In Vivo Monitoring of Renal Tubule Volume Fraction During Acute Tubular Pressure Increase Using Dynamic T_2 Mapping

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Introduction: The increasing incidence of kidney diseases is a global concern. Current diagnostic tools and therapies for renal disease are inadequate. Changes in the renal tubule volume fraction (TVF) may serve as a marker for kidney disease and provide a better understanding of renal (patho-)physiology[1]. T_2 mapping, an established MRI technique, can quantify changes in tissue water fraction noninvasively[2]. This study is the first report on in vivo assessment of relative changes in the renal tubular volume fraction as a (patho)physiological metric and uses T_2 mapping in conjunction with bi-exponential analysis of the T_2 decay to determine relative changes TVF during acute renal pelvis/tubular pressure increase, which is a clinically relevant intervention.

Methods: Tubular fluid, which originates from ultrafiltration in the glomeruli, has a substantially longer T_2 compared to the renal parenchyma. Therefore, the tubular contribution to the signal should be separable from the parenchyma signal by nonlinear least squares regression. The numerical solution for multi-exponential decomposition was done using MATLAB functions. The algorithm was evaluated using synthetic data simulations and measurements in phantoms. Since in vivo experiments are always limited by the constraints of acquisition time, spatial resolution and SNR, we evaluated the multi-exponential decomposition approach in simulations using a broad range of conditions of T_2 mapping. A phantom was designed to mimic realistic changes of TVF in the rat kidney (Fig.1). Water was doped with MnCl2 and CuSO4 to achieve T_1 and T_2 times similar to the tubular fluid and the renal parenchyma. This was followed by a proof-of-principle demonstration using in vivo data obtained during a transient increase of renal pelvis and tubular pressure in rats (Fig.2). MRI data were acquired on a 9.4 Tesla small animal MR system (Bruker Biospec 94/20, Bruker Biospin, Ettlingen, Germany) using a linear radiofrequency (RF) volume resonator and a 4-channel surface RF coil array tailored for rats (Bruker Biospin). For T_2 mapping a multi-echo spin-echo technique (TR=500ms, number of echoes=13, first TE=6.4ms, interecho time ΔTE=6.4ms, number of averages=1, tacquisition=58s) was employed. For T_2 mapping a mid-coronal oblique slice was acquired (in-plane spatial resolution=(226×445) μm^2, FOV=(38.2×50.3) mm^2, matrix size=169×113, slice thickness=1.4mm).

Results: Figure 3 demonstrates the impact of echo spacing (ΔTE=5-50ms) and SNR=5 to 600 on the TVF estimation. Using a high accuracy imaging protocol (TR=4s, number of echoes=13, first TE=15ms, ΔTE=15ms, number of averages=3, $t_{acquisition}$=47min), our approach achieved a high accuracy on the phantom. Since in vivo experiments are limited by acquisition time constraints we developed an accelerated protocol tailored for in vivo T_2 mapping of the rat kidney (TR=500ms, number of echoes=13, first TE=6.4ms, inter-echo time ΔTE=6.4ms, number of averages=1, $\alpha_{refocusing\ pulse}$=180°, $t_{acquisition}$=58s), which resulted in an accuracy of MAE<3%. Fig. 1C shows a T_2 map obtained for the phantom. The histogram (Fig. 1D) shows the T_2 distribution for the selected ROI. Changes in the ratio of the volume fraction of the two compartments were achieved by changing the ROI size. Fig. 1E shows TVF measured for the high accuracy protocol and for the accelerated protocol customized for the in vivo study. Fig. 4 shows representative quantitative TVF maps obtained for baseline, transient pelvis and tubular pressure increase, and recovery. Transiently increasing pressure in the renal pelvis and tubules induced significant changes in TVF in renal compartments: ΔTVF_{cortex}=5.2%, $\Delta TVF_{outer\ medulla}$ =2.6%, and $\Delta TVF_{inner\ medulla}$ =-14.2% (Fig.5).

