physical or chemical damage from crush injury, surgery, or toxins that may result in a rapid deterioration of renal function**
- **glycerol-induced AKI model show multiple ischemic, toxic, and obstructive tubular insults similar to acute tubular necrosis that occurs in humans**







pH



Intramuscular injection
8 ml/kg (50% glycerol)

7T, RF @4.2/5.5 ppm, 3 µTx5s

Italian National Research Council

DOI 10.1002/nbm.3720

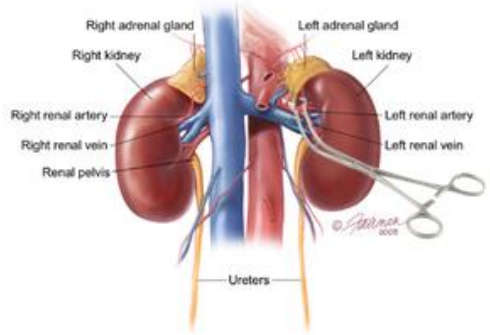
NMR in Biomedicine. 2017;e3720.

WILEY NMR IN BIOMEDICINE

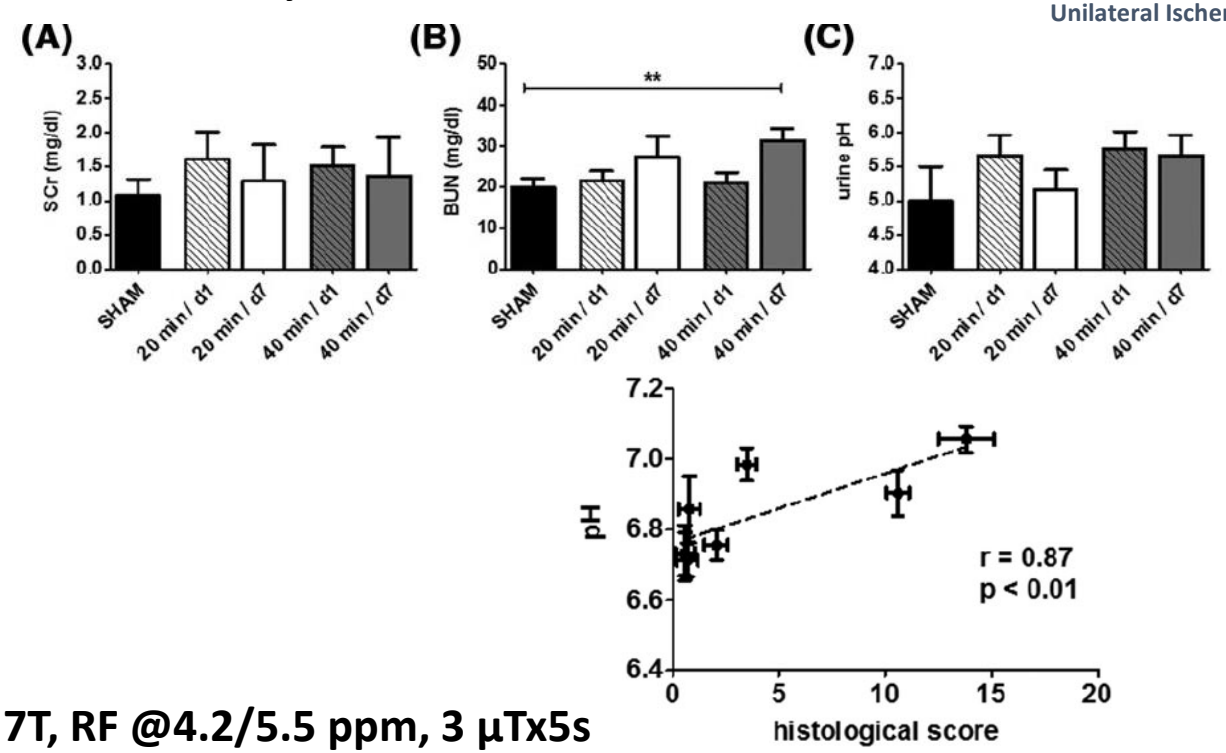
Noninvasive evaluation of renal pH homeostasis after ischemia reperfusion injury by CEST-MRI

Dario Livio Longo[1,2] | Juan Carlos Cutrin[2] | Filippo Michelotti[2] | Pietro Irrera[2] | Silvio Aime[2]

- **Ischemic renal injury is the major cause of acute kidney injury (AKI)**
- **In the unilateral ischemia reperfusion injury (KIRI) model only one kidney is damaged and the contralateral compensate the reduced renal functionality**

