Renal
Blood oxygenation level-dependent (BOLD) MRI
for non experts

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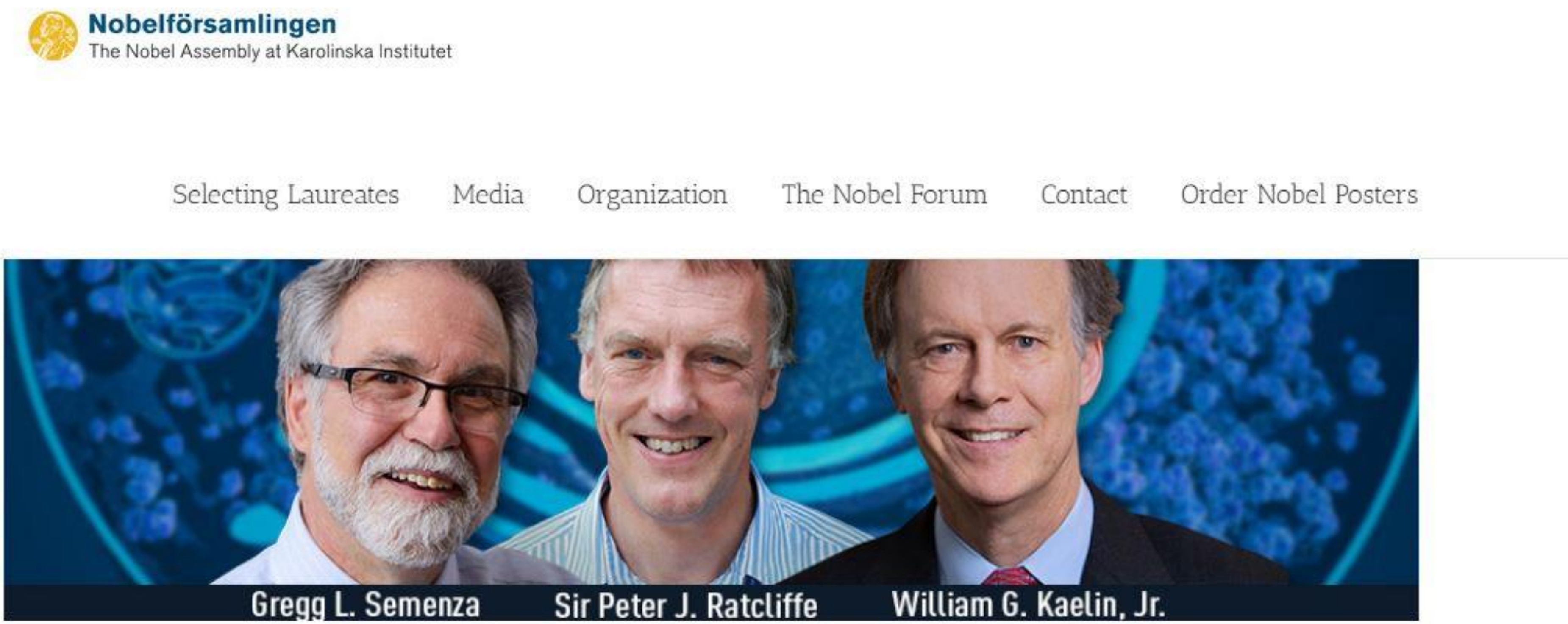
Nottingham, October 2019

Conflicts of Interest:

- Travel fees from: Servier, Amgen, Bbraun, Astellas

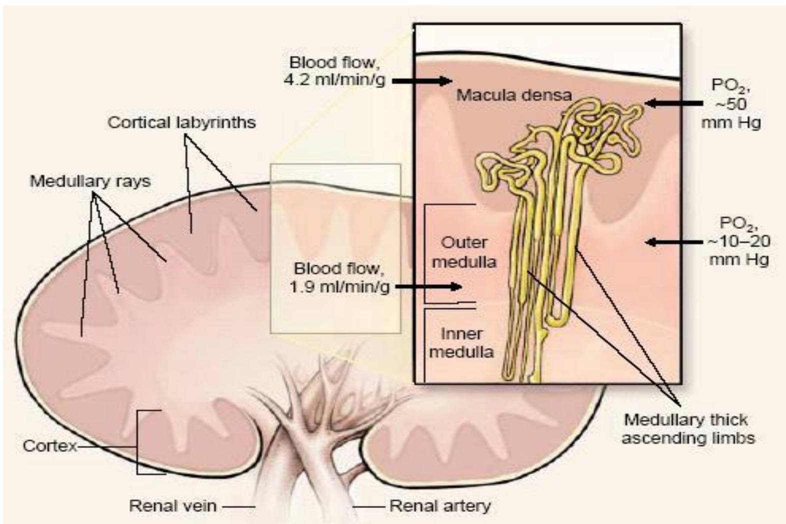
- Research grants from: Astra Zeneca, Boehringer Ingelheim, Sonovue, Amgen

Why measure oxygenation?



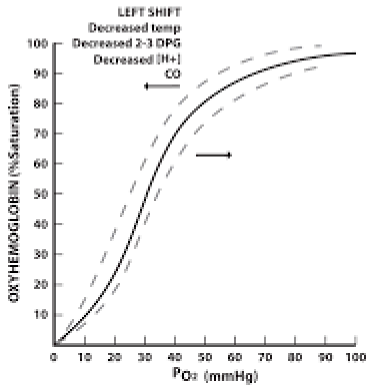
Hypoxia in the kidney:

Anatomical and Physiologic Features of the Renal Cortex and Medulla



Brezis M, Rosen S. 1995 NEJM; 332:647

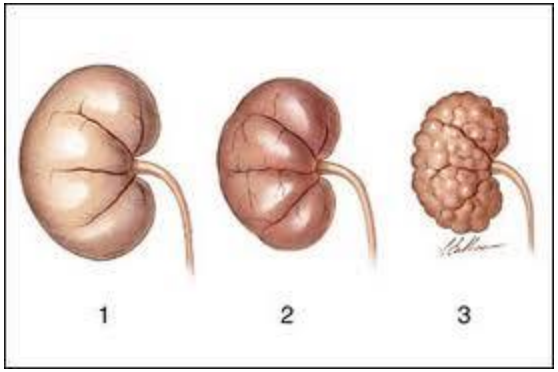
% saturated Hb

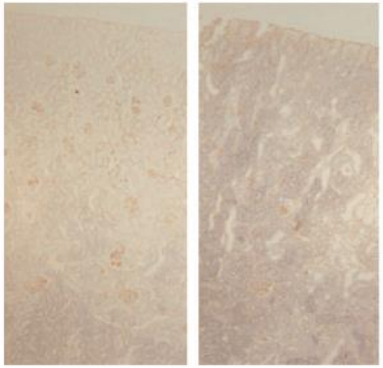


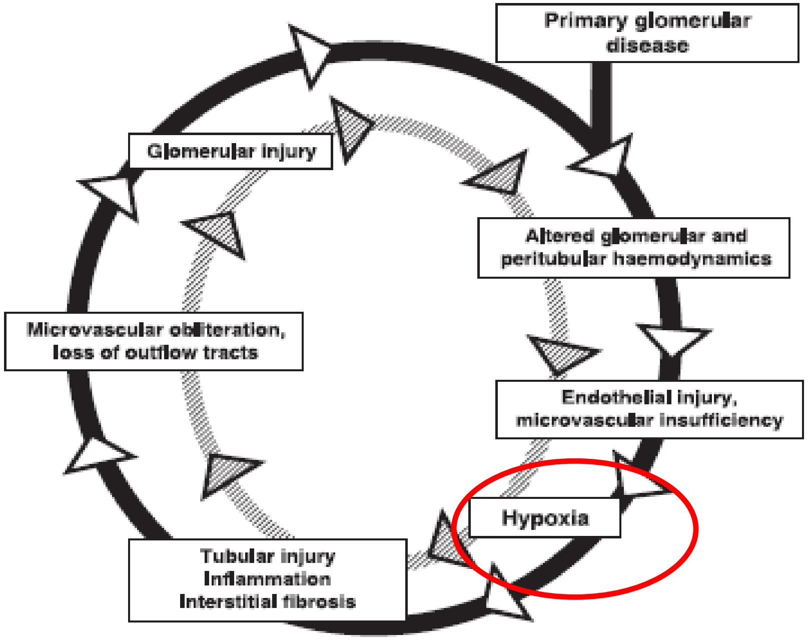
pO2

Rodriguez-Roisin R, Int Care Med 2005.
Brezis, Rosen, NEJM 1995

Role of hypoxia in pathophysiology and progression of Chronic Kidney Disease (CKD):

