# The effect of temperature and closing the eye on T1-based MRI methods to image oxygen tension in the eye

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**INTRODUCTION:** MRI T1 measurements have been used to map oxygen tension in body fluids, such as vitreous, bladder and cerebrospinal fluid, by exploiting the dissolved paramagnetic O2 which shortens T1 (1). However, T1 is also sensitive to temperature (2), which could affect T1-based pO2 methods. The eye is exposed to the environment and temperature gradients across the vitreous of ~0.5°C from front to back of the eye have been reported in anesthetized animals by inserting probes through the eye (3). Such temperature effect on pO2 accuracy in the eye is unknown.

MRI T1-based methods are the only non-invasive way to measure vitreous pO2. Abnormal vitreous pO2 has been associated with ocular diseases, including diabetic retinopathy, retinal ischemic and glaucoma (4). The ability to characterize and minimize the temperature effects on MRI T1-based pO2 measurement is important. This study aimed to determine whether temperature gradient across the eye affects vitreous $pO_2$ measurement in humans. First, calibrations of T1 at different pO2 and temperature were performed on water phantoms and ex vivo eyes. T1 was measured with the eye open and with the eye closed/covered, which should reduce temperature gradients across the eye (5), in normal volunteers.

**METHODS:** Phantoms were made using distilled water bubbled with nitrogen (n=10). pO2 (mmHg) of the phantoms was measured using an oxygen-sensitive fiber optic probe. Fresh ex vivo eyes from a rabbit and a baboon (n=2) were obtained at euthanasia and kept in saline with MRI performed within 12 hours. After MRI, the vitreous pO2 was measured with the fiber optic probe. The phantoms and eyes were imaged in a chamber with circulating heated water to 34, 37, and 40°C. MRI studies were performed on a 3T Philips Achieva with an 8 channel head coil. T1 measurements were made using a Look-Locker sequence (6) with a spoiled gradient echo readout, in which all inversion times are readout after a single inversion pulse. Images at all inversion times were acquired in 2 shots with FOV=100x100mm, matrix=100x100, a single 6mm slice, TR/TE=6.6/3.2ms, FA=4°, 26 inversion times with a minimum TI=108ms and spacing of 264ms, 6-9 repetitions, and 20s between repetitions of the inversion pulse. A non-linear least squares fit using the equation in (6) was used to fit T1, M0, and the flip angle. Linear regression was used to determine the slope and intercept of R1 as a function of pO2 at 37°C, and to the find the slope of T1 as a function of temperature for each phantom (4).

Six studies on different days were performed on 3 normal volunteers (2M, 1F, age 26-28). A custom-made receive-only surface coil (7cm diameter) was used. T1 was measured similar to the phantom study except, matrix=168x167, a single 5mm axial slice, TR/TE~6.5/3.2ms, 21 inversion times with a minimum TI~64ms and spacing of ~325ms, and 5 repetitions. Scans were repeated 3-5 times during each session. The subjects were asked to fixate on a target without blinking during the data readout, and between readouts they could blink but were otherwise asked to keep their eyes open. After the first scan, subjects closed the eye being imaged and covered it with gauze for the remainder of the session to warm the eye. Scans were then repeated 2-3 times over 10-43min after closing/covering the eye.

**RESULTS:** Linear regression of R1 and pO2 at 37°C gave R1=0.205+[pO2]*0.205E-4 ($R^2$=0.99) (**Fig 1**). Vitreous of the ex vivo eye had slightly larger R1 than distilled water, likely due to the gel-like structure of the vitreous. R1 of deoxygenated vitreous, 0.209$s^{-1}$ (calculated using the relaxivity of pO2 in water), was used to calculate pO2 in vivo in place of the value for water (0.205$s^{-1}$). T1 of water and ex vivo vitreous were linearly dependent on temperature, with a slope of 0.106±0.009 s/°C in phantoms. This translates to a ~11mmHg/0.5°C difference at ~37°C. **Fig 2** shows R1 and pO2 maps of the human eye before and after closing the eye. Using ROI analysis (**Fig 3a**), by 10min after closing the eye, T1 and pO2 had noticeably changed in most regions and did not change over the session (**Fig 3b**). pO2 significantly decreased in many regions of the vitreous after closing the eye. The effects of temperature on calculated pO2 were estimated from T1 and these results are shown in **Fig 3c**, giving temperature changes of 0.54-0.85oC, comparable to temperature gradients across animal eyes.

