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Effects of Motion and b-value on Apparent Temperature Measurement by Diffusion-Based Thermometry MRI: Eye Vitreous Study

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Abstract

Purpose: To make noninvasive measurements of temperature in the posterior chamber (vitreous) of the eye using diffusion-based thermometry (DBT) MRI and to explain variability in these measurements due to choice of b-value and the effects of motion.

Methods: Phantom studies of human vitreous and distilled water were performed using b-values from 0-1500s/mm² to determine the liquid-specific calibration factor for vitreous as well as to determine the temperature offsets due to sampling the diffusion curve using three higher routine clinical b-values (b = 0, 500, 1000s/mm²) or four lower b-values (b = 0, 200, 400, 600s/mm²), thought to be optimized for fluids. Retrospective ROI-based measurements of ADC on single slices as well as multi-slice histograms of the eyes were made in 6 patients with peri-orbital cellulitis and 11 age-matched controls, to assess for temperature changes in the presence of peri-orbital inflammation. A prospective study of 10 repeated measurements of eye temperature using both high and lower b-value sampling was performed in 10 asymptomatic volunteers to determine the reproducibility of eye temperature measurements in-vivo as well as to estimate vitreous temperature in the absence of motion.

Results: The diffusion coefficient of vitreous ($2.088 \pm 13 \times 10^{-6} \text{mm}^2/\text{s}$) was significantly lower (-1.9% , $p < 0.001$) compared to distilled water ($2.128 \pm 12 \times 10^{-6} \text{mm}^2/\text{s}$). The calibration factor for temperature measurements of vitreous using DBT is $+0.74 \pm 0.06^\circ\text{C}$. Temperature offsets were smaller ($< -0.2^\circ\text{C}$, $p < 0.01$) when using larger routine clinical b-values to estimate the diffusion coefficient compared to using a series of lower b-values ($< -1.0^\circ\text{C}$, $p < 0.001$). 2D single-slice ROI-based measurement showed significant temperature differences ($T_{LC} = 2.5 \pm 1.2^\circ\text{C}$, $p < 0.001$) between the eyes of patient with peri-orbital cellulitis, higher on the side of inflammation. There was no significant difference in eye temperature when using the 3D histogram (which is likely due to motion averaging as significant slice-to-slice variation was present). However, significant differences in the 3D temperature histograms between the two eyes was observed in one out of six

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patients. Prospective eye temperature measurements in healthy volunteers showed significant intra and inter-subject variability (33.8–41.6°C), which was caused by eye motion. This resulted in +2.4°C cohort-wide elevation in temperature when 3 b-values were used and +4.7°C when 4 b-values were used. Using a pattern of elevated temperature at the periphery of the eye to detect motion, eye temperature in the absence of motion was estimated to be 34.5±0.4°C with three higher b-values and 34.6±1.9°C with four lower b-values; this temperature corresponds with prior mathematical simulations of eye temperature as well as boundary conditions.

Conclusions: Globe vitreous temperature has been measured noninvasively using DBT MRI. Using routine clinical b-values of $b = 0, 500$ and 1000 s/mm^2 produces acceptable ($< -0.2^\circ\text{C}$) temperature offsets. Although DBT measurements are highly susceptible to motion, methods such as temperature differences or regression can be used to reduce or eliminate the effects of motion. Using a single clinical diffusion-weighted MRI, globe temperature difference of 1.6°C is pathological. Using a series of 10 measurements, globe temperature differences larger than 0.6°C are abnormal. This study suggests CSF flow likely artifactually increases core brain temperature measured by DBT MRI.