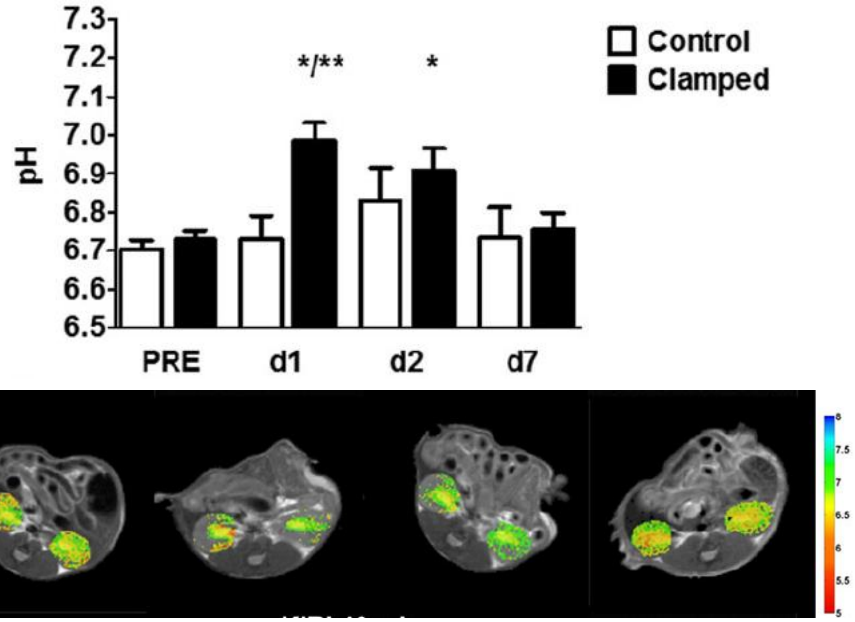


Unilateral Ischemic / Reperfusion Injury model

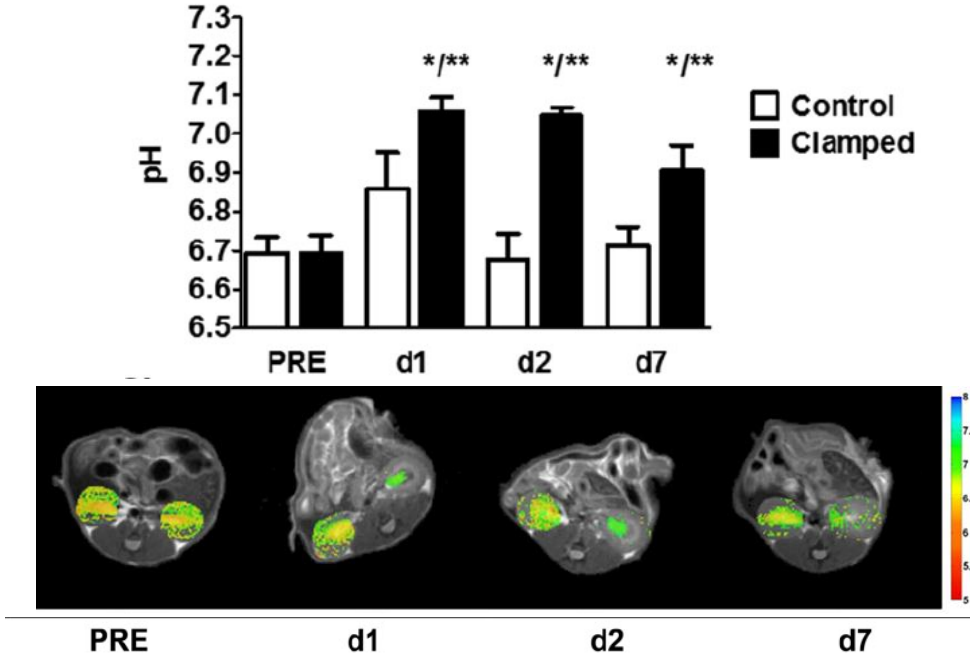


7T, RF @4.2/5.5 ppm, 3 µTx5s

Moderate AKI (20 min ischemia)



Severe AKI (40 min ischemia)



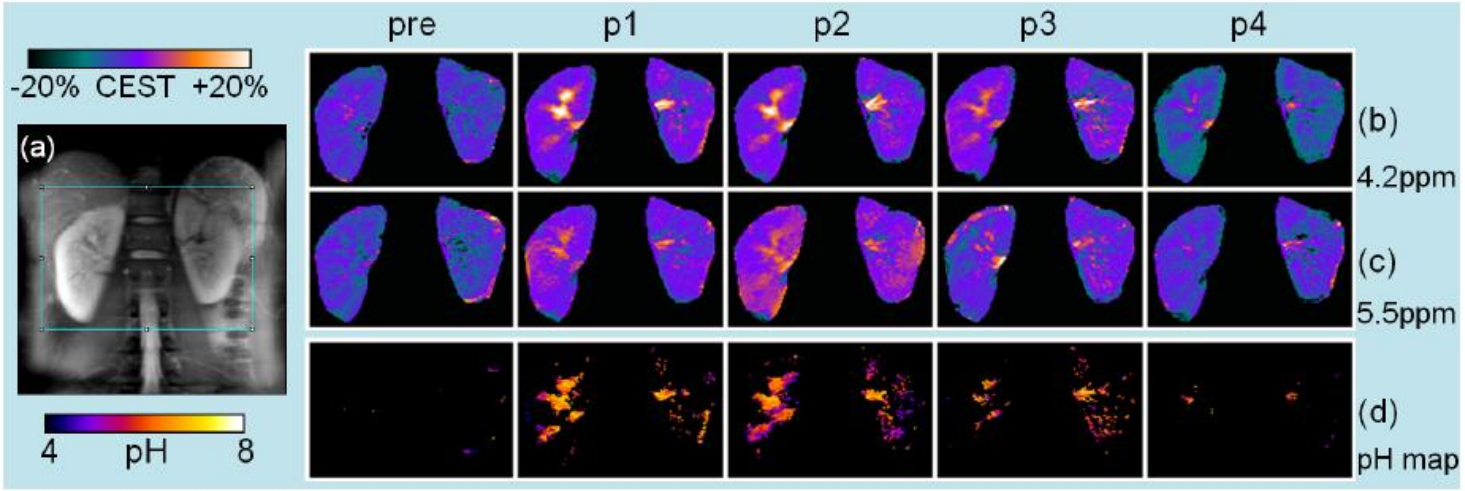
Italian National Research Council

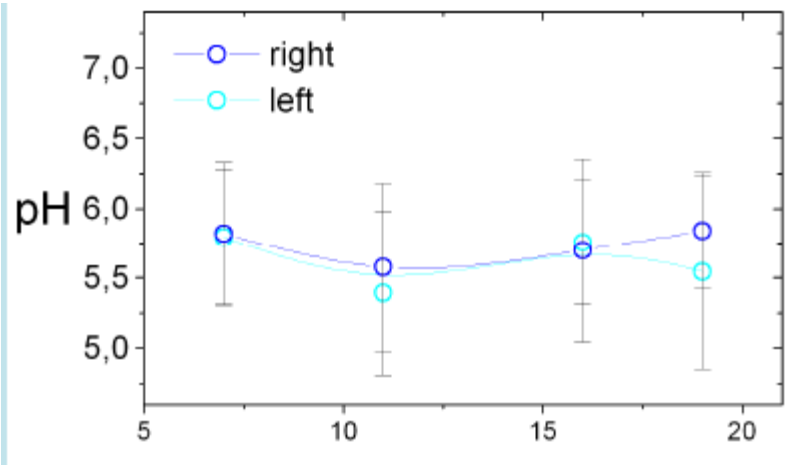
Proc. Intl. Soc. Mag. Reson. Med. 20 (2012)

IN VIVO HUMAN KIDNEY PH MAPPING AT 3T USING TIME-INTERLEAVED PARALLEL RF TRANSMISSION CEST

Ivan E Dimitrov[1,2], Masaya Takahashi[2], Koji Sagiyama[2], A. Dean Sherry[2,3], and Jochen Keupp[4]