**DISCUSSION:** Closing the eye without a cover for 5min increased the eye surface temperature from 34.4 to 35.9°C (5). Thus, we expect closing and covering the eye could remove temperature gradients across the vitreous. A potential confound is that closing the eye may reduce vitreous pO2 because the anterior chamber receives O2 from the surrounding air. However, this effect is likely negligible because: 1) pO2 of the anterior chamber at the cornea does not correlate with pO2 of the anterior chamber at the lens (7), and thus, the vitreous chamber which is farther away is not expected to correlate either, 2) in the cat eye, it takes >30min of breathing 100% O2 for vitreous pO2 to begin to increase (8), indicating O2 diffusion through the vitreous is very slow. T1 changes in our study occurred after only 10min, which is too rapid to be caused by O2 diffusion in the vitreous.

In conclusion, we showed that T1-based pO2 technique of the vitreous is sensitive to temperature gradient across the eye. The temperature effects on T1 in the anterior chamber and vitreous do not appear negligible and need to be taken into account. Closing/covering the eye is a simple method to remove temperature confounds across the vitreous for T1-based pO2 mapping. MRI could provide unique pO2 information for the eye that would otherwise be impossible to obtain non-invasively in humans.

**Reference:** 1) Zaharchuk et al, Acad Radiol 2006, 13:1016. 2) Nelson and Tung, MRI 1987, 5:189. 3) Rosenbluth and Fatt, Exp Eye Res 1977, 25:325. 4) Holekamp et al, Am J Ophthal 2005, 139:302. 5) Mapstone,B J Ophthal 1968, 52:729. 6) Brix et al, MRI 1990, 8:351. 7) Siegfried et al, IOVS 2010, 51:5731. 8) Alder and Cringle, Graefes Arch Clin Exp Ophthal 1990, 228:151.

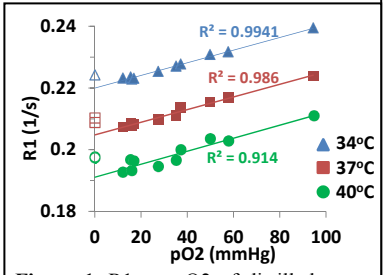


**Figure 1.** R1 vs. pO2 of distilled water phantoms (solid points) and vitreous (open points) at 3 different temperatures.

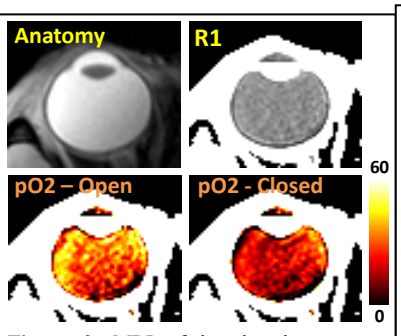


**Figure 2.** MRI of in vivo human eye showing anatomy and R1 (scaled 0.17-0.25 $s^{-1}$) from a single subject. Group-averaged pO2 (n=6) with the eye open or closed.

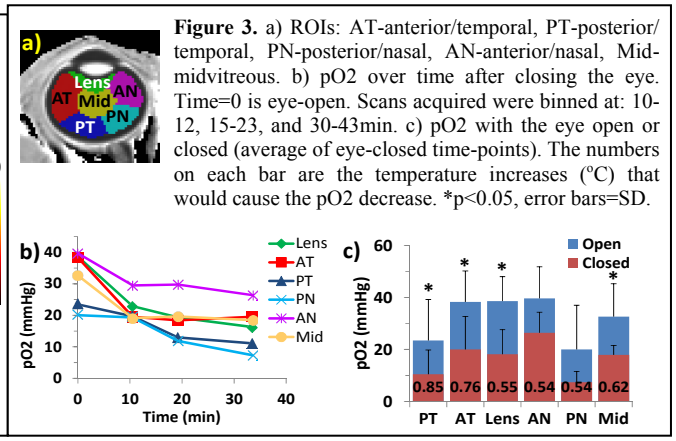


**Figure 3.** a) ROIs: AT-anterior/temporal, PT-posterior/temporal, PN-posterior/nasal, AN-anterior/nasal, Mid-midvitreous. b) pO2 over time after closing the eye. Time=0 is eye-open. Scans acquired were binned at: 10-12, 15-23, and 30-43min. c) pO2 with the eye open or closed (average of eye-closed time-points). The numbers on each bar are the temperature increases (°C) that would cause the pO2 decrease. *p<0.05, error bars=SD.