Discussion: This is the first report on in vivo estimation of the physiological metric renal tubular volume fraction. We demonstrate the feasibility of dynamic parametric mapping of the MRI relaxation time T_2 for TVF cartography and for monitoring physiological changes in the TVF. For the first time, we represent parametric maps of TVF obtained under normal conditions and upon increased pelvis and tubular pressure, which is a clinically relevant intervention. Future in vivo validation of our MRI approach to TVF assessment with intravital microscopy, i.e. for quantitative comparison of changes in the vascular and renal tubular compartments with those observed by and T_2, is warranted. In this work, our MRI-based monitoring was focused on retrospective assessment of changes in TVF during an acute pathophysiological scenario. Future steps will include prospective and real-time application of T_2 decomposition and TVF measurement, integrating our decomposition analysis directly into the image reconstruction and post-processing pipeline of the MR scanner.

Conclusion: Our investigations have the potential to help uncover the mechanisms leading to acute kidney injury and progression to chronic kidney disease. Monitoring of relative changes in renal TVF *in vivo* using dynamic parametric MRI provides a potential rapid, noninvasive marker for kidney disease. This approach will be invaluable for gaining a better mechanistic understanding of renal (patho-)physiology.

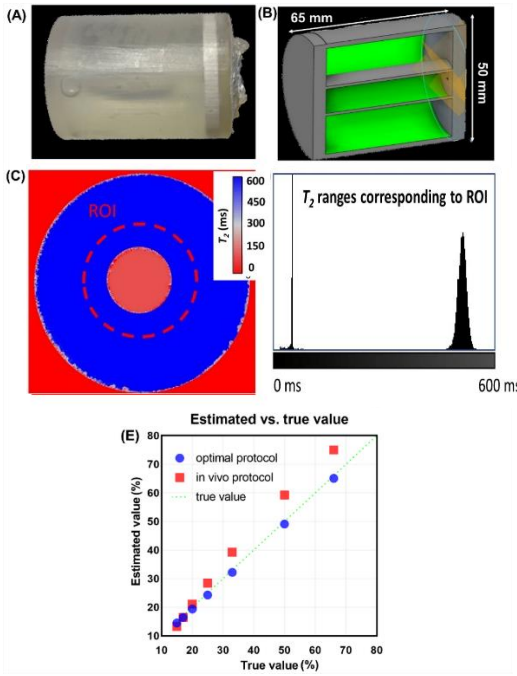

FIGURE 1: (A). Photograph of the phantom. (B). Schematic view of the phantom (C). shows the reconstructed T2 map in milliseconds of the custom-built T1- T2 phantom (scan parameters: T2- (MESE), 13 echoes, echo-spacing=6.4ms, TR=1s; scan time 16 s) (D). an exemplary ROI selection and the histogram shows T2 distribution corresponding to the selected ROI. E. Evaluation of the assessment of the volume fraction with decomposition of parametric T2 in a mechanical phantom using the optimal protocol derived from the simulations (true value, TR = 4 s, number of echoes = 15, first TE = 15 ms, interecho time ΔTE = 15 ms, number of averages = 3) and the protocol adapted for the in vivo measurements (estimated value, TR = 1 s, number of echoes = 13, first TE = 6.4 ms, interecho time ΔTE = 6.4 ms, number of averages = 1, $t_{acquisition}$ = 58 s). The correlation coefficient between the estimated and the true value is: 0.997.