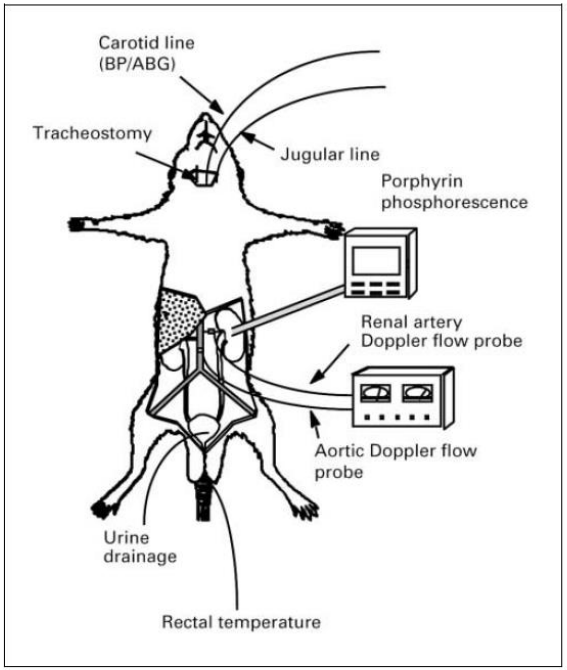




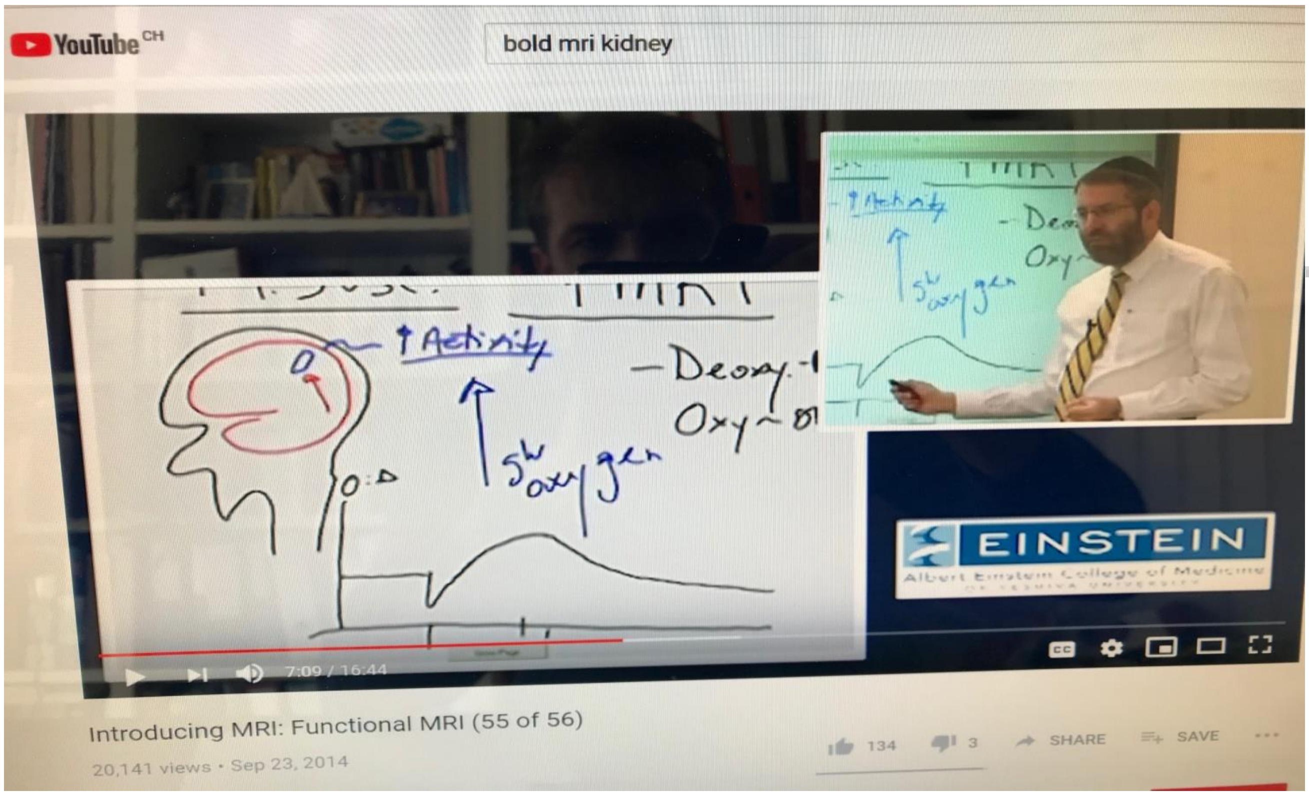


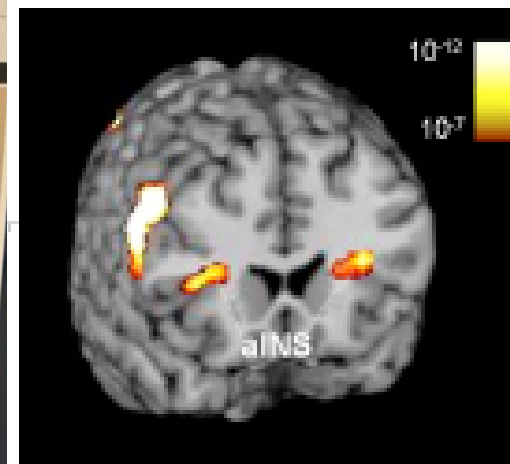
Fine, Norman, KI 1998

How to measure oxygenation in kidneys?



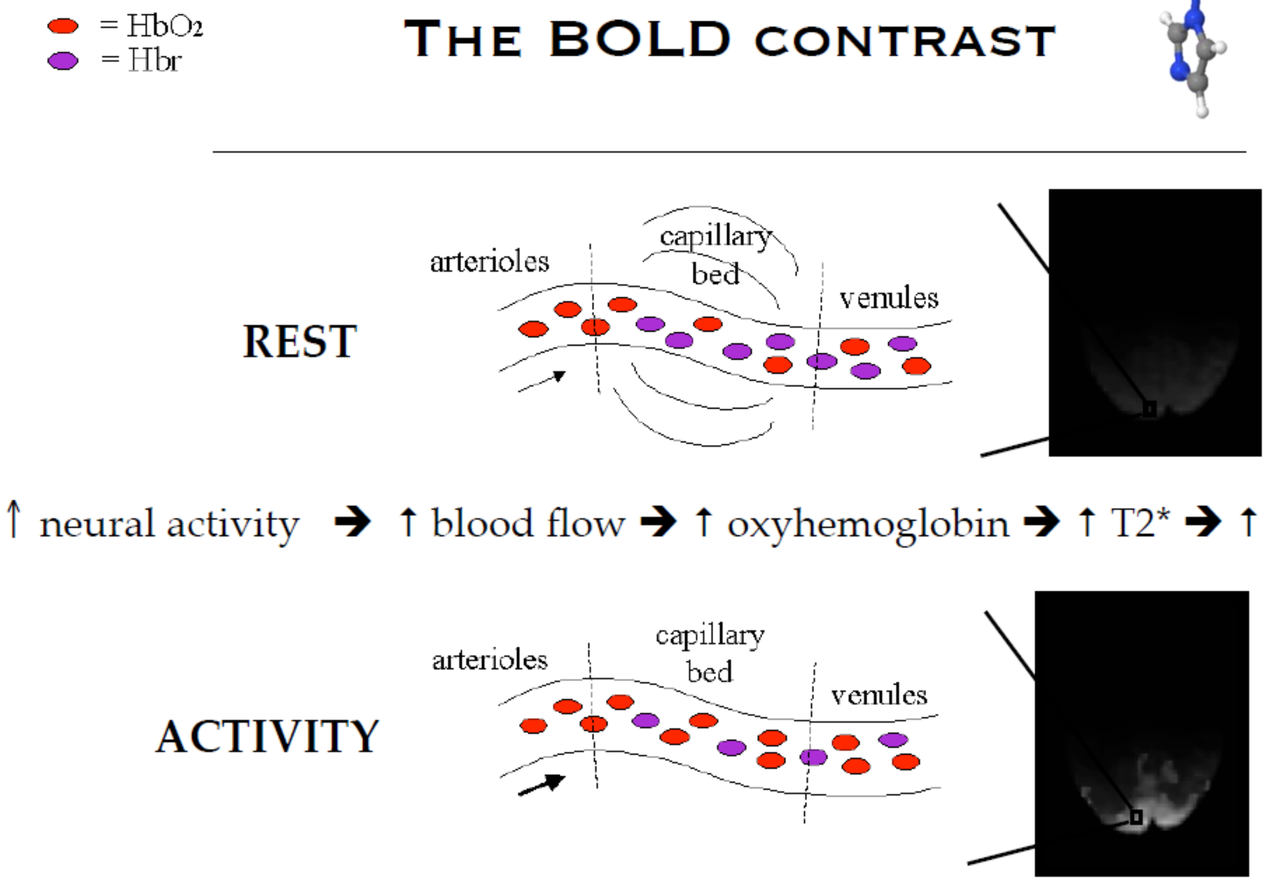
Inspiration from the brain:



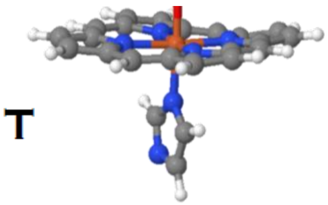


BOLD-effect explained by Prof Michael Lipton,
Einstein University, Bronx, New York, US

Inspiration from the brain (2):



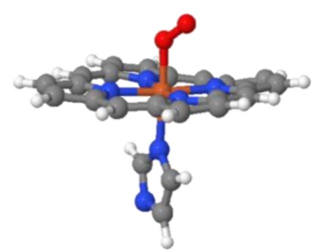
Source: Jorge Jovicich, fMRIB Brief Introduction to fMRI



Deoxyhemoglobin= paramagnetic

Hbr(Deoxy):
paramagnetic properties:

faster disappearance MR signal (in rest)



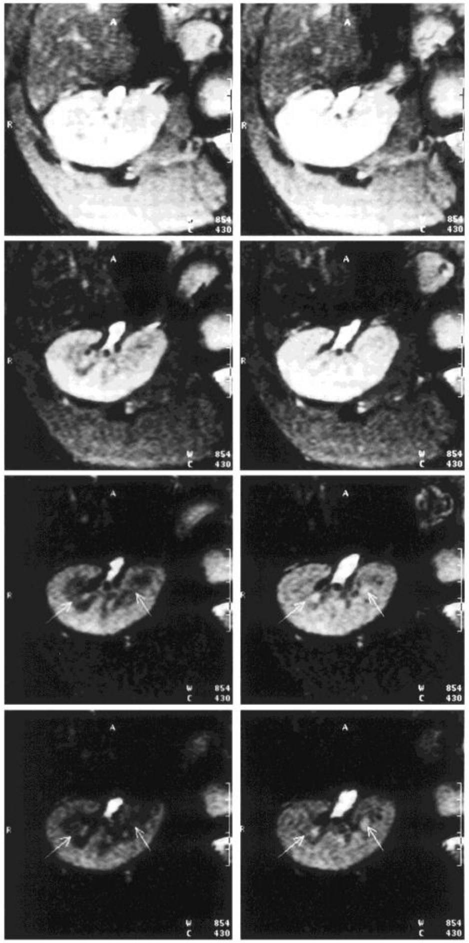
Activity: more HbO2 (oxyHb): slower disappearance of signal

T2*: sensitive to microcopic field inhomogeneities

Noninvasive evaluation of intrarenal oxygenation with BOLD MRI

7 healthy volunteers- T2* axial images

Before After furosemide



Kidney:
higher workload leads to lower HbO2 and higher deoxyHb

Lower metabolic activity (furosemide)

Less oxygen consumption

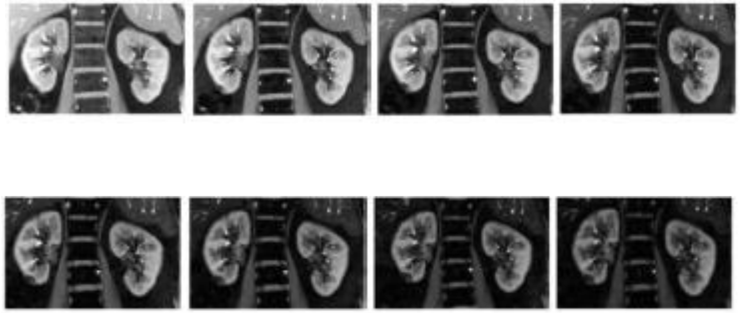
Increase in Ox/Deoxy ratio

Medulla appears brighter After furosemide

Medulla:
- lower pO_2
- lower deoxyHb
- faster disappearance of MR signal so medulla darker than cortex

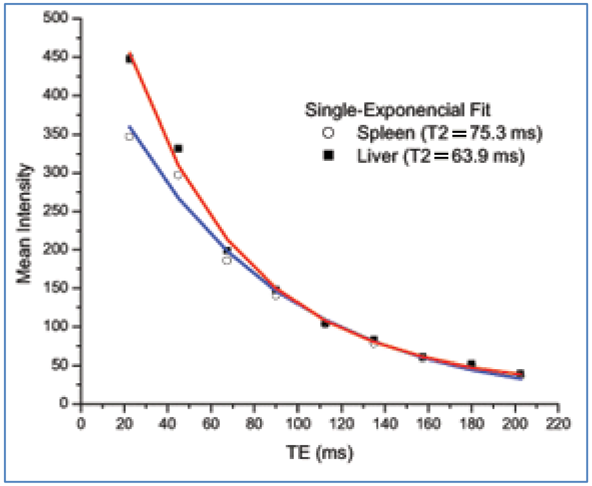
Prasad P et al. Circulation 1996;94:3271-3275

