Introduction: Quantitative MRI measures of T1 and T2* relaxation times offer a noninvasive means to indirectly monitor tissue O2 content. T1 oxygen-dependence is primarily based on the presence of weakly paramagnetic, molecular O2 dissolved in blood plasma and interstitial space; whereas, T2* oxygen dependence is based on the signal loss induced by local magnetic field inhomogeneities generated by paramagnetic deoxy-hemoglobin. The clinical rationale for gas challenge studies originate from radiotherapy strategies aimed at augmenting tissue oxygenation via increased fraction of inspired O2 (FiO2) and/or CO2 (FiCO2). Inclusion of CO2 in the inhaled O2 gas mixture was proposed to reduce O2-induced blood flow reductions, and previous studies have demonstrated differential T1 and T2* responses to breathing carbogen and 100% O2. However, in these studies the tissue oxygenation and perfusion status were not investigated, and gases were delivered in a fixed order. The objective for the current study was to characterize T1 and T2* responses to various combinations of FiO2 and FiCO2 in rabbit abdominal tissues. Potential blood flow and partial pressure of O2 (PO2) dependence on previous gas challenges were examined by randomizing the gas challenge order in each subject. Following the imaging sessions, pilot measurements of tissue PO2 and perfusion were conducted to assess temporal dynamics that may contribute to MR relaxation time changes.

Methods: All animal procedures were approved by the Institutional Animal Care and Use Committee of the University of Toronto. White rabbits (4.0–4.5 kg) were used in six imaging sessions with various combinations of FiO2 and FiCO2. Each rabbit was induced with 5 % isoflurane and maintained at 1 % for the MR experiments and 2 % for the invasive studies. The following gas challenges were delivered in random in 5–8 different steps: room air (21% O2), balanced air (100% O2, 100% O2, 100% O2, and 90% O2). MR imaging was performed on a 1.5 T GE scanner (Signa EXCITE TwinSpeed; General Electric Healthcare, Milwaukee, WI, USA) using a transmit/receive quadrature knee coil, with coronal images slices positioned to encompass the kidney, liver, and paraspinal muscle. T1 quantification was achieved using a variable flip angle approach, with a series of 3D fast spoiled gradient echo scans with the following imaging parameters: TR = 7.2 ms, TE = 3.1 ms, FA = 2°, 10 and 21°, FOV = 160 mm, matrix = 256 × 160, slice thickness (SLH) = 3 mm, number of slices (NSL) = 10, NSL = 4. T2* quantification was achieved using a 2D multi echo sequence with the following parameters: TR = 100 ms, 6 equally spaced TE = [2.1–47.1] ms, FOV = 30°, FOV = 160 mm, matrix = 256 × 192, SLH = 3 mm, NSL = 6, and NSL = 4. Pixel-wise T1 and T2* maps were generated using in-house Matlab (V.7.0, Mathworks Inc., Natick, MA, USA) scripts. T1 parameter maps were generated using the signal equation for the SPGR steady state magnetization with analytical-based flip angle correction using B0 field maps acquired separately. T2* parameter maps were computed by fitting T2* signal intensity versus echo time to a monoexponential signal decay function. Regions-of-interest were outlined in the liver, kidney and muscle to extract mean T1 and T2* values for each gas challenge.

Invasive tissue measurements were conducted in a separate session with OxyLite and OxyFlo (Oxford Optronics, Oxford, UK) fibre optic probes that were inserted into the three tissue types (liver, kidney, and muscle). The OxyLite uses fluorescence lifetime measurements to quantify absolute tissue PO2 and OxyFlo uses laser Doppler to provide relative measures of tissue perfusion.

Relative ΔT1 and ΔT2* values were computed for each transition between the different gas challenges, and a series of one-tailed one-sample t-tests were performed to determine significant differences from zero (null hypothesis).

Results: Figure 1 provides the ΔT1 and ΔT2* values for each of the transitions from air to one of the three inspired gas challenges. All transitions exhibited expected trends, except for any gas transitions including air to carbogen. ΔT1* for air → 100% O2, negative ΔT2* on air → 10% CO2, and equivocal ΔT2* on air → carbogen. Significant for ΔT1* transitions existed for air → 100% O2 in liver (p < 0.01) and air → 100% O2 in kidney (p < 0.05). Muscle ΔT2* were very small and insignificant, and air → carbogen transitions produced inconsistent ΔT1* in all tissues. ΔT1 values exhibited variability, with only kidney air → 100% O2 (p < 0.05) transition exhibiting significance. Figure 2 provides ΔT1 and ΔT2* transitions for the three different gas transitions. Expected trends were also observed: positive ΔT* and negative ΔT1 on 10% CO2 → 100% O2/carbon, and reverse changes for 100% O2 → carbogen. ΔT1* significance was achieved in both liver and kidney on all transitions: 10% CO2 → 100% O2/carbon (p < 0.05) and 100% O2 → carbogen (p < 0.01). For muscle, only the negative ΔT1* for 100% O2 → carbogen (p < 0.05) was significant. ΔT1 did not reach statistical significance for any gas transitions, except muscle transitions from 10% CO2 → 100% O2 and 100% O2 → carbogen (p < 0.05).

Discussion: Although the principle clinical application for MR-based oxygenation monitoring is in oncology, there is still much to learn from normal tissue changes. In this study, we found that T2* changes followed predicted patterns: ↑ T2* on 100% O2 (due to higher PO2 and lower blood volume) and ↑ T1 on 100% O2 (due to higher Hb and blood volume). Similarly, T1 changes followed predicted trends toward a ↓ T1 on 100% O2 (due to higher PO2 and lower blood volume) and ↑ T1 on 10% CO2 (due to greater blood volume). However, T1 changes were much less predictable, compared with T2*. The air → carbogen transition generated the most variable T1 and T2* transitions, possibly attributed to opposing influences from observed perfusion and PO2 changes. A previous study in normal human abdominal tissues found results which are inconsistent with the T1 and T2* transitions in our study. This cited study reported T1 and T2* increases and non-PO2 changes for air → 100% O2 and T1 increases and T2* decreases for air → carbogen. This distinction suggests physiological differences between the two studies may exist. For the invasive measures, we found large variability in the temporal dynamics of tissue perfusion and PO2, which is a consideration for future studies. In conclusion, we found that T2* provided greater sensitivity to changes in tissue PO2 and perfusion compared with T1, and we also found independence of relaxation time changes from order of gas administration. Variability in our study and the literature may be partly attributed to organ-specific PO2 and perfusion dynamics exhibited in this study.


Figure 1. ΔT1 (a) and ΔT2* (b) values for each gas transition from air in three tissues. * p < 0.05, ** p < 0.01

Figure 2. ΔT1 (a) and ΔT2* (b) values for transitions between gas challenges in three tissue types. * p < 0.05, ** p < 0.01, † p < 0.005

Figure 3. Representative OxyLite PO2 values (a) and OxyFlo relative perfusion measurements (b) in the rabbit liver, kidney, and muscle.