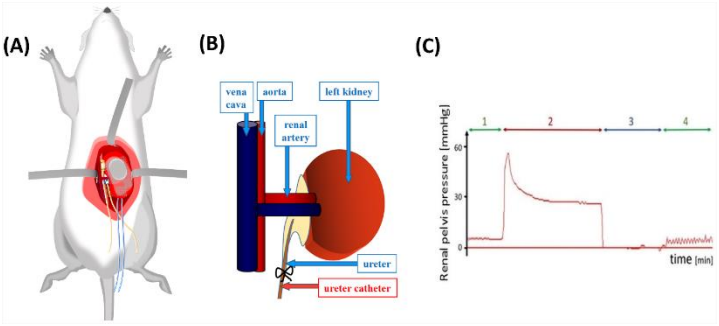

FIGURE 2: Illustration of the methods utilized for remotely controlled brief increases in renal pelvis and tubular pressures. (A) Schematic view depicting the relevant positions and fixations of probes. (B) Catheter placed in the left ureter and connected via a catheter (length about 1.5 m) to a container filled with isotonic saline. Elevating the container 41 cm above the level of the rats' kidneys increased pelvis and tubular pressures by about 30 mm Hg. (C) Pressure trace obtained for the renal pelvis of a rat (pressure transducer: DT-XX, Viggo-Spectramed, Swindon, UK; amplifier & acquisition: TAM-A Plugsys & HAEMODYN, Hugo Sachs Elektronik, March, Germany) recorded (1) during baseline control conditions (green), (2) during pressure increase achieved by injection of saline fluid via the ureteral catheter (red), (3) following disconnection of the catheter to obtain zero pressure for calibration of the pressure measurement (dark blue) and (4) during another control measurement (green). Note that the oscillations observed during first (1) and, even enlarged, during second control (4) represent the spontaneous peristaltic contractions of the ureter.