BOLD-MRI=Blood Oxygenation Level Dependent MRI



Rate of disappearance=R2*

decay rate R2* correlates with local deoxyHb level



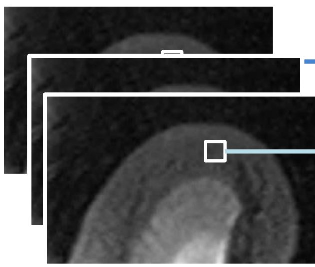
Echo time

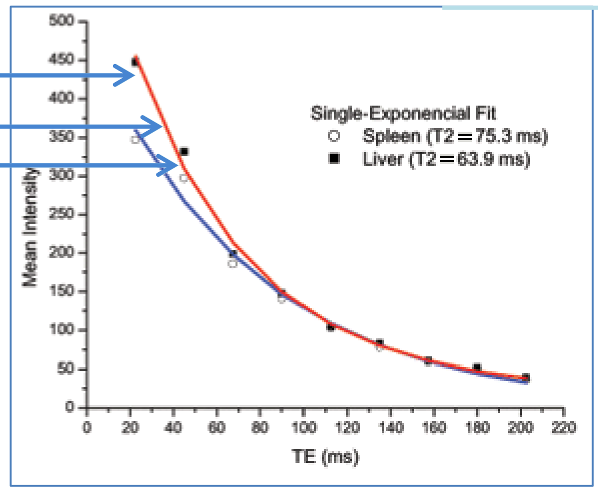
Prasad, Circulation 1996
Pruijm, Int J of Hypertension 2013

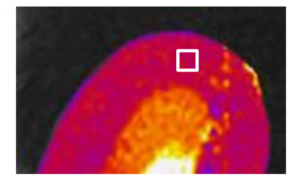
Pixel-per-pixel build up of MR parameter map

Matlab/IDL/other software

MR parameter map



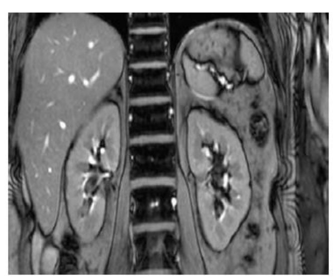


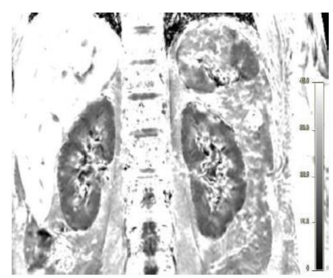


R2* of each pixel

T2* images at
different echo times (TE)

Anatomic image





R2* map

BOLD-MRI acquisition

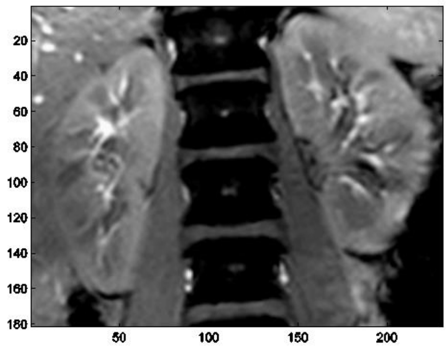
	BOLD MRI
Field strength	**1.5 T or 3.0 T, 3T preferred if available**
Sequence	**2D multiple Gradient Echo**
Orientation	Coronal oblique to kidneys
In-plane resolution	**3 mm**
Slice thickness	**3-5 mm**
Coverage	3-5 slices centered on renal hilum
Parallel imaging factor	**2**
Fat suppression	Yes
TR (s)	60 - 75 ms
TE (ms)	**8-16 echoes, up to 50 ms (~T_2* cortex) at 3T** with choice of in phase for fat-water
Averages	1
Breathing mode	**Breath hold**

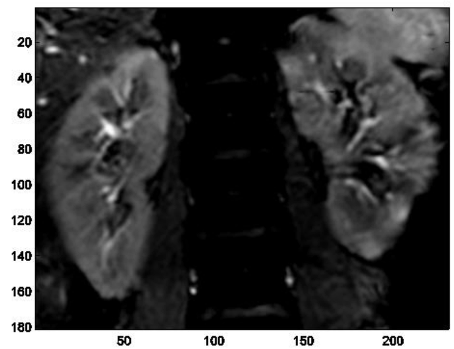
Bane et all, under review

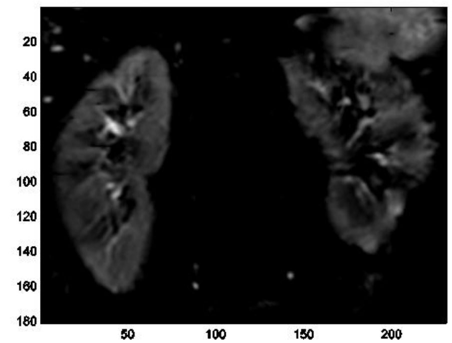
..Prof. Prasad’s talk

For dummies like me:

R2* ↑ ⟶ Deoxy Hb ↑ ⟶ Tissue pO_2 ↓



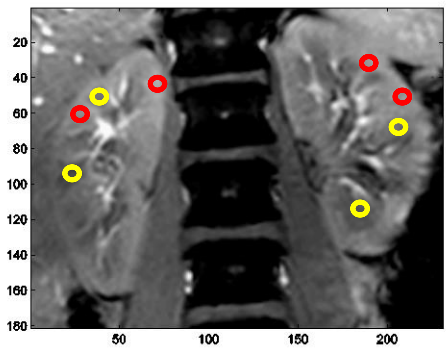


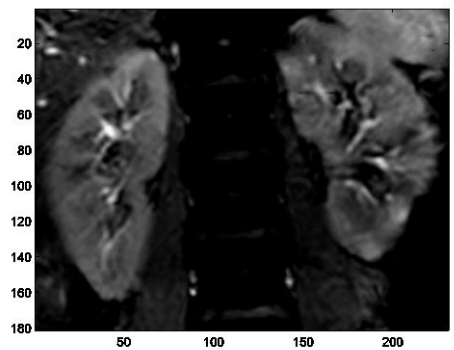


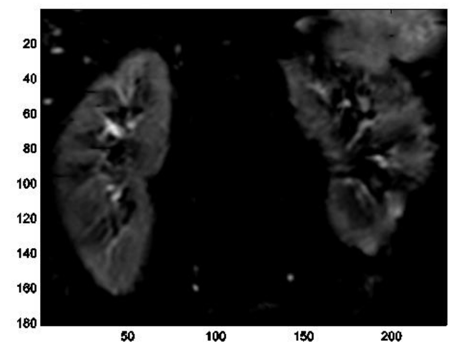
Assumption: blood pO2 in equilibrium with tissue pO2

Classical ROI technique to analyse R2* map

R2* ↗ ⟶ Desoxy Hb ↗ ⟶ Tissue pO_2 ↘



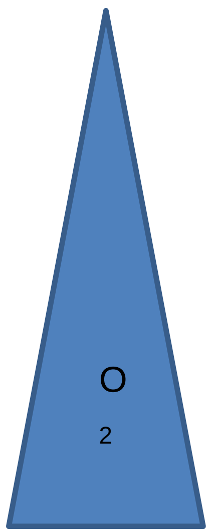


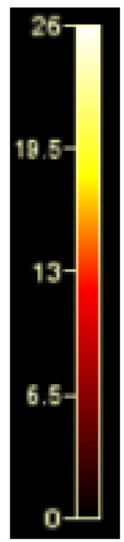


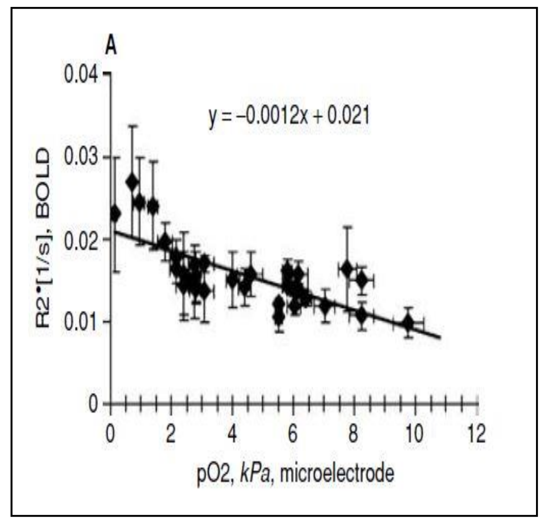
Assumption: blood pO2 in equilibrium with tissue pO2