[1]*Philips Medical Systems, Cleveland, OH, United States,* [2]*Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, TX, United States,* [3]*Chemistry, University of Texas Dallas, Richardson, TX, United States,* [4]*Philips Research Europe, Hamburg, Germany*





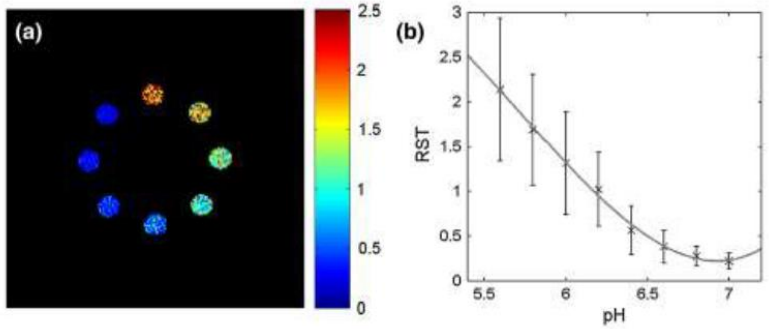
3T scanner (Achieva TX, Philips)
RF 2.3 µT, 2x49 ms
100 ml iopamidol (Isovue 300), dose: 0.4 g I / kg

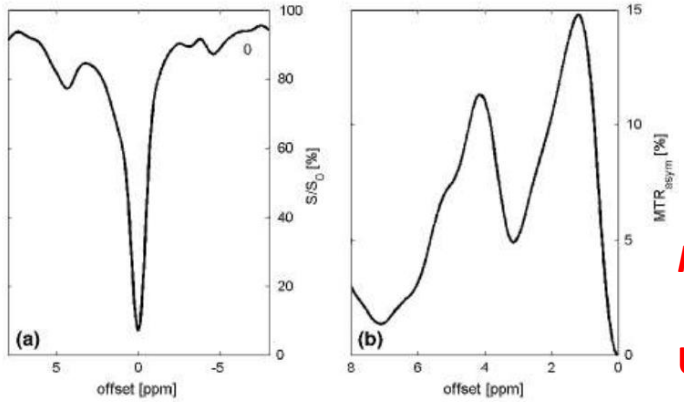
Magn Reson Mater Phy (2014) 27:477–485
DOI 10.1007/s10334-014-0433-8

RESEARCH ARTICLE

Pilot study of Iopamidol-based quantitative pH imaging on a clinical 3T MR scanner

Anja Müller-Lutz · Nadia Khalil · Benjamin Schmitt · Vladimir Jellus · Gael Pentang · Georg Oeltzschner · Gerald Antoch · Rotem S. Lanzman · Hans-Jörg Wittsack





Human bladder
CEST pH= 6.65
Urine pH = 6.72

3T scanner (Magnetom Trio A, Siemens)
RF 0.4 µT, 10x100 ms
65 min after CT examination

ACKNOWLEDGMENTS

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Molecular Imaging Center

University of Torino / Molecular Imaging Center
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Simonetta Geninatti
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Walter Dastrù
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Juan Carlos Cutrin
Rachele Stefania
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Enza Di Gregorio
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Eleonora Cavallari

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University of Copenhagen
Stine Falsig Pedersen

Medical Faculty Mannheim
Frank Gerrit Zöllner

National grants:

EU projects:

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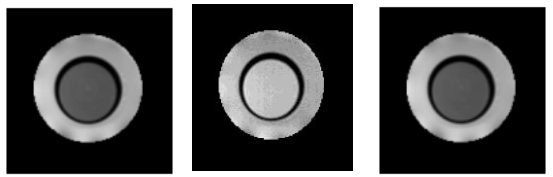
ADVANTAGES OVER CONVENTIONAL MRI CONTRAST AGENTS

