Effect of Anesthesia on Renal R_2* Measured by BOLD MRI

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TARGET AUDIENCE: Researchers with an interest in renal BOLD MRI, particularly in pre-clinical small animal models.

PURPOSE: The purpose is to evaluate the effects of different anesthetic agents on renal R_2* during BOLD MRI in mice. BOLD MRI provides a means to infer the oxygenation of tissues based on the effect of deoxyhemoglobin on R_2* and may be clinically important for a variety of renal diseases [1]. General anesthesia produces several reversible physiologic effects in the kidney, including changes of blood flow, glomerular filtration, and sodium excretion [2]. Because R_2* is influenced by hemodynamic parameters, its value may differ depending on the choice and dosage of anesthetic agent used during imaging. In this study we evaluated five common agents to determine their effects on renal R_2*. Because inhaled anesthetics are typically administered with 100% oxygen while injected agents are not, we also evaluated the effect of fraction of inspired oxygen (F_iO_2) together with the anesthetics.

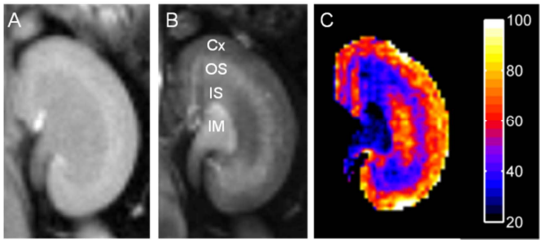

Figure 1. Typical T_1- (A) and T_2*-weighted (B) images of the kidney, and the corresponding R_2* map (C). Four concentric layers are clearly visible in the T_2*-weighted image: cortex (Cx); outer stripe (OS) and inner stripe (IS) of the outer medulla; and inner medulla (IM). R_2* is expressed in s^{-1}.

METHODS: ***Animals:*** The study included five healthy female sibling ICR mice (mean 28.6 g; 12 weeks old) and five common types of anesthesia: 1.5% isoflurane (Iso), 1.0% Iso, ketamine/xylazine (Ket; 1.5/0.02 g/kg), pentobarbital sodium (Pento; 60 mg/kg), and tribromoethanol (TBE; 500 mg/kg). Injected doses were chosen in order to achieve a 45-minute anesthetization period, which is realistic for MR studies. In initial experiments, Iso was delivered with 100% O_2. Each animal received one of the agents on each of five days, and BOLD MRI was performed approximately 30 minutes post-induction. The order of anesthetics was determined by a randomized Latin square design, and experiments were performed at five-day intervals to minimize hormonal variation with the estrus cycle. In follow-up experiments to determine the effect of F_iO_2, three of the mice were anesthetized with Ket and imaged while breathing 100% O_2, or anesthetized with 1% Iso while breathing 21% O_2. All experiments complied with IACUC policies and approved protocols. ***MR Imaging:*** Coronal BOLD images were acquired at 4.7 T (Agilent Technologies, Santa Clara, CA) using a respiratory-triggered multi-gradient-echo sequence with parameters as follows: TR/TE/ΔTE=350/2.0/2.4 ms; echoes/NEX/flip=64/4/30°; 0.23-mm in-plane resolution; 1-mm slice thickness; and fat saturation. Mouse temperature was maintained above 35°C using a warm air blower. ***Analysis:*** R_2* maps were calculated by linear fitting of log(signal) vs. echo time. Voxels with signal below the Rose criterion (5 times the background standard deviation) were excluded from fitting to avoid bias from noise amplification. Average R_2* was calculated within regions of interest drawn in the renal cortex, outer stripe (OS) and inner stripe (IS) of the outer medulla, and the inner medulla (IM; **Fig. 1**). Regions with susceptibility artifacts were excluded. Statistical analyses were performed with ANOVA.

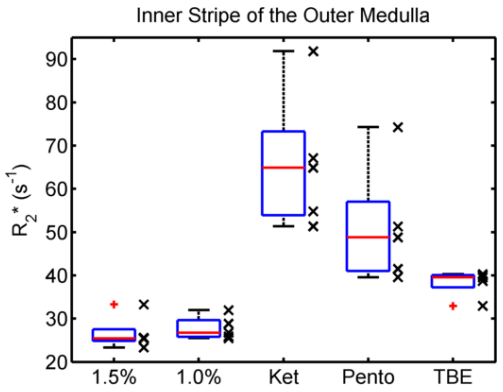

Figure 2. Average R_2*within the inner stripe of the outer medulla. Values for individual mice are plotted to the right of each boxplot (**x**; N=5). Significant differences ($p < 0.05$) were found for all but two pairwise comparisons of anesthetics (1.5% Iso vs 1.0% Iso; and Pento vs. TBE).

RESULTS AND DISCUSSION: We report results only for the IS for purposes of brevity and because this region has been found to be most clinically relevant [3,4]. However, similar relationships between anesthetics were observed for all tissue regions. R_2* was highly dependent on anesthetic agent ($p < 0.0001$; **Fig. 2**). R_2* was significantly different between anesthetics for all comparisons except for 1.5% Iso vs. 1.0% Iso and Pento vs. TBE. Because R_2* was higher for all injected agents compared to Iso, follow-up experiments were performed to test whether this could be attributed to differences in F_iO_2 rather than chemical effects of the agents themselves (**Fig. 3**). R_2* was not different for 1% Iso in either 100% or 21% O_2. Inhalation of 100% O_2 did reduce the R_2* under Ket; however, this accounted for only 48% of the difference between Ket and 1% Iso shown in **Fig. 2**. Therefore chemical effects have a major role in the observed differences in R_2* within the IS.

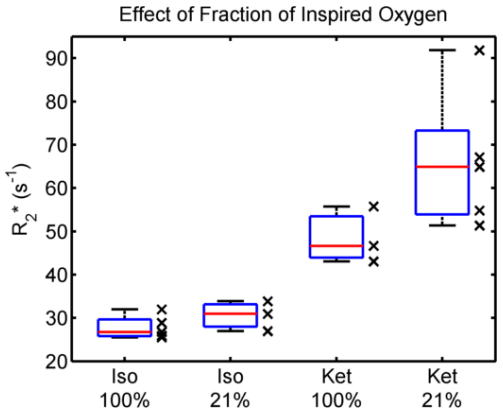

Figure 2. Comparison of R_2* within the inner stripe for 1% Iso and Ket, administered with either 100% or 21% O_2. Although R_2* for each agent was slightly higher with 21% O_2, the R_2* difference between 1% Iso and Ket could not be explained by oxygen fraction alone.

CONCLUSIONS: This study highlights the influence of anesthetic effects on renal R_2* in small animals. A large range of R_2* was observed in the inner stripe of the outer medulla depending on the choice of anesthesia and F_iO_2. We recommend consideration of the anesthetic agent when designing or evaluating BOLD MRI studies.

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