Validation of BOLD-MRI in pig studies

R2*





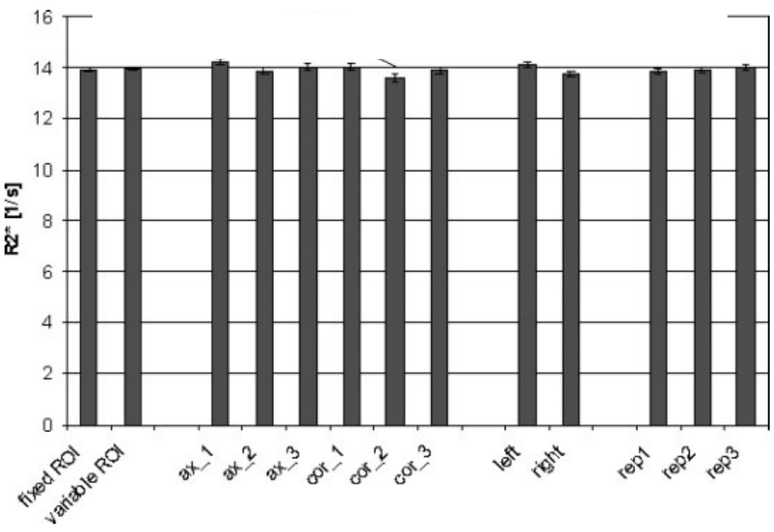


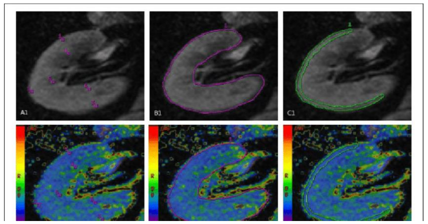
Pedersen, KI 2005

Warner L, Glockner JF, Woollard J, *et al.Invest Radiol* 2011; 46:41-7

Reproducibility

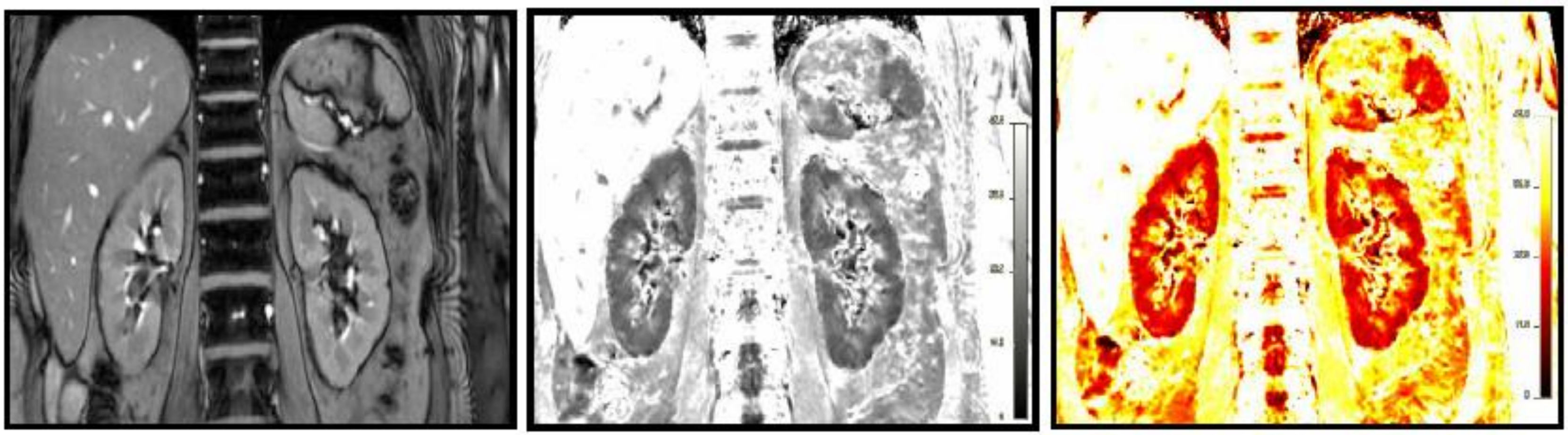
- [1]n=18, three scans same day: CV 3-4%
- [2]n=10 healthy volunteers, 2 MRIs at two week interval: CV 2-3%
- [3]n=12 DM, non CKD, 2 MRIs at one month interval: CV 3-4%
- [4] n= 11 CKD patients, 2MRIs 1-2 week interval, CV 8%





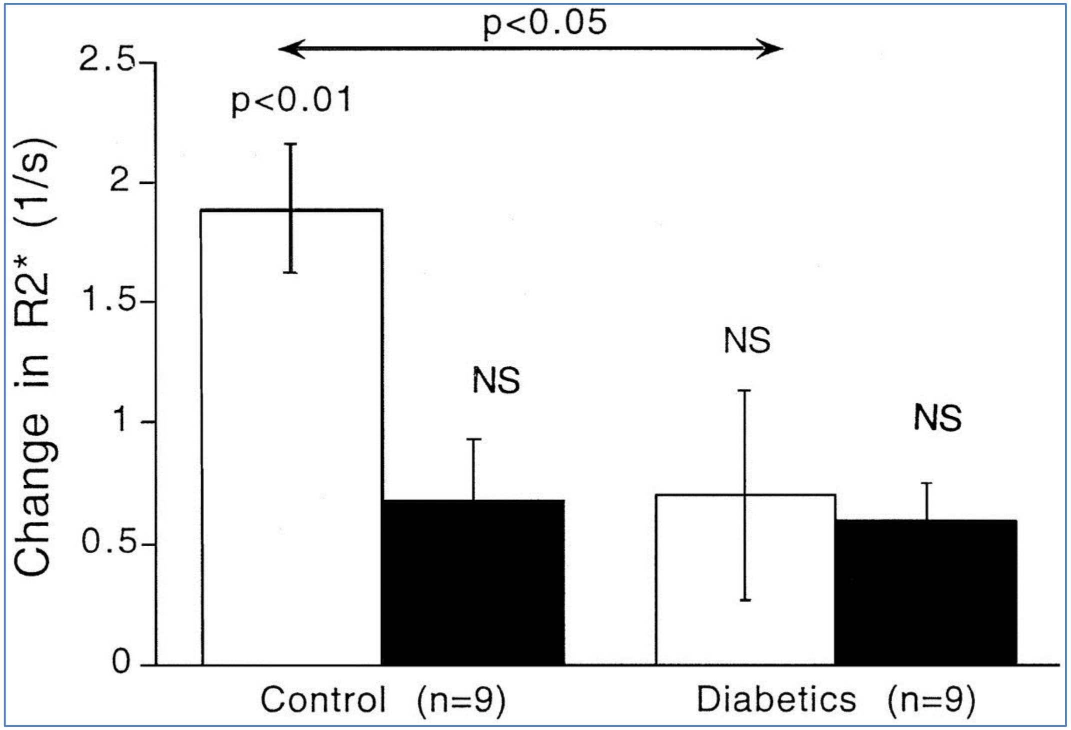
[1]Simon-Zoula, NMR Biomed 19:84-89 , 2006
[2]Pruijm, Clin Nephrol 2013
[3]Pruijm, Diab Res Clin Practice 2013
[4] Khatir, *J Magn Reson Imaging* 2014; 40:1091-8.

Factors influencing T2*:



-motion artefacts (breathing)
-water-fat chemical shift (arms)
-bulk magnetic susceptibility (BMS), shape of organs and air
-IV iron

Water intake and R2*



=medulla

=cortex

Acute decrease in medullary R2* in 9 healthy volunteers, but not in 9 patients with T2DM

Epstein, Diabetes Care 2002

Different hydration protocol

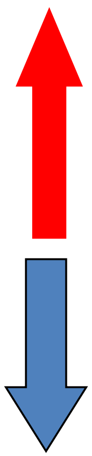
N=9; cross over study.
Dehydrated: no water intake for 5 h;
Hydrated: 3ml/kg every hour

R2*	**Medulla**		**Cortex**	
	dehydrated	*hydrated*	*dehydrated*	*hydrated*
Female	28.25	28.28	17.35	18.08
Female	24.65	27.94	15.17	15.92
Female	30.04	31.15	16.99	18.25
Male	33.2	32.8	17.7	16.76
Male	28.02	28.11	16.63	15.99
Male	26.36	28.57	15.24	14.12
Male	29.72	30.55	16.07	16.03
Male	30.86	29.54	17.85	17.44
Male	30.25	30.44	16.14	16.28
Mean	**29.0±2.5**	**29.7±1.7**	**16.6±1.0**	**16.5±1.3**

Pruijm, Plos One, 2014

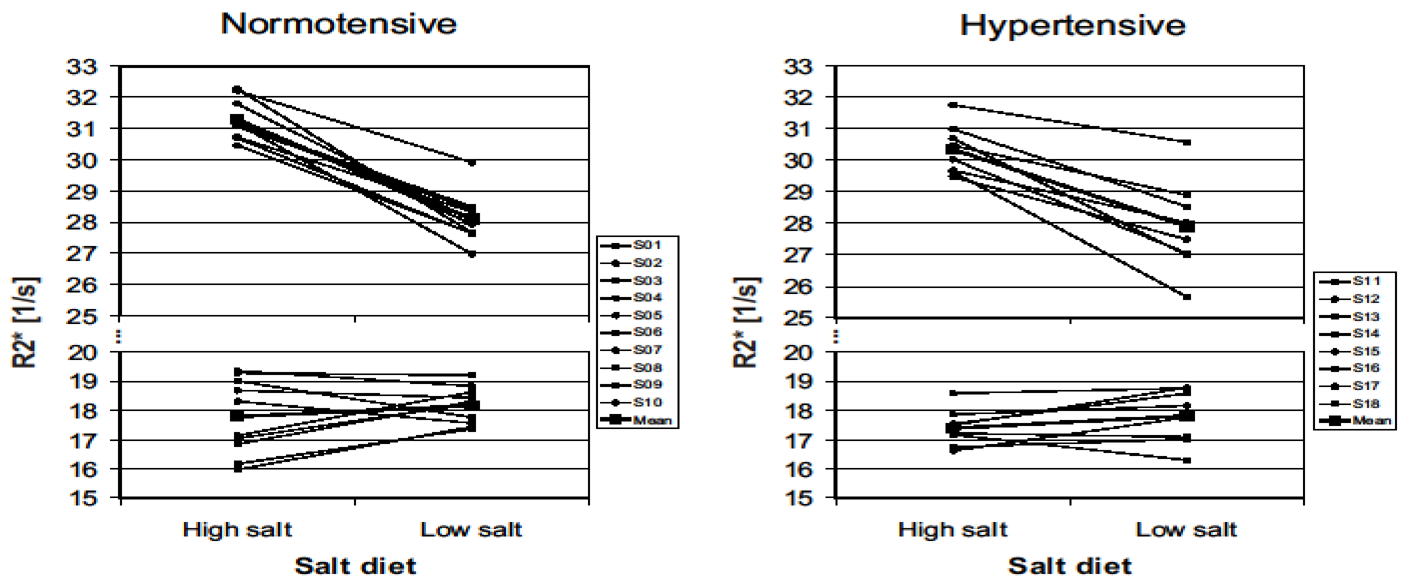
Salt intake and R2*

hypoxia



Medulla

Cortex



Pruijm, Hofmann et al. Hypertension 2010:1116-22

Blood glucose and R2*:

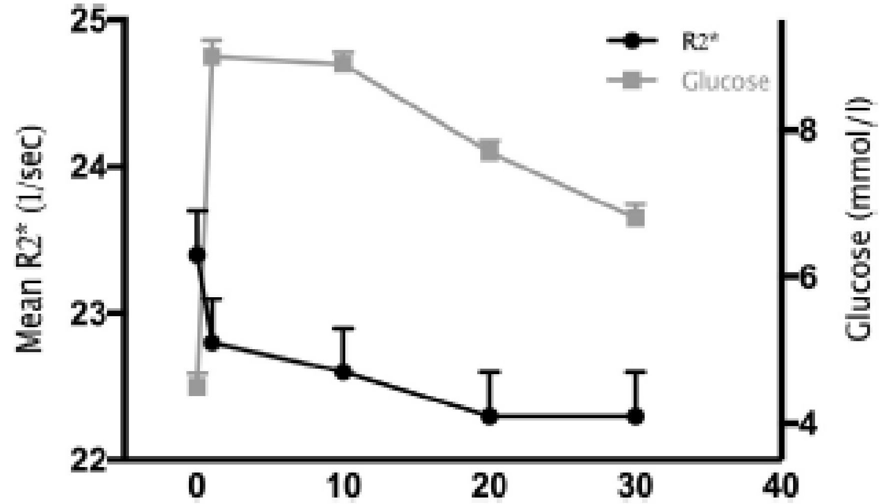


Fig. 1 – illustrates global mean R2* (defined as the mean R2* value of all twelve layers together at each time point) and glucose level variation in time (x-axis, minutes).