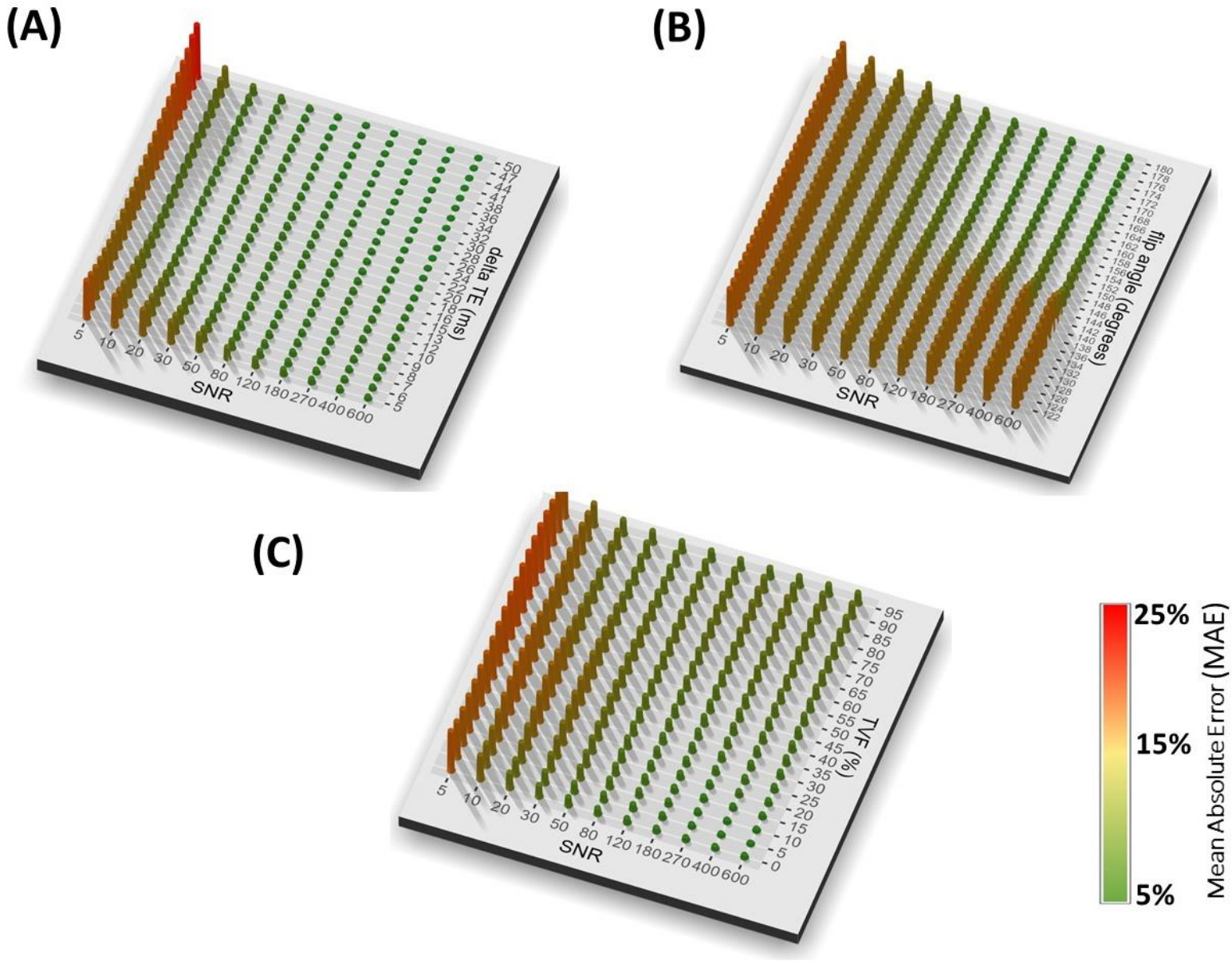

FIGURE 3: A. Representative example of Mean Absolute Error (MAE) calculated after analyzing the T_2 decay of the synthetic data with bi-exponential analysis. The table shows the impact of SNR, and the echo spacing on accuracy of TVF estimation. Other simulation parameters were $T_{2\,long}$=500ms, $T_{2\,short}$=50ms, $T_{1\,long}$=2800ms, $T_{1\,short}$=1500ms, NumOfEchoes= 13, flipAng=180°. Numbers are in percentage. B: Representative example of Mean Absolute Error (MAE) calculated after analyzing the T_2 decay of the synthetic data with bi- exponential analysis for a variety flip angle and SNR. Other simulation parameters were $T_{2\,long}$=500ms, $T_{2\,short}$=50ms, , $T_{1\,long}$=2800ms, $T_{1\,short}$=1500ms, NumOfEchoes= 13, esp=6. Numbers are in percentage. C. Representative example of Mean Absolute Error (MAE) calculated after analyzing the T_2 decay of the synthetic data with bi-exponential analysis for a variety of TVF and SNR of simulation parameters: other parameters were $T_{2\,long}$=500ms $T_{2\,short}$=50ms, , $T_{1\,long}$=2800ms, $T_{1\,short}$=1500ms, NumOfEchoes= 13, flipAng=180°. Numbers are in percentage.