Keywords

Diffusion Based Thermometry MRI; Ocular; Globe; Vitreous Temperature

Introduction

Temperature is an important biomarker as it increases with infection and inflammation and decreases with vascular disease. In the eye, it may reflect a balance between metabolism and vascular supply in the retina and radiative losses to the environment. There is currently no non-invasive method to measure temperature in the posterior chamber of the eye. This is due to the presence of the lens which divides the eye into a smaller anterior and larger posterior chamber. Ocular temperature has been studied for over 130 years and it is hypothesized that the ability to measure ocular temperature will increase the understanding of ocular pathology¹. Mathematical as well as experimental studies have established that there is a posterior to anterior temperature gradient in the eye, with temperature close to core body temperature at the retina and approximately 2.5°C lower near the lens^{2,3}. Currently, infrared cameras can be mounted on slit-lamps and surface temperature of the eye can be readily mapped, with reported ocular surface temperatures of $32\text{--}35^\circ\text{C}$ ^{4,5}. These studies have established the importance of the tear film in adding warmth to the eye surface; surface temperature dissipates by 1°C 10s after blinking. Eye temperatures are lower in dry eye⁵ and elevated in conditions such as Graves' ophthalmopathy⁴ and decrease with treatment. Prior studies have shown that carotid artery stenosis as well as cavernous-carotid fistulas lower ipsilateral eye temperature by $0.8\text{--}1.3^\circ\text{C}$ ⁶.

Multiple MRI parameters are temperature-dependent and can be used to measure temperature including: proton density, T1, T2, diffusion, magnetization transfer and proton resonant frequency shift spectroscopy⁷. Since most clinical brain MRI protocols include diffusion weighted images (DWI)⁸, the ability to measure temperature using existing DWI images was investigated in this study. Using a liquid-specific calibration factor, the diffusion coefficient measured by MRI can be used to measure absolute temperature in liquids

(diffusion not restricted by a physical boundary) without the need for baseline images or subtraction. Diffusion-based thermometry (DBT) was initially used to measure temperature in the lateral ventricles of children to assess for infection⁹. Kozac et al. found a constant -1.0°C temperature offset between measured apparent temperature for artificial CSF and distilled water, which was constant over the temperature range of $32\text{--}42^{\circ}\text{C}$. Therefore, a $+1.0^{\circ}\text{C}$ temperature calibration offset was used to correct the measured in-vivo CSF temperature. Motion in CSF is thought to alter the measurement and using specific diffusion directions and histogram analysis methods have been proposed to reduce the effects of flow on the measurement¹⁰⁻¹². Core brain temperature measured using DBT has been shown to be reduced in aging¹³, mild traumatic brain injury¹⁴, neurodegenerative disease¹⁵ and multiple sclerosis and is increased in Moyamoya¹⁶ and normal pressure hydrocephalus¹⁷. However, these studies show large unexplained fluctuations between individual core brain temperature measurements in both healthy controls and patients (between $36\text{--}41^{\circ}\text{C}$), which in some studies produces average lateral ventricular temperatures $1\text{--}2^{\circ}\text{C}$ higher than core body temperature (e.g. DBT-measured core brain temperature in 14 controls range $35.2\text{--}39.7^{\circ}\text{C}$, with average 38.0°C while average tympanic temperature was 36.6°C ¹⁴; Moyamoya DBT measured average ventricular temperature was 38.3°C , range $36.0\text{--}40.9^{\circ}\text{C}$ ¹⁶; DBT measured core brain temperatures in controls range $34.4\text{--}41.3^{\circ}\text{C}$ ¹⁵).

The goal of this study was to extend diffusion-based thermometry to another non-restricted liquid (eye vitreous) and thereby provide a novel method to non-invasively assess eye temperature and to explain temperature variations observed among subjects.