Vakilzadeh et al, Diab Res Clin Practice 2019

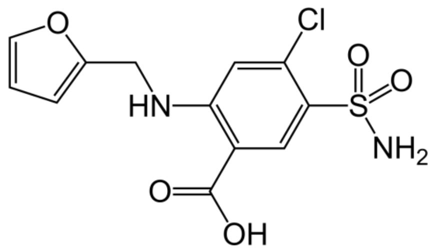
Other factors:

- Oxygen or cabon breathing
- Hemoglobin level

- Theoretically:
  - Smoking
  - pH
  - Body temperature

Pruijm, Mendichovszky, Liss et al,
NDT supplement 2018

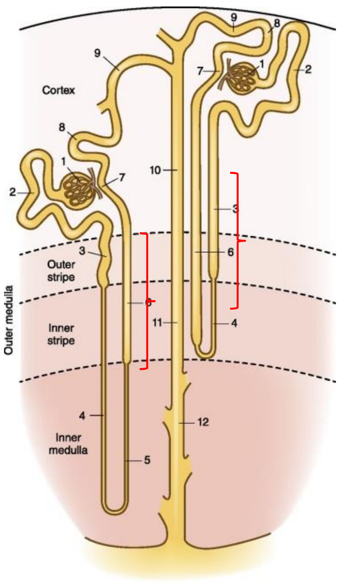
Furosemide



- Blocks NKCC in thick part of ascending loop driven by basolateral NaK ATPase

- Acute decrease in oxygen consumption

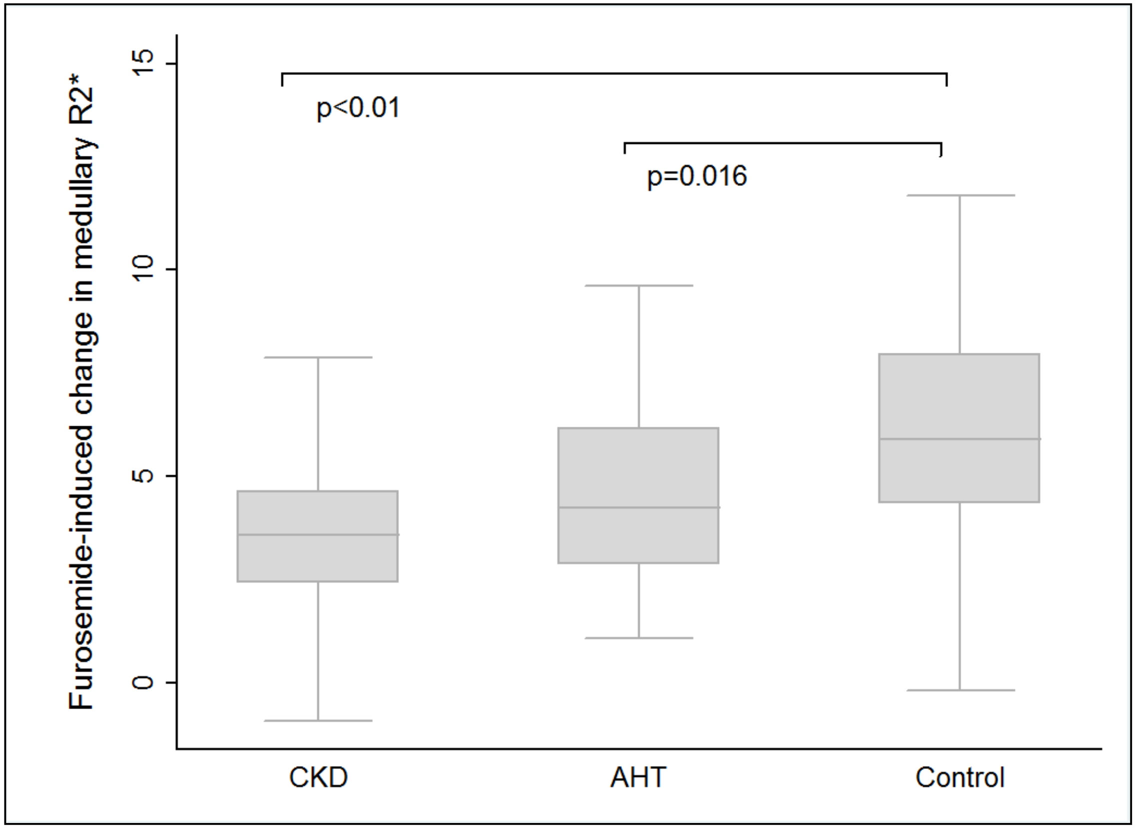
- *Functional test* of tubular function



Spitalewitz S, Circ Res 1982

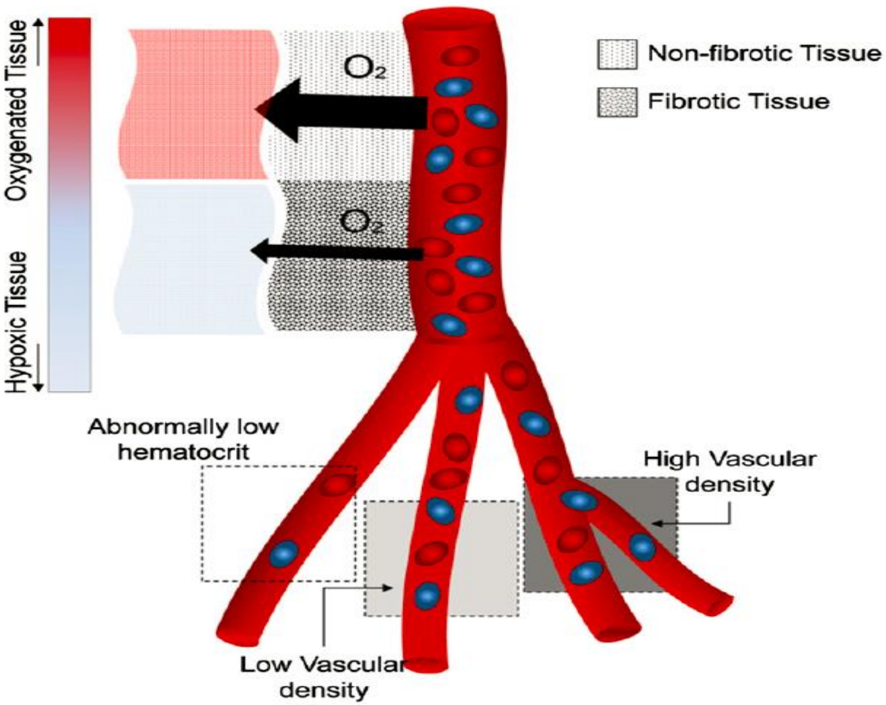
DB Mount, CJASN 2014

LauBOLD: furosemide change in R2*



Pruijm, Plos One, 2014

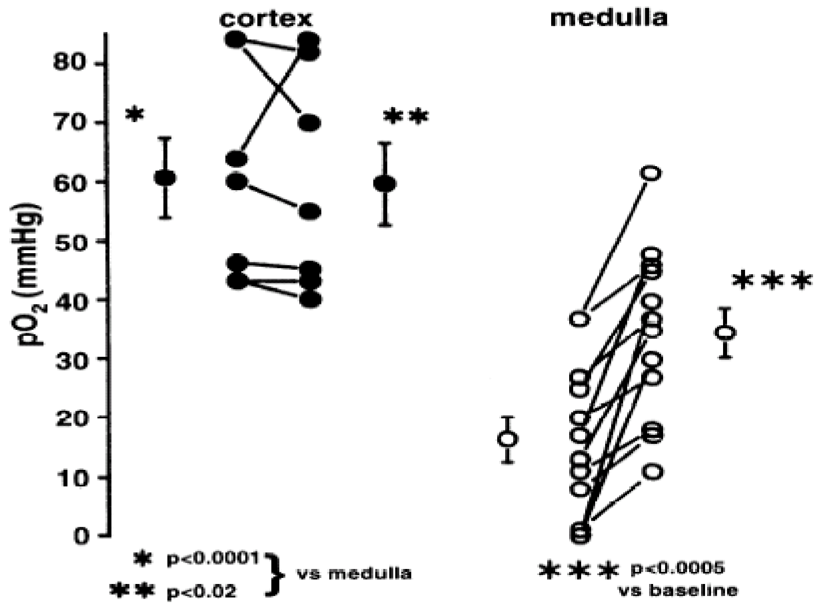
Change in oxygenation or artefact?



- T2* influenced by:
  - Blood volume fraction
  - Hemoglobin

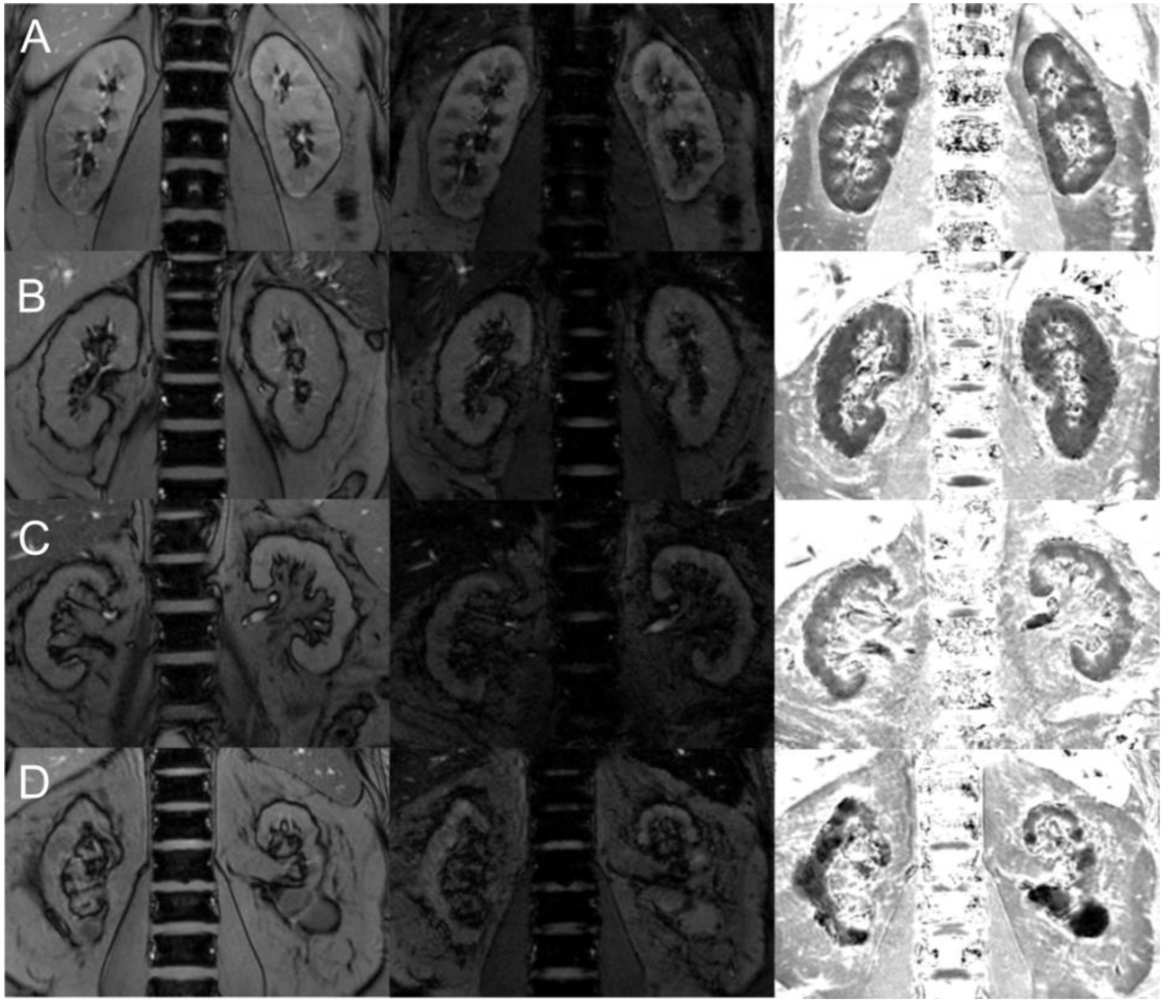
Ebrahimi, CJASN 2014

Effects of furosemide on intrarenal oxygen tensions



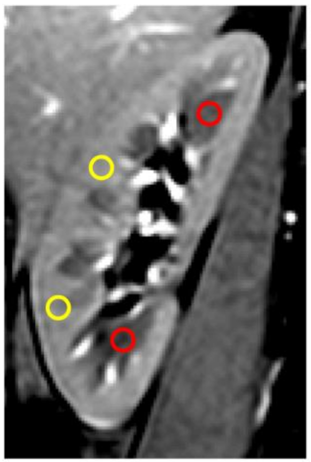
M. Brezis et al. , AJP 1994

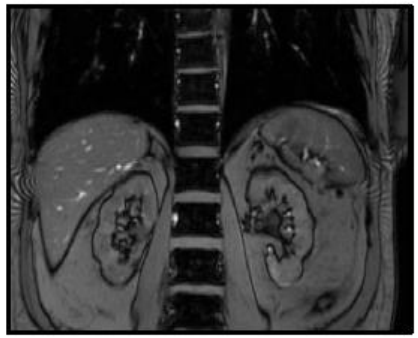
BOLD too bold for CKD?