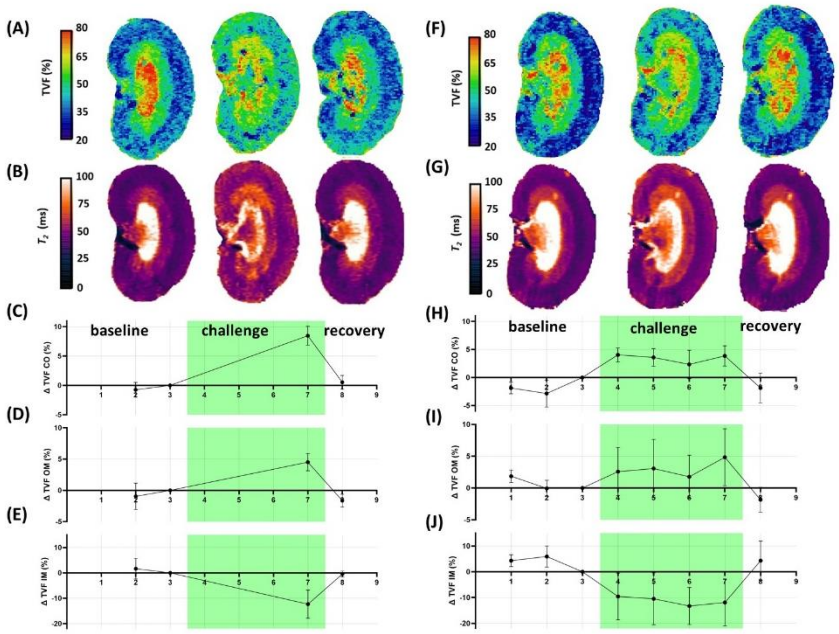

Figure 4: Time courses during renal pelvis/tubular pressure increase. (A, B) Exemplary TVF and T_2 maps obtained for a rat kidney in vivo of the first subgroup (n=3). Time course of the TVF changes (mean ± SEM) for (C) cortex (CO), (D) outer medulla (OM), and (E) inner medulla (IM) before the intervention (baseline), during the intervention (green area), and during recovery acquired for the first subgroup n=3. (F-J) Time courses during renal pelvis/tubular pressure increase, obtained for the second sub-group (n=4). Exemplary TVF and T_2 maps obtained for a rat kidney in vivo (F,G) . Time course of the TVF changes (mean ± SEM) for (H) cortex (CO), (I) outer medulla (OM), and (J) inner medulla (IM) before the intervention (baseline), during the intervention (green area), and during recovery acquired for the second subgroup n=4.

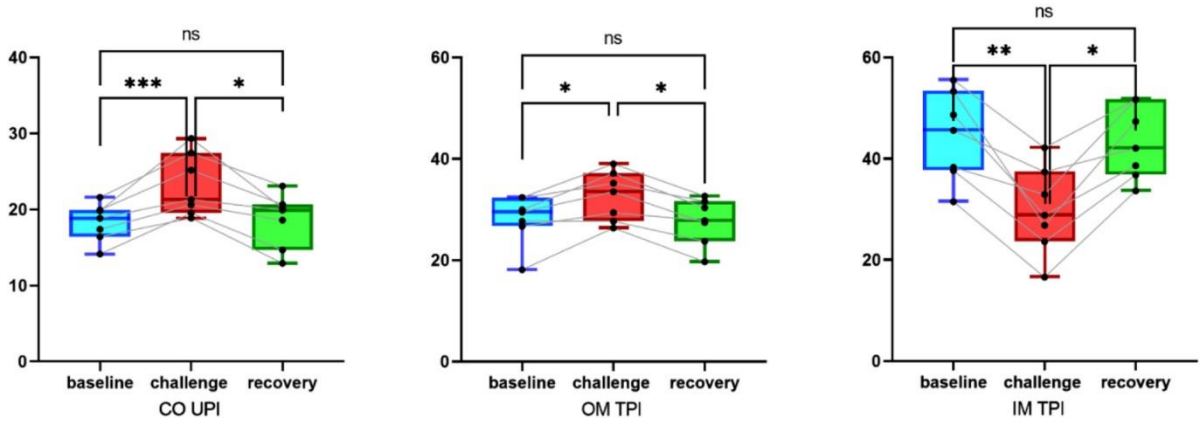

FIGURE 5: Box-and-whisker plots showing changes of tubular volume fraction (TVF) during pelvis/ureter pressure increase. TVF was significantly increased in the kidneys' cortex and outer medulla during intervention (p = 0.0005/p = 0.0162; Dunn's multiple test vs. baseline). TVF reduction was significant for inner medulla (p = 0.0075; Dunn's multiple test vs. baseline). The box-and-whisker plots display the first and third quartiles, with the line within the box representing the median value. The whiskers denote the minimum and maximum values. Volumes were examined by non-parametric multicomparison, comparing TVF among all three conditions using Dunn's multiple test for multiple comparisons (n = 7 subjects).

Synopsis

Motivation: The increasing incidence of kidney diseases is a global concern and current biomarkers are inadequate. Changes in renal tubule volume fraction (TVF) may serve as a rapid biomarker for kidney disease and provide a better understanding of renal (patho-)physiology.

Goal(s): This study aims to measure TVF in in vivo rat kidney during acute tubular pressure increase

Approach: This study uses the amplitude of the long T2 component as a surrogate for TVF in rats, by applying multiexponential analysis of the T2 driven signal decay

Results: The results demonstrate that our approach is promising for research into quantitative assessment of renal TVF in in vivo applications.

Impact: This is the first report on in vivo assessment of relative changes in the renal TVF, which provides a potential rapid, noninvasive marker for kidney disease. This approach will be invaluable for gaining a better mechanistic understanding of renal (patho-)physiology.

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