CONTRAST

ALWAYS ON

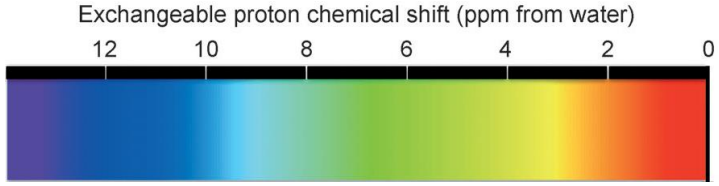
SWITCHED ON/OFF AT WILL



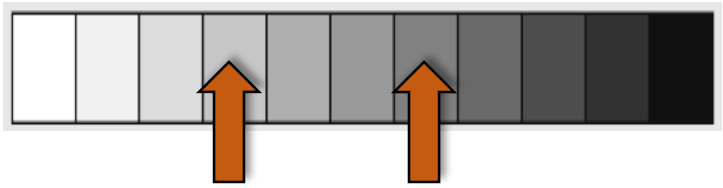
ON OFF ON

RELAXIVITY-ENCODED

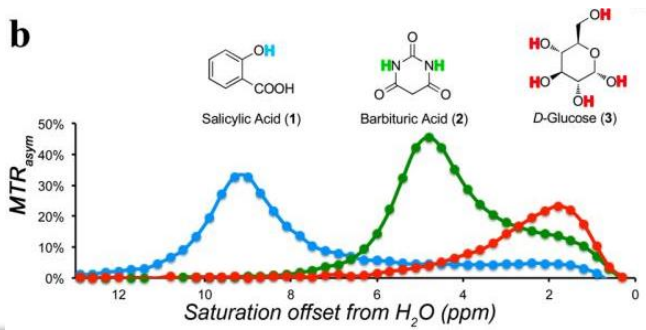
FREQUENCY-ENCODED



SINGLE VISUALIZATION



MULTIPLE VISUALIZATION



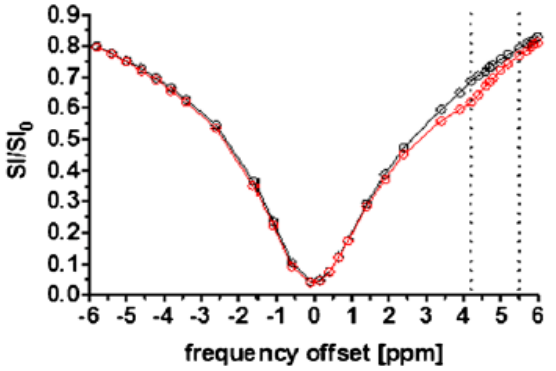
GADOLINIUM-based

CEST-based

DISADVANTAGES TO CONVENTIONAL MRI CONTRAST AGENTS

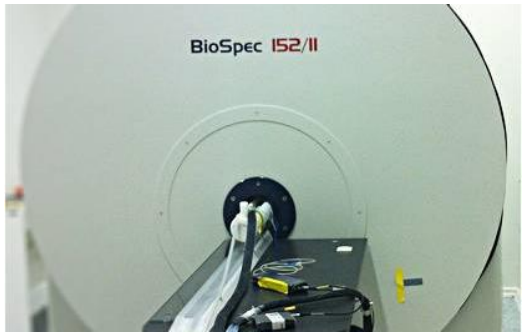
Specificity only for exogenous contrast agent

Low sensitivity (mM-µM range, dependent on exchange rate / chemical shift / number of protons)



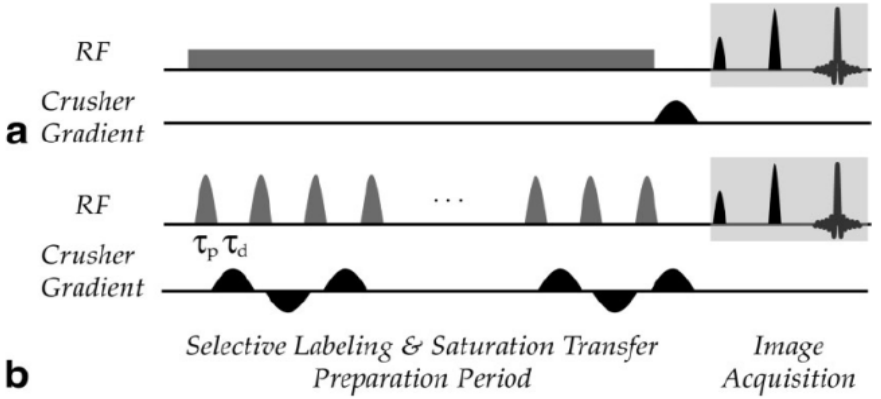
- PRE
- POST

High magnetic field (>= 3T)



low temporal resolution (saturation module + multiple offsets)

SAR limitations (low/high B_1, long/short period)



PRE-CLINICAL APPLICATIONS OF MRI-CEST pH-sensitive agents

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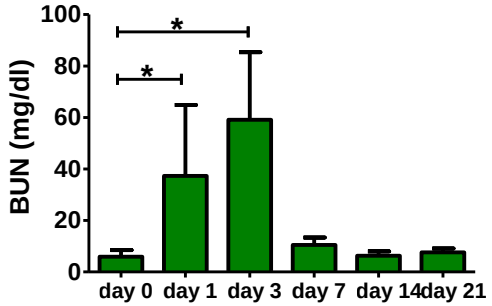
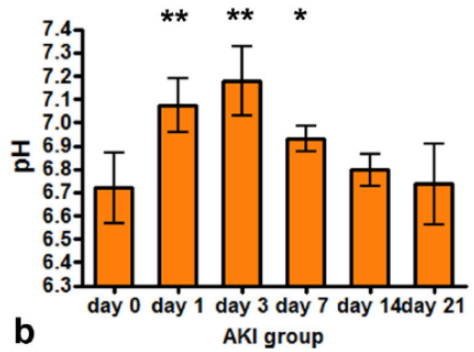
PRECLINICAL AND CLINICAL IMAGING – Note

Magnetic Resonance in Medicine 70:859–864 (2013)

Imaging the pH Evolution of an Acute Kidney Injury Model by Means of Iopamidol, a MRI-CEST pH-Responsive Contrast Agent

Dario Livio Longo,[1] Alice Busato,[1] Stefania Lanzardo,[2] Federica Antico,[3] and Silvio Aime[1]*





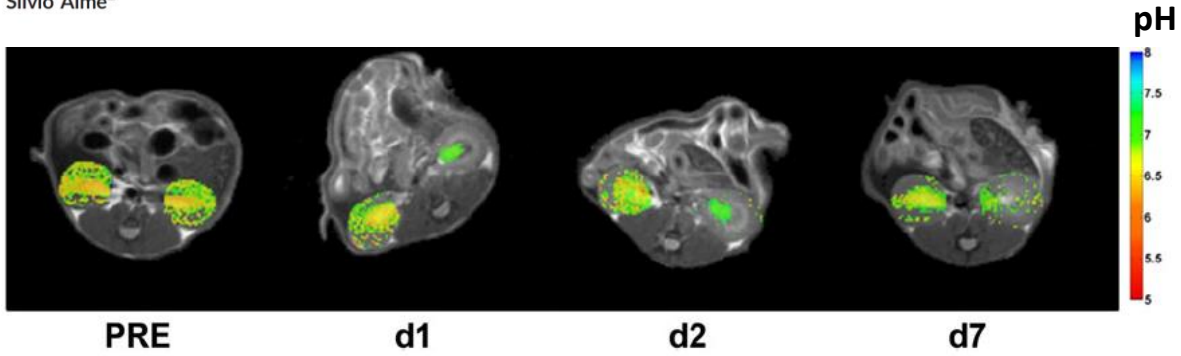
DOI 10.1002/nbm.3720

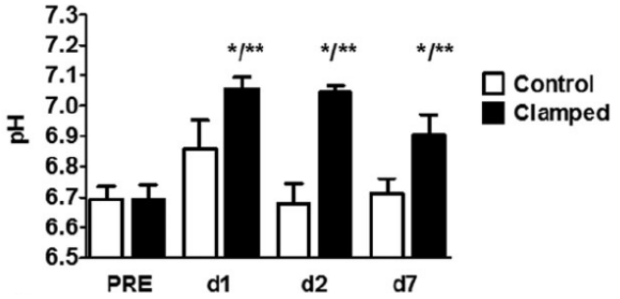
WILEY NMR IN BIOMEDICINE

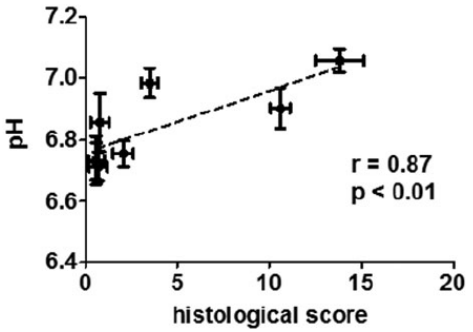
RESEARCH ARTICLE

Noninvasive evaluation of renal pH homeostasis after ischemia reperfusion injury by CEST-MRI