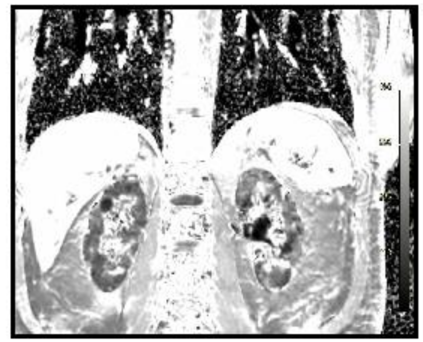


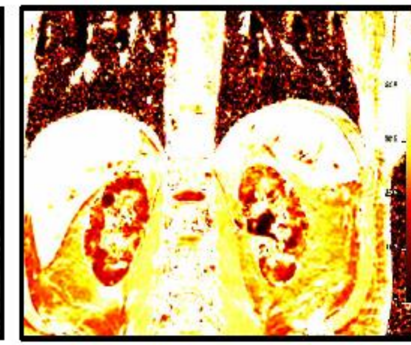
Pruijm et al, Int J Hypertension 2013

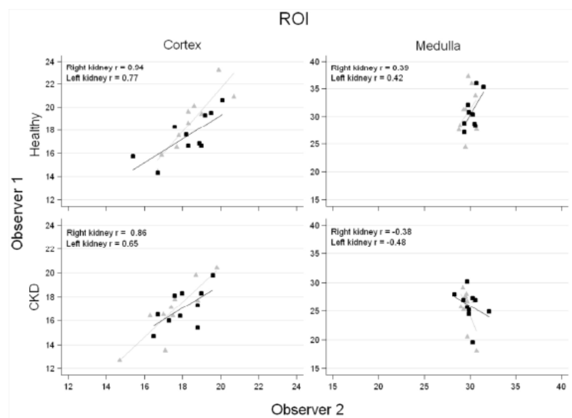
ROI technique to analyze BOLD-MR images







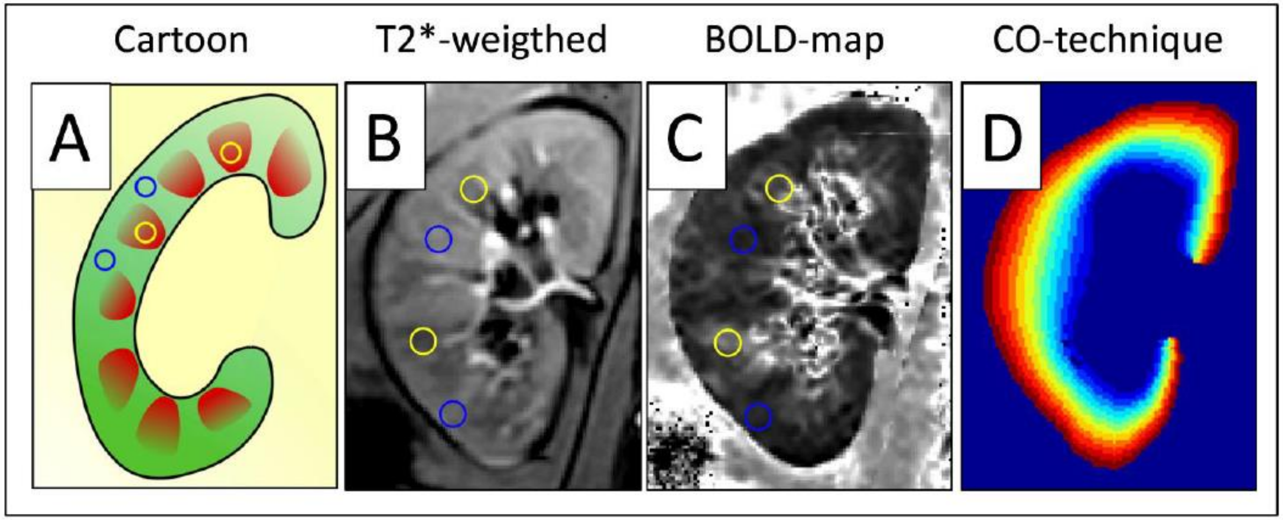


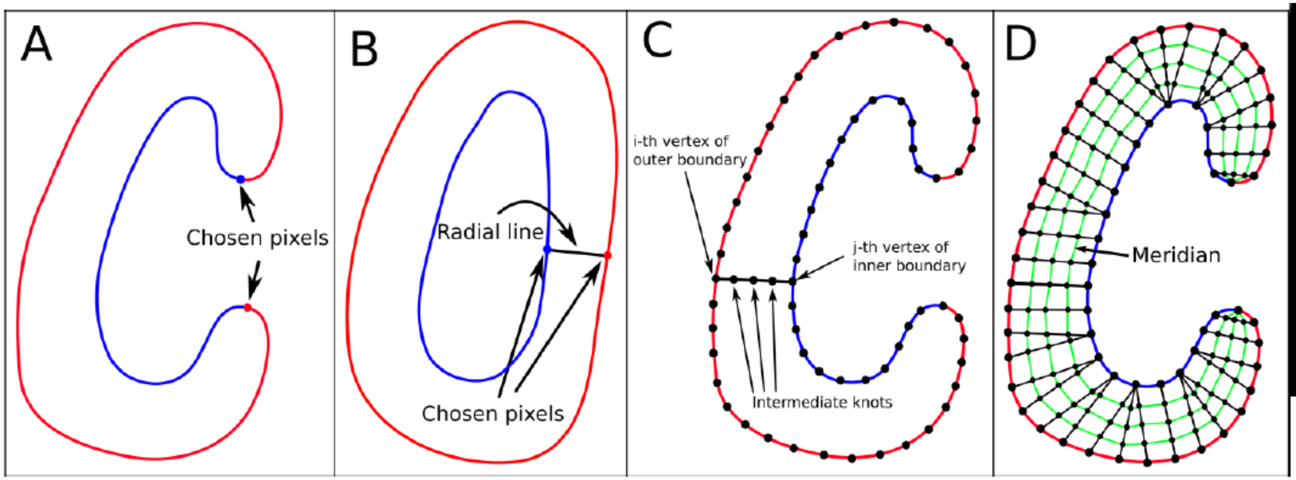


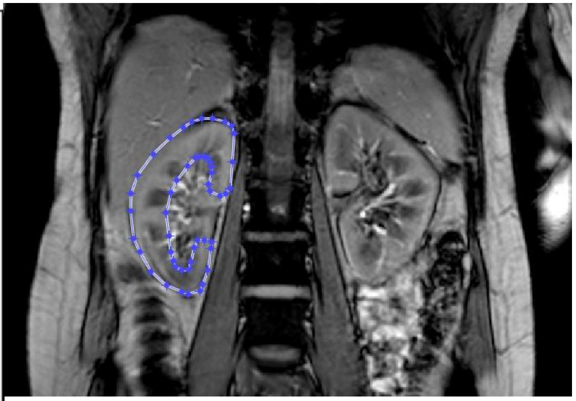
healthy CKD

Piskunowicz et al, MRI 2015

Twelve layer concentric objects (TLCO)