Materials and Methods

Phantom study of human vitreous and distilled water

A phantom study was performed to assess the difference in diffusion coefficient in human vitreous compared to distilled water and to understand differences in temperature measured with different b-values. Human vitreous was obtained from an unrestricted autopsy and measured within 48 hours of death on a 3T scanner (Magnetom Prisma, Siemens Healthineers, Erlangen, Germany). IRB approval was not required for bodily fluids. Three capped glass vials with 2, 5 and 10 mL distilled water in each vial as well as one vial with 2 mL vitreous were partially submerged in a water bath and allowed to equilibrate overnight. The phantom was placed on the spine array with a flexible body array placed on top (both used for signal reception) and imaged using an EPI DWI sequence (acquisition parameters: $\text{FA} = 90^{\circ}$, $\text{TE/TR} = 90\text{ms}/10,000\text{ms}$, $\text{FOV} = 220 \times 200 \text{ mm}^2$, slice thickness = 2 mm, matrix = 192×192 , bandwidth = 1,445 Hz/pixel, number of phase encoding steps = 143, echo train length = 71, 1 average, 6 diffusion directions). Scans with three sets of b-values were obtained: $b = 0, 500$ and 1000 s/mm^2 ($T_{\text{acq}} = 160\text{s}$, $n=7$), $b = 0, 200, 400$ and 600 s/mm^2 ($T_{\text{acq}} = 220\text{s}$, $n=5$) as well as a set of 16 b-values from $0\text{--}1500 \text{ s/mm}^2$ in steps of 100 ($T_{\text{acq}} = 940\text{s}$, $n=3$). Water bath temperature was measured with a Thermco Scientific National Institute of Standards and Technology factory-calibrated mercury containing glass thermometer with 0.1°C markings (ACC10033FC, Fischer Scientific, Waltham, MA) immediately before and after the experiment.

Temperature was derived from the scanner-reported diffusion coefficient (D) as follows⁹ (this equation is derived from data in¹⁸):

$$T = \frac{2256.74K}{\ln \left[\frac{4392.21 \times 10^{-3} \frac{mm^2}{s}}{D} \right]} - 273.15K \quad [1]$$

In order to better understand the effects of sampling the diffusion curve (the effects of the choice of b-values), the fully sampled diffusion data was further analyzed in MATLAB. The fully-sampled diffusion data were fit using a least-squares approach to a mono-exponential decay:

$$S = S_0 e^{-bD} \quad [2]$$

The signal in the absence of diffusion weighting (S_0) and the diffusion coefficient (D) were calculated. Diffusion coefficients were also calculated using subsets of 3 higher b-values ($b = 0, 500, 1000 \text{ s/mm}^2$) and 4 lower b-values ($b = 0, 200, 400, 600 \text{ s/mm}^2$) from the fully sampled diffusion data. The temperature corresponding to each estimate of the diffusion coefficient was calculated using equation 1 and plotted. Full diffusion curves were constructed from the estimated diffusion coefficients and the error between the predicted and the measured diffusion data were plotted. The sum-of-squares (SOS) of the error was calculated to assess the overall fidelity of the fully-sampled and subsampled diffusion curves.

Retrospective case-control study of peri-orbital cellulitis

An IRB-approved retrospective case-control study of periorbital cellulitis was performed. The picture archiving and communication system (PACS) database of a large tertiary care academic medical practice as well as associated community hospitals was searched using Montage 2.0 (Nuance, Burlington, MA) for all MRI studies with peri-orbital cellulitis. Inclusion criteria included a diagnosis of pre or post-septal orbital cellulitis by MRI as well as having both DWI and apparent diffusion coefficient (ADC) maps. Exclusion criteria were bilateral disease, prior surgery, trauma, radiation, stroke, seizure, severe artifacts on DWI and aspherical globe. 6 males met the criteria with average age of 57.3 ± 13.0 years (range 35-70). A circular region-of-interest (ROI) was drawn in the center of the orbit at the level of the optic nerve insertion (see Fig. 1) and the mean ADC value was recorded, taking care to avoid clear artifacts on the corresponding DWI images.

Twice the number of cases of age-matched controls were identified with a normal brain MRI; patients with sinus disease were excluded. Control group included 11 males with average age 56.5 ± 12.5 years (range 34-75 years). Data were obtained from multiple Siemens MRI scanners (Espree (n=9), Avanto (n=2), Aera (n=1), Essenza (n=1), Vario (n=1), Skyra (n=2) and Trio (n=1)) including both 1.5T (five cases and eight controls) and

3.0T (one case and three controls). Some scanners used two b-values of 0 and 1000 s/mm² while some also had an intermediate value of 500 s/mm².

