

Relaxation effects of oxygen on T2 and T1 with application to vitreous pO2 measurement

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PURPOSE: Abnormal vitreal oxygen tension has been implicated in a number of ocular and retinal diseases, such as diabetic retinopathy and nuclear cataract of the lens (1,2). Oxygen content of the vitreous can be measured in animals using invasive techniques that require inserting probes into the eye, which cannot be used in humans. Molecular oxygen is paramagnetic, leading to shortening of water T1 (3), an effect which has been used to non-invasively map oxygen tension of body fluids (4), providing unique physiological data that could otherwise be impossible to obtain in humans. Paramagnetic agents should also have some effect on T2, but the effect of oxygen on T2 has yet to be thoroughly explored, unlike with T1.

The aim of this study was to develop and calibrate MRI measurement of T1 and T2 with oxygen and to apply these methods to non-invasively measure the partial pressure of oxygen (pO2) in the human vitreous, which is 99% water. Calibration of T1 and T2 to pO2 was made using ex vivo vitreous in addition to water phantoms with the aim of correcting for protein that makes up a small fraction of the vitreous.

METHODS: Phantoms were made using distilled water bubbled with nitrogen to various pO2 and sealed in glass vials (n=4). pO2 (mmHg) of the phantoms was measured using an oxygen-sensitive fiber optic probe (Oxylab, Oxford Optronics) before and after MRI. Ex vivo eyes from goats (n=2) were obtained at the time of euthanasia and kept in saline with MRI performed within 12 hours. After MRI, the fiber optic probe was inserted into the vitreous to measure pO2. The phantoms and eyes were imaged together in a chamber with circulating water heated to 34, 37, and 40°C. Multiple temperatures were used to determine the effect of temperature on T1 and T2 (5). MRI studies were performed on at 3T. A head coil receive-only coil was used for phantoms. T1 measurements were made using inversion recovery FLASH with FOV=100x100mm, matrix=128x128, a single 5mm slice, TE=3.6ms, TR>30s, FA=7°, 11 inversion times between 370 to 9000ms. T2 measurements were made using half-fourier fast spin echo with FOV=100x100mm, matrix=128x128, a single 5mm slice, TR=10s, and TE=40, 723, and 1410ms. T1 and T2 were fit pixel-by-pixel. Linear regression was used to determine the slope and intercept of R1 and R2 as a function of pO2, and to find the slope of T1 and T2 as a function of temperature for each phantom (5).

Multiple experiments were performed on 3 normal human volunteers (male, age 24-29). The eye that was imaged was kept closed and covered with gauze during imaging to minimize the effect of known ocular temperature gradients on T1 and T2 (6). A custom-made receive-only surface coil (7cm diameter) was used. T1 and T2 measurements were made similar to the phantom except with FOV=80x80mm. During the data readout train (<2s), the subjects were asked to fixate on a target without blinking and between readouts they could blink freely. Data are given as mean±SD.

RESULTS: The relationship between R1 and R2 with pO2 at 37°C were found to be $R1=0.214s^{-1} + [pO2]*2.00 \times 10^{-4}s^{-1}/mmHg$ and $R2=0.402s^{-1} + [pO2]*5.46 \times 10^{-4}s^{-1}/mmHg$. The slope of T1 and T2 as a function of temperature were 0.0866 and 0.0226 s°C, respectively. pO2 of the ex vivo vitreous was measured to be 1.5 and 6 mmHg, and R1 and R2 at 37°C were 0.221 and 0.545 s⁻¹, respectively. R1 and R2 of ex vivo vitreous were larger than that of water at the same pO2, due to relaxation from vitreous proteins. Using the relaxivities of O2, R1 and R2 of deoxygenated vitreous were calculated and then used as an offset for the calculation of in vivo human vitreous pO2 from R1 and R2 MRI. **Fig 1** shows R1 and R2 maps of in vivo human eye. Whole vitreous R1 and R2 were 0.229±0.007 and 0.670±0.017 ms⁻¹, respectively. With the phantom/ex vivo vitreous calibration, whole vitreous pO2 calculated from R1 and R2 were 53.9±36.8 and 230.2±30.5 mmHg.

DISCUSSION: Previous reports of vitreous pO2 measured by inserting electrodes or fiber optics into eyes of animals or humans undergoing eye surgery were 10-23mmHg (1,7). Our pO2 value calculated from R1 was between previous reports using T1 MRI of 17 (6) and 63mmHg (4). The protein and gel structure of the vitreous causes additional relaxation, which could explain the higher R1 and R2 in the ex vivo eye compared to phantom at the same pO2. Thus, a linear correction was made. Without correction with the ex vivo vitreous, the average human vitreous pO2 derived from R1 and R2 would be 77.2 and 490.8 mmHg, respectively. R1 gave much closer values compared to invasive oxygen measurement than R2. R2 has been reported to be more sensitive to protein in solution than R1 (8), so it is possible that simple correction with ex vivo vitreous will not work as well for R2 as it did with R1. Possibly, the discrepancy in pO2 calculated from R1 and R2 could be used to estimate relative amount of protein in the vitreous, but this remains to be explored.

In conclusion, both T2 and T1 were found to be sensitive to oxygen. T2 appeared to yield lower accuracy for measuring vitreous oxygen tension compared to T1. T1 MRI could be used to non-invasively map oxygenation of the vitreous, providing unique information on ocular physiology that would otherwise be impossible to obtain in humans. Future studies will improve spatial resolution to map pO2 around the anterior chamber and lens.

Reference: 1) Holekamp et al, Am J Ophthalmol 2005, 139:302. 2) Berkowitz et al, Invest Ophthalmol Vis Sci 1999, 40:2100. 3) Chiarotti et al, Il Nuovo Cimento 1955, 1:863. 4) Zaharchuk et al, Acad Radiol 2006, 13:1016. 5) Nelson and Tung, Magn Reson Imaging 1987, 5:189. 6) Muir et al, Radiology 2012, in press. 7) Quiram et al, Retina 2007, 27:1090. 8) Chen and Kim, PLoS One 2010, 5:e8565.

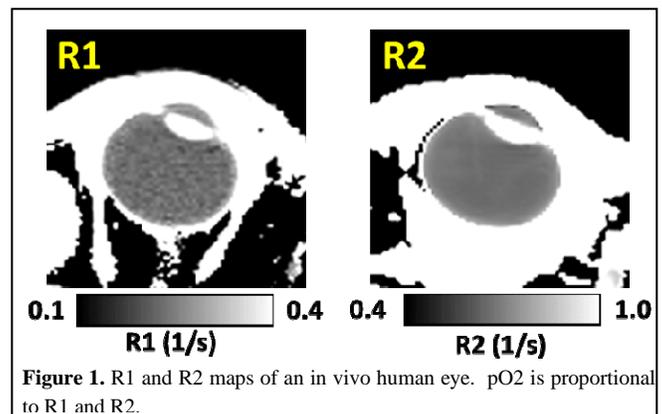


Figure 1. R1 and R2 maps of an in vivo human eye. pO2 is proportional to R1 and R2.