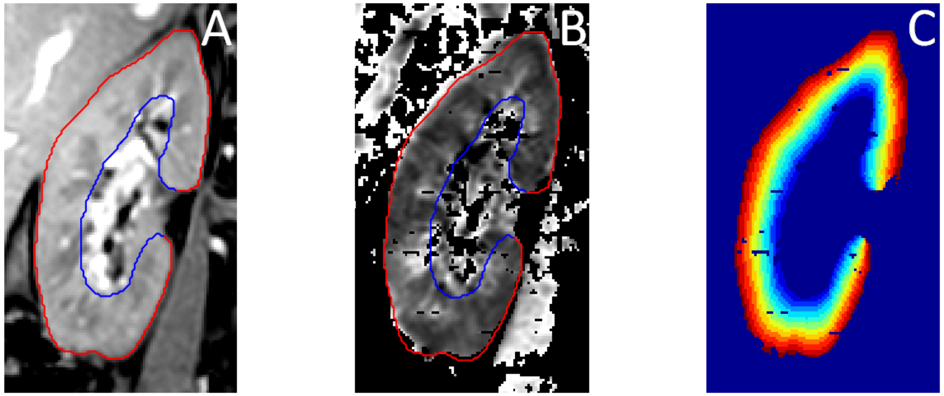


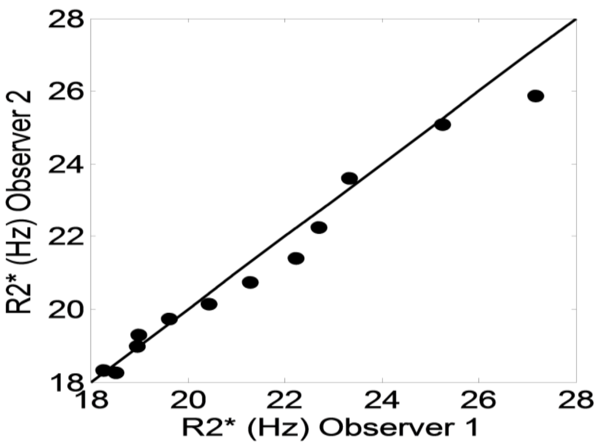




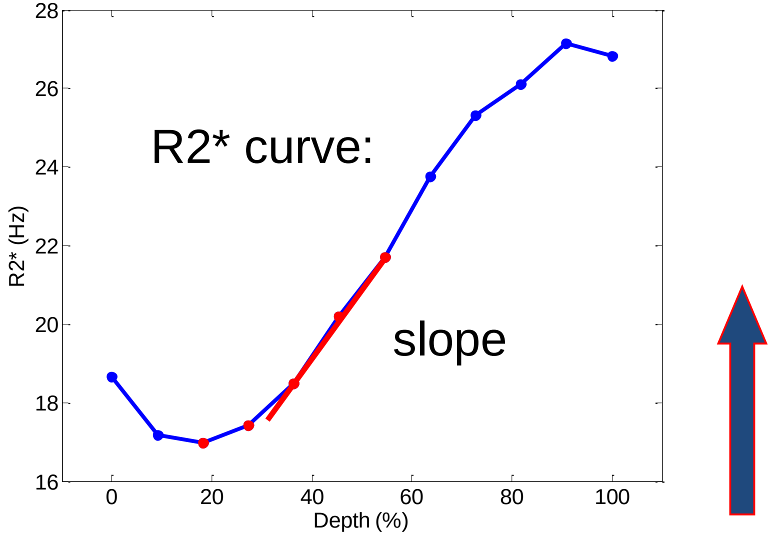
PhD thesis Bastien Milani 2018

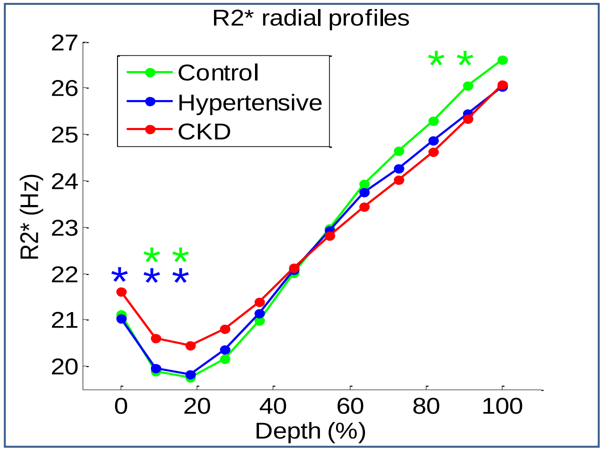
TLCO: twelve layer concentric objects





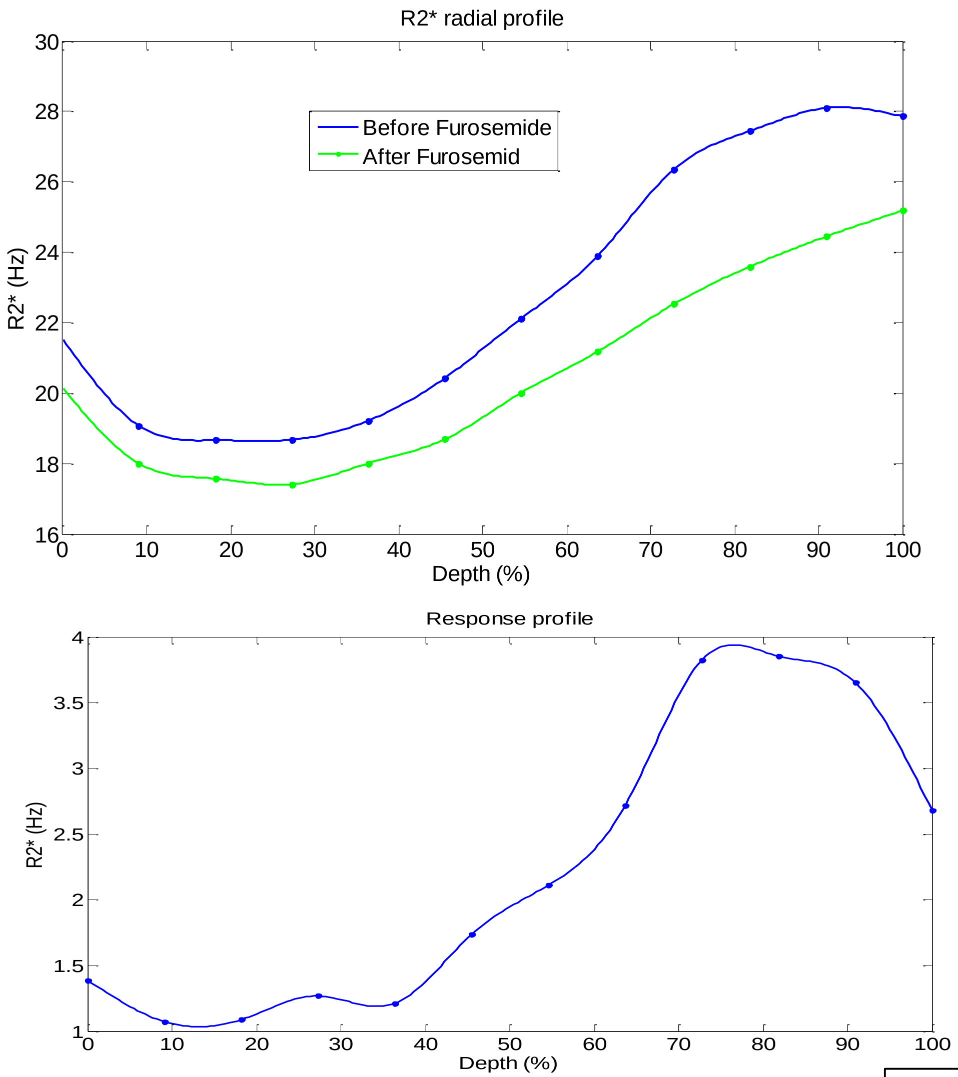
Hypoxia





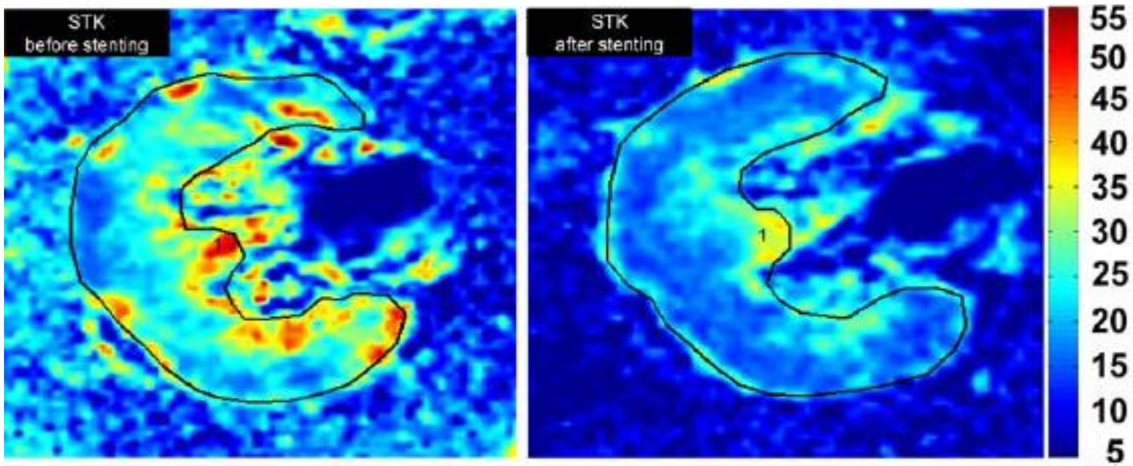
Milani B et al, NDT 2017

Furosemide-induced change in R2*:



Milani et al, Nephrology Dialysis Transplantation 2017

Fractional tissue hypoxia technique: R2* before and after stenting RAS



Single Kidney		EH (n=32)	STK (n=17) Baseline	STK (n=17) 3 mo
Fractional hypoxia (% R^2*>30/s)	Pre furosemide	8.7 (3.5, 13.3)‖	19.2 (9.2, 28.3)*‖	11.5 (5.5, 16.5)‖†
	Post furosemide	2.6 (1.35, 6.4)‖§	12.5 (3, 21.5)*‖§	5.2 (2.5, 12.6)‖†‡§

Saad, Textor, Circ Cardiovasc Intervent 2013

Multiparametric Renal Magnetic Resonance Imaging: Validation, Interventions, and Alterations in Chronic Kidney Disease

Eleanor F. Cox[1], Charlotte E. Buchanan[1], Christopher R. Bradley[1], Benjamin Prestwich[1], Huda Mahmoud[2], Maarten Taal[2], Nicholas M. Selby[2] and Susan T. Francis[1]*

N=127

N=11

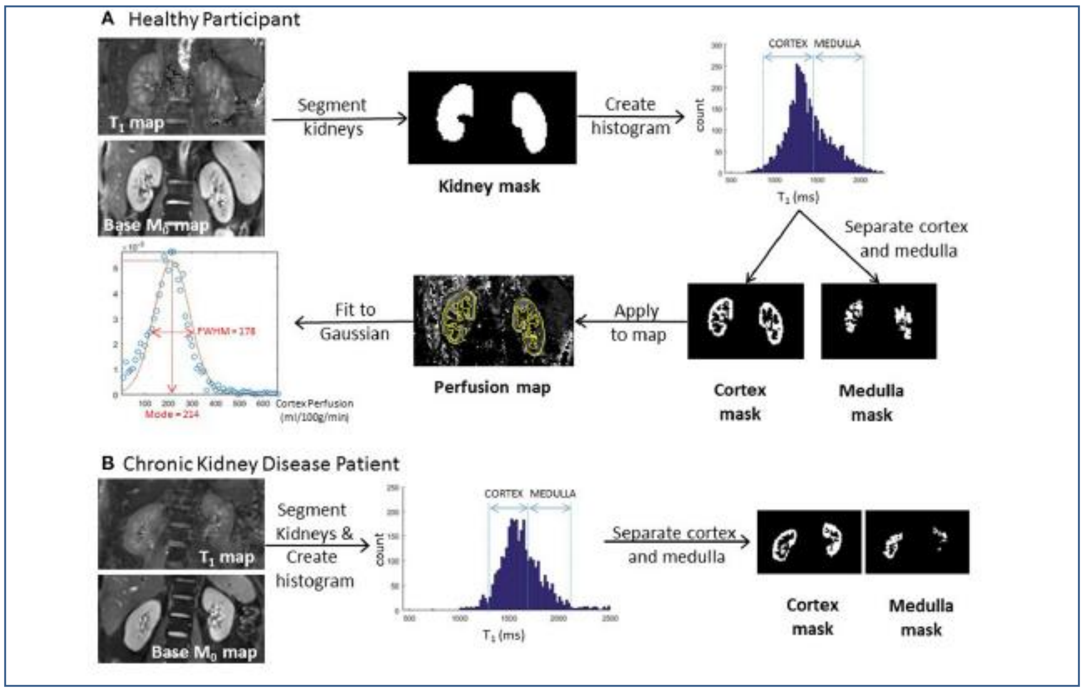
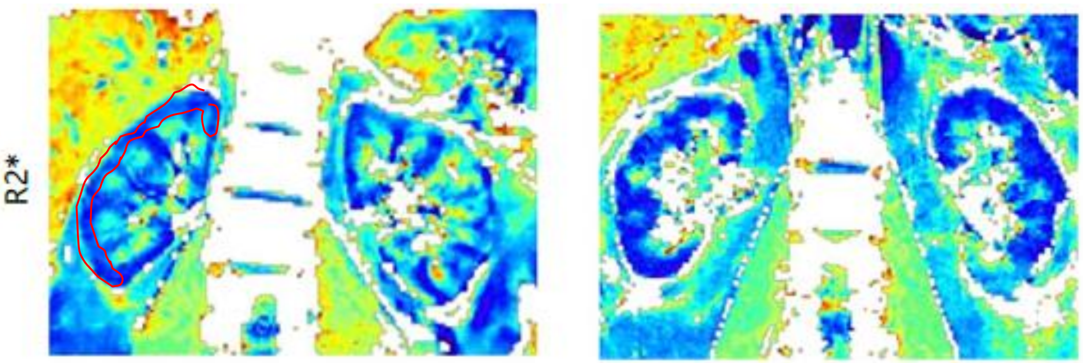


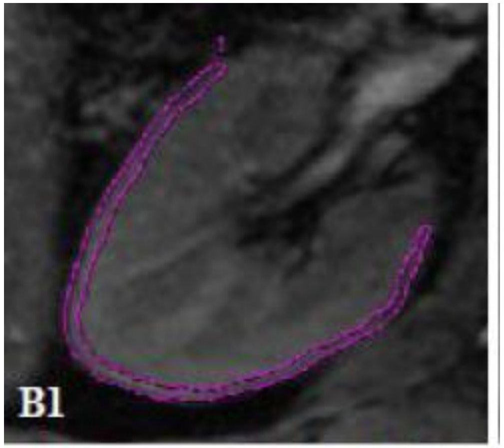
TABLE 3 | Intra subject repeatability for the multiparametric MRI measures in healthy participants.