Due to observed slice-to-slice variability in the globe temperature, a multi-slice histogram analysis of eye temperature was performed in MATLAB. The analysis method is summarized in Fig. 2 and is similar to a method used by Sakai et al. to measure temperature in the lateral ventricle¹³. The ADC map generated by the scanner was imported into MATLAB and converted to temperature using equation 1. The inner vitreous boundary of the posterior chamber of the eye was manually segmented, by drawing a large ROI while avoiding the retina and lens. A histogram of the globe temperature on each slice was combined into a single histogram from all slices on which the globe was present and automatically analyzed. The envelope of the histogram was extracted and fit to an 8th order polynomial. The first derivative of the polynomial was calculated. Characteristic temperatures of the globe temperature distribution included $T_{\min}$ (temperature at the maximum of first derivative curve), T_{peak} (maximum of the temperature curve), $T_{\max}$ (temperature at the minimum of the first derivative) and T_{mean} (average of $T_{\min}$ and $T_{\max}$). The temperature histogram of the right eye from orbital cellulitis case 3 was abnormally widened without a discernable peak (not Gaussian), and therefore patient 3 was excluded from the multi-slice analysis.

Prospective study in asymptomatic human volunteers

An IRB-approved prospective study was performed to assess the reproducibility and effect of b-value choice on repeated diffusion measurements on a 1.5T scanner (Siemens Avanto) in 10 healthy volunteers (without history of eye disease or extensive metallic dental fillings). After obtaining informed consent, volunteer oral temperature was measured using a digital thermometer (SureTemp Plus 690, Welch Allyn, Skaneateles Falls, New York) immediately before and after placing the volunteer in the bore of the magnet. In the first volunteer, 24 consecutive routine clinical whole-brain diffusion-weighted echo-planar images were obtained using routine clinical b-values of 0, 500 and 1000s/mm² (acquisition parameters FOV = 220x220mm², matrix = 130x130, slice thickness = 5mm, resolution = 1.7 x 1.7 x 5mm³, FA = 90°, 105 phase-encoding steps, echo train length = 53, TE/TR = 94ms/6700ms, 32 contiguous slices with two averages, bandwidth = 1,200Hz/pixel, acquisition time (T_{acq}) = 120s). Since the ADC of CSF is $\sim 2,800 \times 10^{-6} \text{mm}^2/\text{s}$ ¹⁹, only 6% of signal is present in the b = 1,000s/mm² image (using equation 2). The SNR of eye vitreous in the b = 1,000s/mm² image was 20.0 ± 6.4 in the retrospective study. There was concern that such a large b-value may bias or degrade the ADC calculation of liquids, due to low signal-to-noise ratio at the high b-value data point. An optimal b-value for liquid ADC calculation was presumed to be that which reduced the signal by 2/3 or 67%, which would be b = 400s/mm². Therefore, a second set of “lower” b-values extending to above this presumed optimum b-value was chosen as b = 0, 200, 400, 600 s/mm², in order to accurately sample the diffusion decay curve of a liquid. In the subsequent nine volunteers, two sets of whole-brain diffusion-weighted echo-planar images were each repeated ten times using routine clinical b-values of 0, 500 and 1000 s/mm² (T_{acq} = 120s per acquisition) as well as a series of lower b-values of 0, 200, 400 and 600 s/mm² (T_{acq} = 160s per acquisition). Volunteers were instructed to keep their gaze fixed on a cross on the center of the bore and were allowed to briefly relax their

gaze every three to four scans. Total scan time was just under one hour per subject. The data were analyzed in MATLAB using the histogram method. Temperature maps from each slice were simultaneously displayed and presence of peripheral high temperature (due to eye motion) was visually graded on each acquisition as present or absent by JJD, a trained radiologist. The average eye temperature for each subject was plotted as a function of the percentage of scans with motion and linear regression was performed. The intercept of the regression provided the temperature in the absence of motion while the slope of the fit provided the sensitivity of each technique (3 b-values vs. 4 b-values) to motion.