Dario Livio Longo[1,2] | Juan Carlos Cutrin[2] | Filippo Michelotti[2] | Pietro Irrera[2] | Silvio Aime[2]







NOTE

Magnetic Resonance in Medicine 00:00–00 (2017)

A Generalized Ratiometric Chemical Exchange Saturation Transfer (CEST) MRI Approach for Mapping Renal pH using Iopamidol

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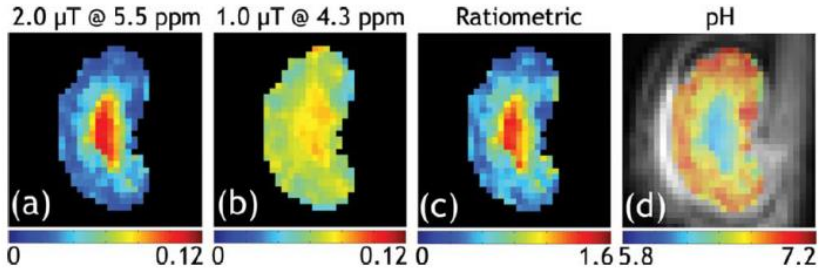

4.7 T, rats

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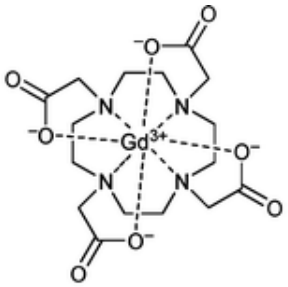
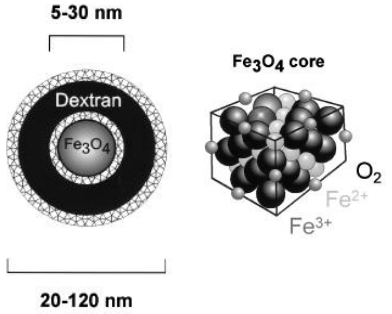
CEST (CHEMICAL EXCHANGE SATURATION TRANSFER)

Gd-complexes and iron-oxide particles generate a relaxivity-based contrast



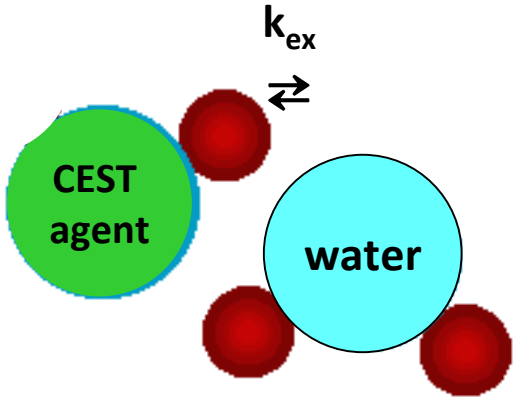


Gd-based / T_1 agents

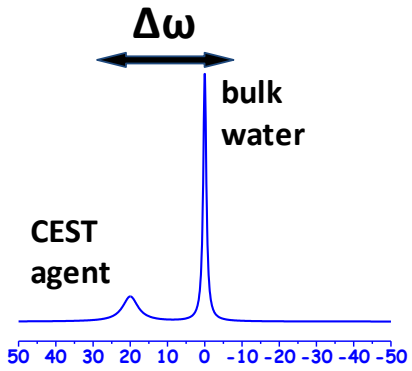
Iron oxide nanoparticles / T_2 agents

CEST agents generate a “frequency-encoded” MR contrast

mobile protons in exchange with water molecules



distinct NMR signals



$\Delta\omega \geq k_{ex}$

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Magn Reson Mater Phy (2014) 27:477–485
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Clinical

RESEARCH ARTICLE

Pilot study of Iopamidol-based quantitative pH imaging on a clinical 3T MR scanner

Anja Müller-Lutz · Nadia Khalil · Benjamin Schmitt · Vladimir Jellus · Gael Pentang · Georg Oeltzschner · Gerald Antoch · Rotem S. Lanzman · Hans-Jörg Wittsack

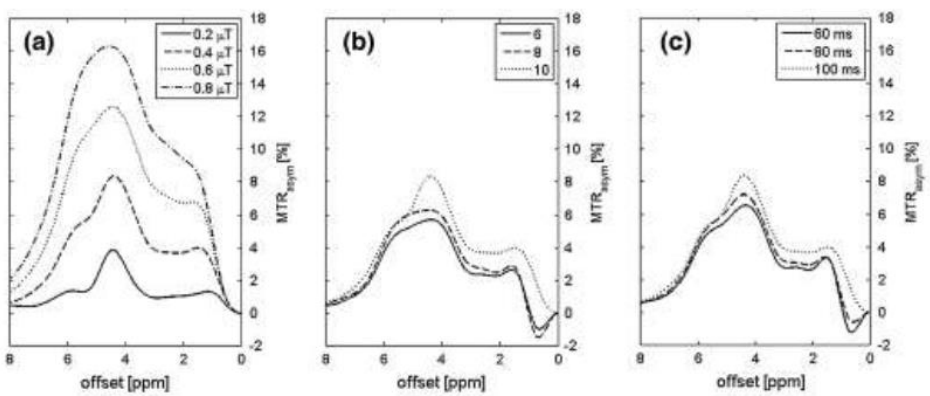
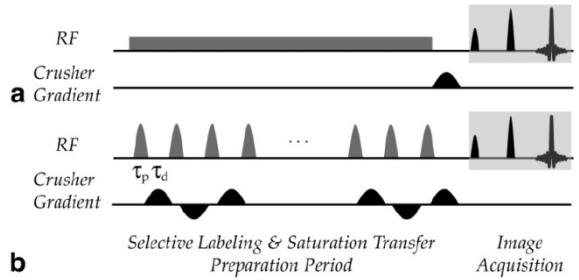