Parameter		Repeatability measures			
		CoV (%)	ICC	Number of subjects	Number of visits
Single renal artery flow		14.4 ± 4.3	0.844	11	3
Single renal vein flow		18.8 ± 10.3	0.649	11	3
Total perfusion to single kidney		14.9 ± 3.8	0.611	10	3
Cortex perfusion		9.3 ± 4.4	0.801	11	3
Cortex T_1 (at 3 T)	SE-EPI	2.0 ± 1.5	0.848	9	2
	bFFE	2.3 ± 1.3	0.616	11	3
Medulla T_1 (at 3 T)	SE-EPI	1.8 ± 1.5	0.997	9	2
	bFFE	2.9 ± 2.4	0.239	11	3
Cortex T_2^* (at 3 T)		4.1 ± 3.0	0.718	4	2

Cox, Frontiers in Physiology, 2017

Whole-cortex techniques





Prasad, Am J
Nephrology 2019

Coefficients of Variation of different analysis techniques

CoV (%)	healthy	CKD
ROI[1]	3.6-6.8	5.7-12.5
TLCO[2]	2.2	2.0-3.1
Segmentation[3]	4.1	
Fractional Hypoxia[4]	<7	

[1]Piskunowicz, MRI 2015
[2]Milani, NDT 2017
[3]Cox EF, Frontiers Physiology 2017
[4]Saad, Radiology 2013

Image analysis:

ROI placement	**Manual**
Cortical ROI	1 stripe / slice ;> 3 slices
Medullary ROI	3 samples / slice ;> 3 slices
Fitting	**Monoexponential or log-linear**
Reporting	**Cortex and medulla**
Reported metric	**R_2* (sec^{-1})**
Metric statistics reporting	Mean, Median, Standard deviation, ROI size
Map format	Color map

Bane, Prasad et all,consensus paper, under review

Future applications:

Applications of BOLD-MRI

- Prediction of adverse renal outcome[1]
- Renal artery stenosis
- Drug research

- ..in combination with other fMRI techniques

[1]Pruijm, Kidney Internaitonal 2018

Risk prediction in chronic kidney disease

Ibrahim Ali and Philip Kalra

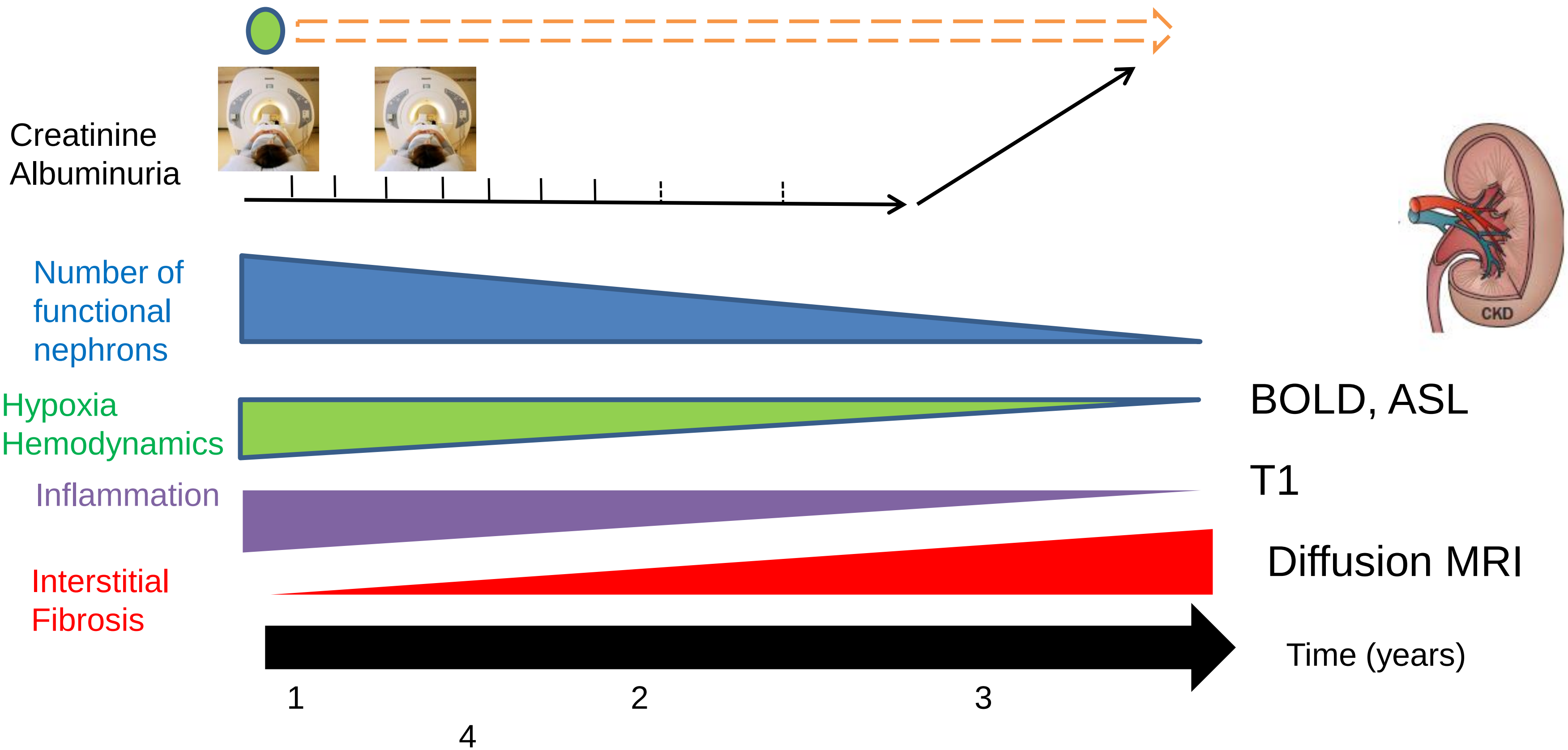
Purpose of review
Accurate risk stratification in patients with chronic kidney disease (CKD) is highly desirable to help guide earlier, targeted treatment in high-risk individuals. In this review, we report recent developments in our understanding of risk factors and risk prediction in patients with CKD.

Recent findings
A large meta-analysis has shown that conventional cardiovascular risk factors continue to play an important role in disease progression and adverse outcomes in patients with advanced CKD where the estimated glomerular filtration rate (eGFR) is $<30\,ml/min/1.73\ m^2$). Several studies have shed light on novel biomarkers in CKD, including peptides (LG1M), genes (*MUC1*) and metabolic factors (urinary oxalate excretion). Cortical oxygenation measured by BOLD-MRI also provides a novel radiological measure predictive of future eGFR decline. A new risk prediction score for patients with CKD G4-5 has been developed, offering an aid to decision-making in these patients.

Summary
Ongoing work across various disciplines continues to unravel the determinants of CKD progression. A few notable risk prediction tools in CKD have now surfaced but whether they can be utilised to offer improved care remains a key unanswered question.

Curr Opinion Nephrol Hyp 2019

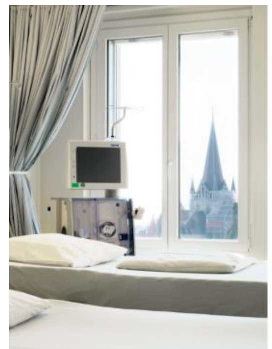
Perspectives in drug research:



Conclusions

- BOLD-MRI can estimate (changes in) renal tissue oxygenation, when taking all possible factors into account and using robust analysis techniques.
- BOLD-MRI can predict CKD outcome.
- BOLD-MRI provides early insight in the effect of new drugs on renal hemodynamics and functioning.
- Multiparametric fMRI can obtain a wealth of information within a single MRI session and should/will be further developped.

Thank you for your attention!



« If you want to go fast, go alone
If you want to go far, go together »

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CHUV

Swiss National Science Foundation (FN 320030-169191)

Spare slides

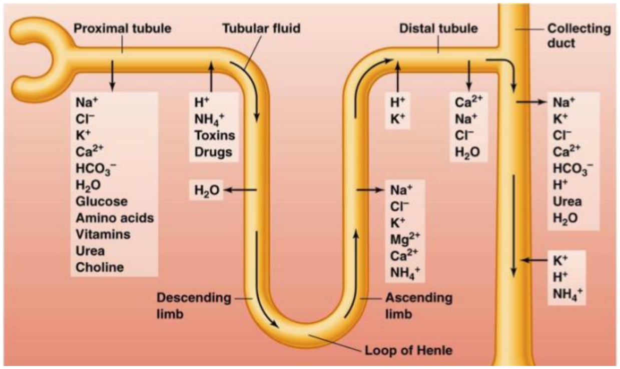
Main issue in BOLD-MRI

High R2* suggesting low pO2

<u>Low Delivery (DO2)</u>:

Low flow
High degree
of fibrosis

<u>High Consumption (QO2)</u> :
-GFR
-active tubular transport



Epstein, Kidney Int: 51, 1997

BOLD-MRI acquisition

- Four coronal slices with good cortico-medullary differentiation selected from morphological images
- Twelve T2*-weighted images were recorded for each coronal slice within a single breath-hold of 16.6 seconds (in expiration) with a modified Multi Echo Data Image Combination sequence (MEDIC) for BOLD analysis
- following parameters: repetition time (TR) 65 ms, echo time (TE) 6-52.2 ms (equidistant echo time spacing of 4.2 ms), radiofrequency excitation angle 30°, field of view (FOV) 400 x 400 mm2, voxel size 0.8 x 0.8 x 5 mm3, slice thickness 5 mm, slice distance 5.5 mm, bandwidth 331 Hz/pixel, matrix 256x256 (interpolated to 512x512).