For statistical analysis paired and unpaired T-tests were performed as well as linear regression in MATLAB. A p-value of 0.05 was used to define statistical significance.

Results

Figure 3 shows the results of the distilled water and human vitreous phantom experiment for each vial. Using the fully sampled diffusion data (16 b-values), the scanner provided diffusion coefficient of vitreous was $2,088 \pm 13 \times 10^{-6} \text{ mm}^2/\text{s}$ and distilled water was $2,128 \pm 12 \times 10^{-6} \text{ mm}^2/\text{s}$. The resultant apparent temperatures (calculated using equation 1) of the phantoms are provided in table 1. The top portion of the table provides apparent temperatures calculated from the scanner-provided ADC values using 3 higher ($b = 0, 500, 1000 \text{ s/mm}^2$), 4 lower ($b = 0, 200, 400, 600$) or full (16 b-value) acquisitions. The errors using fewer b-values compared to the full acquisition are provided. The bottom portion provides the temperature estimates obtained using the diffusion coefficients from manually fitting the fully sampled (16 b-value) DWI data, as well as subsamples using only 3 higher ($b = 0, 500, 1000 \text{ s/mm}^2$) or 4 lower ($b = 0, 200, 400, 600 \text{ s/mm}^2$) b-values. The resulting errors introduced by subsampling the fully-sampled data are also provided. Using the fully-sampled diffusion acquisition (16 b-values), the temperature offset of vitreous relative to water was found to be $-0.74 \pm 0.06^\circ\text{C}$ ($p < 0.001$). Manual fitting of the diffusion data resulted in small ($< 0.5^\circ\text{C}$) but statistically significant reductions in apparent vitreous and water temperatures; however, the vitreous temperature offset was not significantly different. Calculating the diffusion coefficient with 3 larger b-values ($b = 0, 500, 1000 \text{ s/mm}^2$) resulted in smaller temperature offsets (insignificant for vitreous) compared to the four lower b-values ($b = 0, 200, 400, 600 \text{ s/mm}^2$). The lower b-value diffusion acquisitions resulted in significant reductions in both vitreous (-1.0°C) and water (-0.4°C) apparent temperatures. Manually subsampling the fully-sampled diffusion data resulted in similar small but significant errors in temperature estimates, confirming that the higher b-value acquisition provides a better (less biased) estimation of the diffusion coefficients and thus temperature. The sum-of-squares of the residuals of the fit using both sets of b-values were not significantly different from each other but were both significantly higher than the fully sampled diffusion curve. The water bath temperature measured with a thermometer was 21.2°C and raised to 21.7°C over the course of the experiment (average temperature 21.5°C). There was a $+0.65^\circ\text{C}$ temperature offset between the DBT estimated distilled water temperature ($22.15 \pm 0.14^\circ\text{C}$) and the average thermometer measured water bath temperature (21.5°C), which could indicate background gradients/shimming errors, eddy current effects or gradient calibration errors among other possibilities²⁰, some of which can be corrected for by using two scans with opposite diffusion gradient polarity²¹ or bipolar diffusion gradients.

Another possible explanation for the temperature offset is incomplete equilibration of the thermometer and water bath.