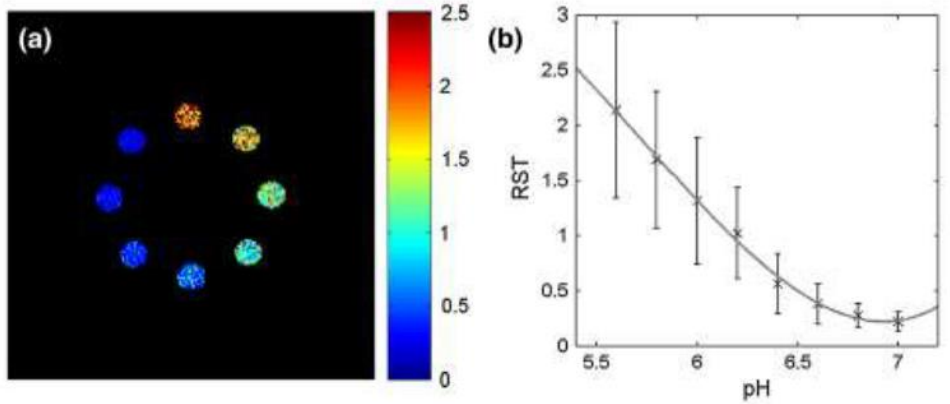
Fig. 1 MTR_{asym} curves of the Iopamidol solution measured with different B_1-CWAE field strengths (**a**), different number of pulses (**b**), and different pulse durations (**c**)

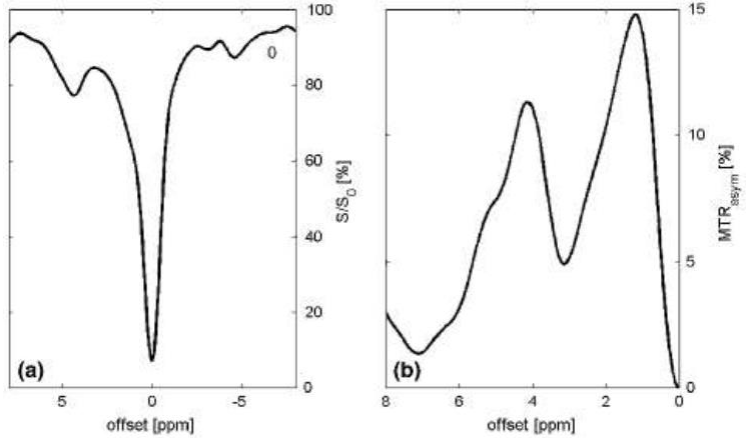


Human bladder

Iopamidol-CEST pH= 6.65

Urine pH = 6.72





Full paper

CONTRAST MEDIA & MOLECULAR IMAGING

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Developing imidazoles as CEST MRI pH sensors

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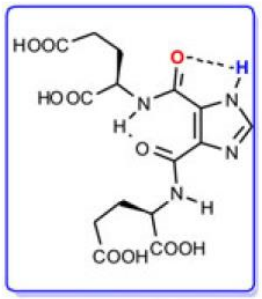
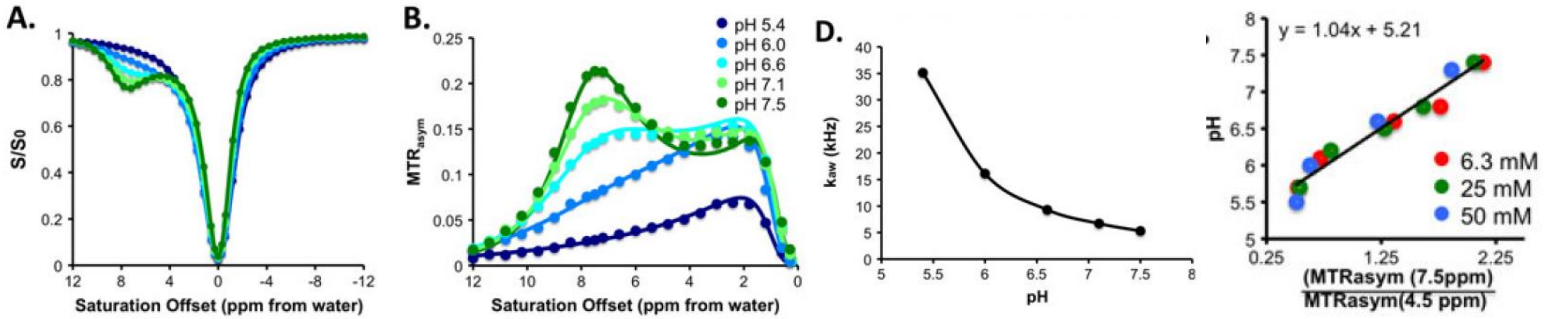
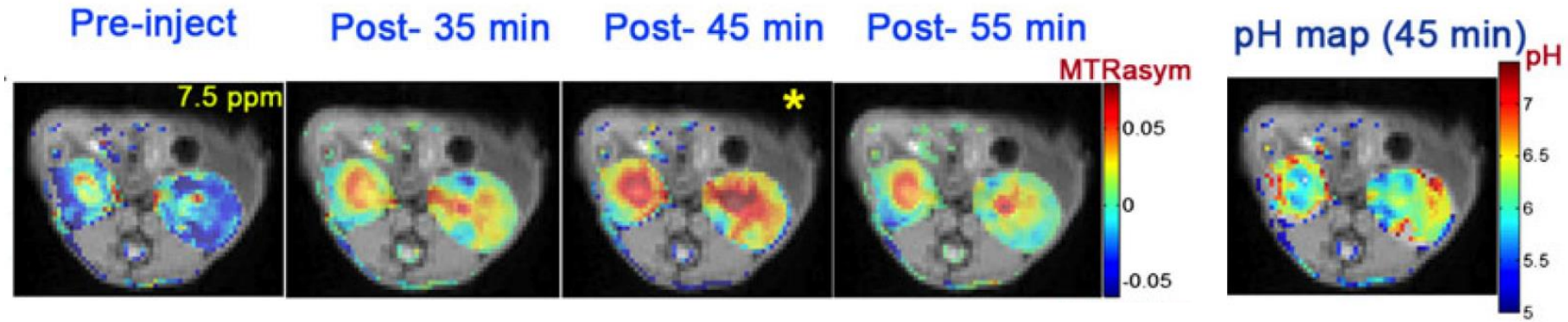


