

Ex vivo ischemic kidney damage ²³Na relaxometry

C. Laustsen^{1,2}, S. Ringaard¹, M. Damkjær³, and M. Pedersen¹

¹Klinisk Institut, The MR Research Centre, Aarhus University, Aarhus, Denmark, ²Danish Research Centre for Magnetic Resonance, Hvidovre Hospital, Hvidovre, Denmark, ³Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark

Introduction

²³Na mapping has showed useful as a sensitive diagnostic marker in kidney damage [1,2]. We hypothesize that changes in intra/extra-cellular sodium pool composition can be used as an early indicator for intrarenal tissue impairment, even when the total sodium concentration is unaltered. When sodium nuclei experience restrictions in motion or orientation, the quadrupolar component is not averaged to zero and the signal arising from these restricted nuclei will show quadrupolar splitting and/or relaxation as a result. In mammalian physiology, the cells maintain a concentration gradient across the cell membrane of intracellular sodium (10 mM) against extracellular sodium (150 mM). The ion gradient will be transiently or chronically disrupted in damaged cells, which may be encountered in chronic and acute kidney damage. This study investigates the use of ²³Na relaxometry as a marker for damage in excised kidneys.

Methods

Experimental studies were performed using adolescent Labrador dogs (~15 kg). In each anesthetized dog, the left renal artery was exposed through a flank incision, and acute renal artery occlusion was achieved for 45 min by placing a ligature around the renal artery. At day 7 after the surgical procedure, it was euthanized, and the excised kidney was immersed in formalin and phosphate buffer. MRI experiments were performed on a 7 T horizontal bore magnet, bore diameter 11 cm (Oxford Instruments, Oxford, UK) with a Unity Inova console (Varian, Palo Alto, CA, USA) equipped with a double tuned ¹H/²³Na volume coil (RAPID Biomedical GmbH). ²³Na relaxometry was performed with a CPMG sequence with 31 echo times, ranging from 1.2 ms – 181.2 ms. ¹H T₂-weighted spin echo multi-slice images were acquired to show the ischemic damage and to measure the total kidney volume. ²³Na 3D SPRITE images were acquired to evaluate the total sodium concentration. Spin echo diffusion-weighted were acquired to obtain ADC maps that were correlated with the maps of the total ²³Na content. Multi-component analysis of the ²³Na relaxometry data by a Non Negative Least Square (NNLS) algorithm was performed with the open source software AnalyzeNNLS [3]. This computation generated exponential components related to different ²³Na compartments (separated by individual T₂ values).

Results

Ultra fast imaging sequences are required for total concentration mapping of sodium, we where used the 3D standard SPRITE technique. The total sodium concentration is equally homogeneously distributed with slightly higher values in the cortex, results not shown. While these measurements fail to differentiate between the diseased and the healthy kidney, the CPMG ²³Na measurements clearly show a significant change upon ischemia, as seen in fig. 1 (A) and in table 1. Where a resulting 40% increase in the fast relaxing sodium pool indicate an extremely sensitive biomarker for ischemic damage in the excised kidney. The ischemic damage in the occluded kidney is well resolved in ¹H 2D T₂-weighted multi-slice images fig. 1 (B) and (C), while the total kidney volume showed no significant changes upon ischemia, results not shown.

Discussion

This study demonstrated that NNLS analysis fig. 1 (A) of ²³Na CPMG multi-echo sequence is capable to extract information about the intra- and intercellular T₂ values of ²³Na by taking advantage of the intrinsic quadrupolar relaxation of the ²³Na nuclei. Of particular interest, we observed a clear difference in the found two sodium pools between the diseased and healthy kidney. The 3D SPRITE ²³Na images indicate that the total sodium concentration is equally distributed in the kidney. However, the cell concentration gradient can be disturbed without altering the total concentration. The ADC maps and the T₂-weighted images fig. 1 (B) and (C) show clear ischemic damage in the occluded kidney. Further investigations involve image T₂ measurements of the ²³Na relaxation, for mapping of the intra/extra-cellular ion gradient.

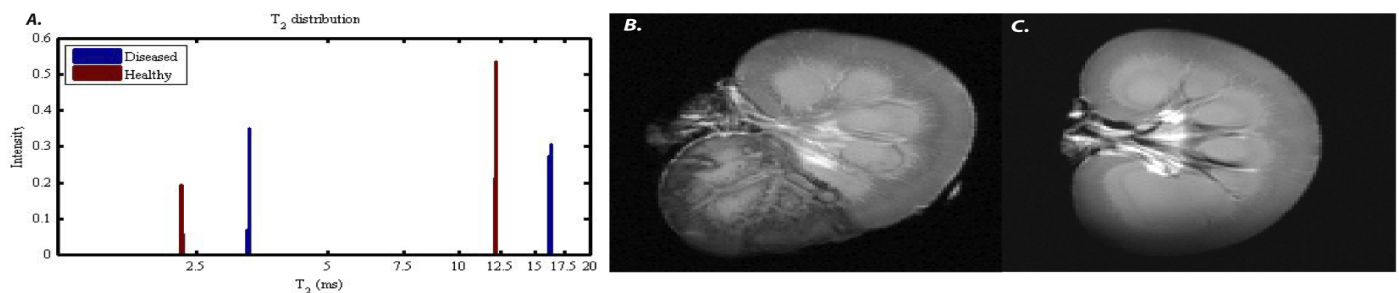


Fig 1. A. ²³Na T₂ distributions derived from NNLS analysis from a diseased (B) and healthy (C) kidney. The sodium pool distribution is significantly shifted towards more fast relaxing nuclei. The ¹H T₂ weighted images clearly show the kidney damage.

Table 1: The parameters found in the NNLS fitting of the ²³Na CPMG experiments. A_s and A_f are the amplitude of the sodium pools and T_{2f} and T_{2s} the relaxation times of the fast (f) and slow (s) relaxing sodium pool.

Table 1	T _{2s} [ms]	A _s [%]	T _{2f} [ms]	A _f [%]
Diseased	16.30	0.58	3.31	0.42
Healthy	12.19	0.75	2.30	0.25

References

[1] B.K. Atthe, A.M. Babsky, P.N. Hopewell, C.L. Phillips, B.A. Molitoris, and N. Bansal, Early monitoring of acute tubular necrosis in the rat kidney by ²³Na-MRI. *Am J Physiol Renal Physiol* 297 (2009) F1288-1298. [2] N. Maril, R. Margalit, J. Mispelter, and H. Degani, Functional sodium magnetic resonance imaging of the intact rat kidney. *Kidney Int* 65 (2004) 927-935. [3] T.A. Bjarnason, and J.R. Mitchell, AnalyzeNNLS: Magnetic resonance multiexponential decay image analysis. *Journal of Magnetic Resonance* 206 (2010) 200-204