5 (7.8 ppm)





9.4 T

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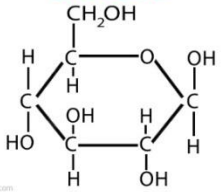
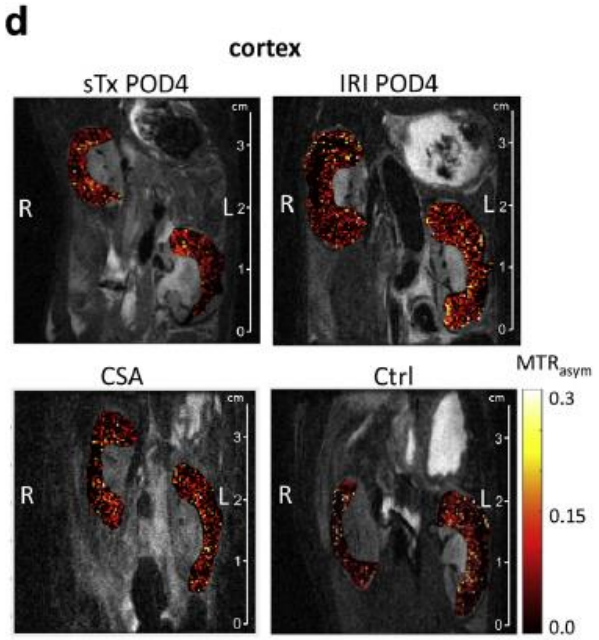
GlucoCEST magnetic resonance imaging *in vivo* may be diagnostic of acute renal allograft rejection

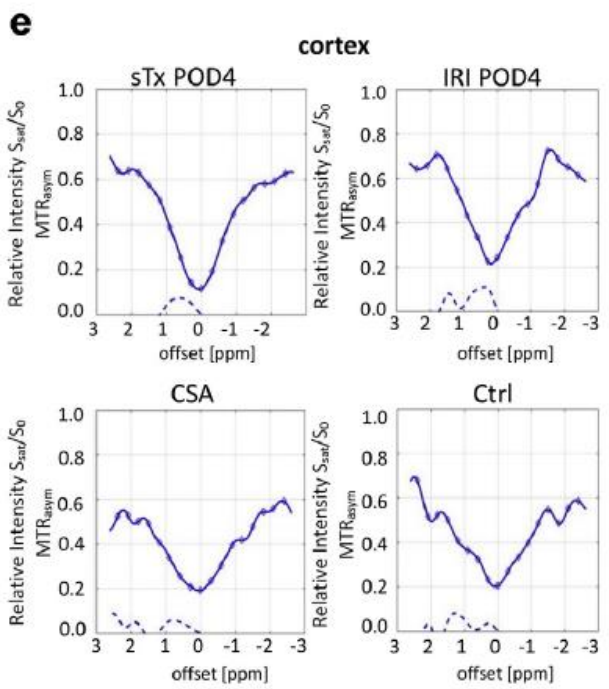
Dominik Kentrup[1,8], Philipp Bovenkamp[2,8], Annika Busch[2], Katharina Schuette-Nuetgen[1], Helga Pawelski[1], Hermann Pavenstädt[1], Eberhard Schlatter[1], Karl-Heinz Herrmann[3], Jürgen R. Reichenbach[3], Bettina Löffler[4], Barbara Heitplatz[5], Veerle Van Marck[5], Nirbhay N. Yadav[6,7], Guanshu Liu[6,7], Peter C.M. van Zijl[6,7], Stefan Reuter[1,9] and Verena Hoerr[2,4,9]

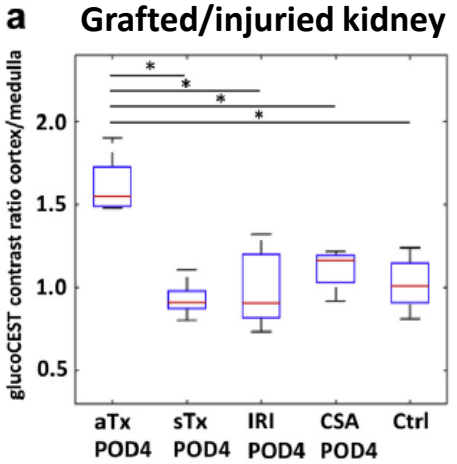
Glucose

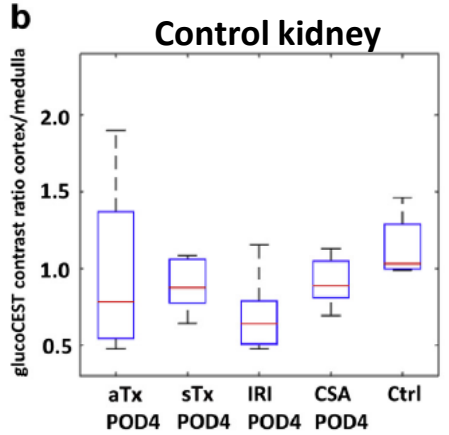


9.4 T









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Angewandte Communications

Angew. Chem. Int. Ed. 2015, 54, 8662–8664

Imaging Agents

International Edition: DOI: 10.1002/anie.201502497
German Edition: DOI: 10.1002/ange.201502497

A pH-Responsive MRI Agent that Can Be Activated Beyond the Tissue Magnetization Transfer Window**

*Xiaojing Wang, Yunkou Wu, Todd C. Soesbe, Jing Yu, Piyu Zhao, Garry E. Kiefer, and A. Dean Sherry**

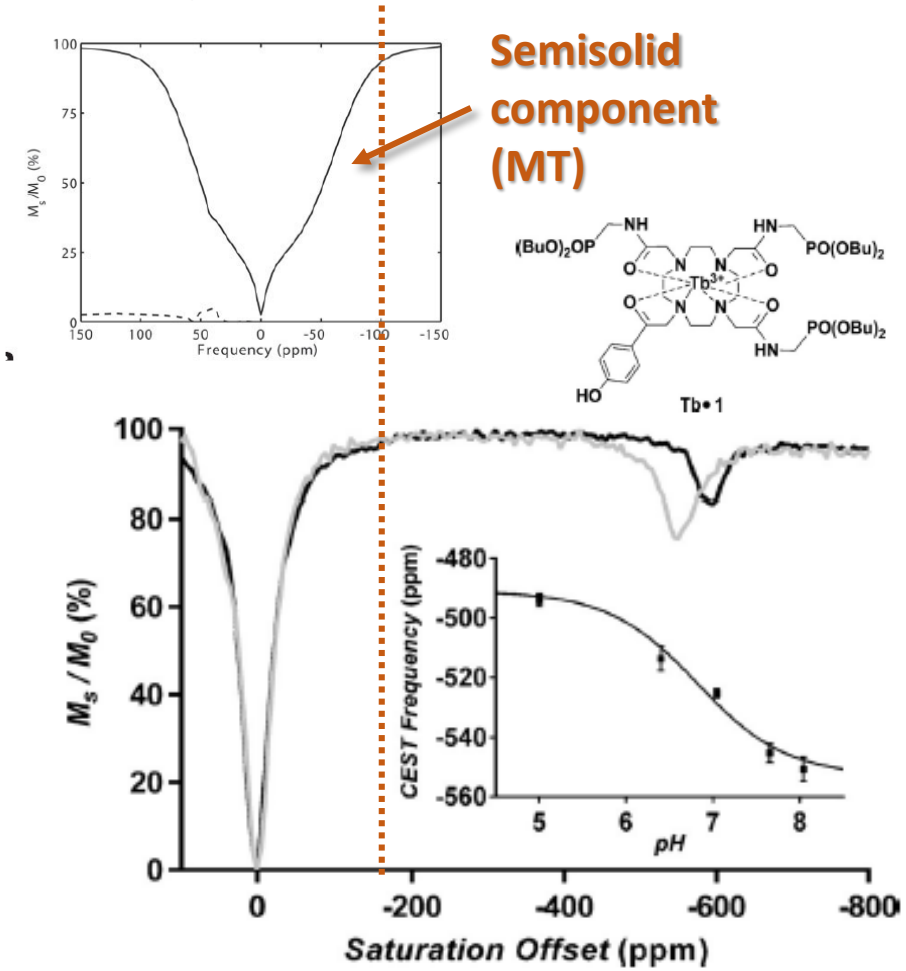

Figure 1. CEST spectra of 20 mM Tb·1 agent recorded at pH 8.2 at 298 K (black line) and 310 K (gray line) in CD_3CN/H_2O (1:1) with a B_1 of 100 μT. The inset shows a plot of the chemical shift of the water exchange CEST peak as a function of pH (T = 310 K).

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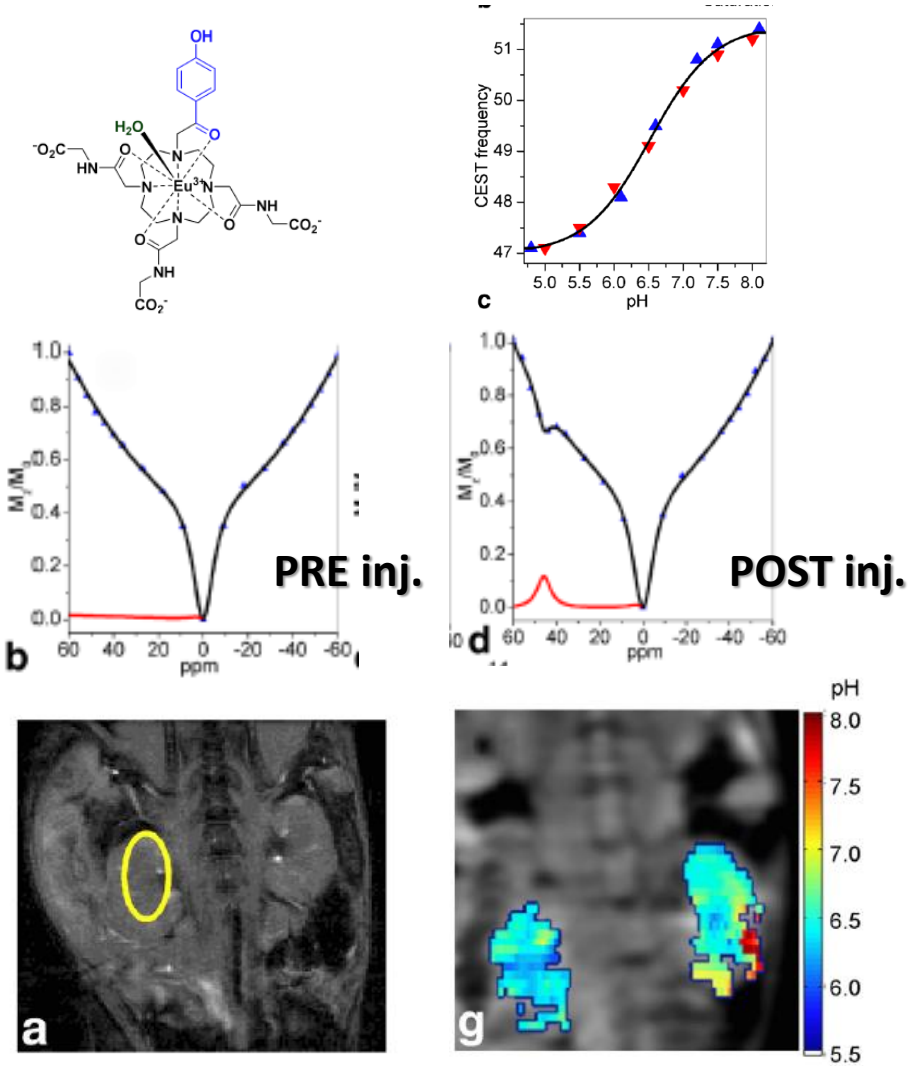
pH Imaging of Mouse Kidneys In Vivo Using a Frequency-Dependent paraCEST Agent

Yunkou Wu,[1,2,3] Shanrong Zhang,[1] Todd C. Soesbe,[1,2] Jing Yu,[4] Elena Vinogradov,[1,2] Robert E. Lenkinski,[1,2] and A. Dean Sherry[1,2,4]*