Average apparent globe temperatures as well as globe temperature differences measured in patients with and without peri-orbital pathology (from the retrospective study) are summarized in table 2. There was no right-left ocular temperature differences with either single slice ROI or multi-slice histogram techniques in controls. Using the single-slice ROI technique, mean apparent vitreous temperature in controls was $37.4 \pm 2.1^\circ\text{C}$, with average right vs. left vitreous temperature difference of $0.4 \pm 0.6^\circ\text{C}$. In the patients with peri-orbital pathology, there was both a significant drop in the contralateral (opposite the side of peri-orbital pathology) apparent eye temperature to $34.9 \pm 1.5^\circ\text{C}$ as well as a significant difference in globe temperature, higher on the side of pathology by $2.5 \pm 1.2^\circ\text{C}$ ($p=0.02$). Using the multi-slice histogram technique, characteristic temperatures of the vitreous apparent temperature distribution were obtained in controls ($T_{\min} = 34.3 \pm 1.8^\circ\text{C}$, $T_{\text{peak}} = 37.5 \pm 2.2^\circ\text{C}$, $T_{\text{mean}} = 37.6 \pm 2.2^\circ\text{C}$ and $T_{\max} = 40.9 \pm 2.8^\circ\text{C}$). In the patients with peri-orbital pathology, there was again a significant reduction in T_{mean} in the contralateral globe to $35.0 \pm 2.2^\circ\text{C}$ as well as significant reduction in $T_{\min}$ compared to the controls. However, there was no significant difference between the apparent vitreous temperatures in the two eyes.

Individual apparent globe temperatures as well as temperature differences obtained using the single-slice ROI technique are shown in figure 4. Using a temperature difference threshold of 1.0°C , there was 83% sensitivity and 91% specificity for discriminating patients with peri-orbital pathology from the controls.

ROI-based measurements of apparent globe temperature on all the slices traversing the globe in the peri-orbital pathology cases are provided in figure 5. These demonstrate slice-to-slice variability in apparent globe temperature. Note however case 4, where there is sustained elevation of apparent eye temperature ipsilateral (on the same side) to pre-septal cellulitis (soft tissue inflammation in front of the globe) on all slices.

Figure 6 shows results from the multi-slice histogram-based analysis of the retrospective study. In Fig. 6a, note the similarity in bilateral apparent globe temperature measured in controls as well as the variability in absolute apparent temperature from patient to patient. In Fig. 6b and 6c there is higher apparent temperatures on the side of infection (ipsilateral) compared to the opposite (contralateral) eye, which is significant for case 4.

Figure 7 demonstrates eye vitreous apparent temperature histograms for case 4, demonstrating temperature drop opposite to the side of peri-orbital cellulitis and a significant difference in eye temperatures, higher on the side of inflammation.

The results of repeated prospective measurement of vitreous apparent temperature in 10 asymptomatic volunteers using two different sets of b-values are summarized in table 3. There was no significant difference in the temperature of the right and left eyes for 7 out of 8 characteristic temperatures (all except $T_{\min}$ using 3 b-values). There was also no significant difference between T_{peak} and T_{mean} , indicating that the temperature histograms were not significantly skewed. Interestingly, there was a significant increase in all apparent

characteristic temperatures when using 4 b-values compared to 3 b-values to acquire the data (an average of 1.5 °C increase).

Prospective apparent temperature measurement results from individual volunteers are shown in figure 8. Fig. 8a shows 24 consecutive measurements of globe temperature distribution in a healthy volunteer using 3 larger routine clinical b-values ($b = 0, 500, 1000 \text{ s/mm}^2$; $T_{\min} = 32.6 \pm 1.3^\circ\text{C}$, $T_{\text{peak}} = 37.0 \pm 1.2^\circ\text{C}$, $T_{\text{mean}} = 37.1 \pm 1.2^\circ\text{C}$ and $T_{\max} = 41.6 \pm 1.4^\circ\text{C}$). Note the variability in absolute apparent globe temperature as well as temperature difference from scan to scan. Fig. 8b shows the average apparent globe temperature distribution in the ten volunteers acquired using the 4 lower b-values ($b = 0, 200, 400$ and 600 s/mm^2). There was no difference between the T_{peak} and T_{mean} . Apparent T_{peak} varied from 35.6 to 41.5°C. Average apparent globe temperature distribution measured using 3 higher b-values ($b = 0, 500$ and 1000 s/mm^2) are provided in Fig. 8c. There is higher variability in the temperature measurement (error bars) at the higher globe temperatures for both techniques and larger variability (standard deviation) when using four b-values compared to three. Average right and left globe temperatures for both acquisitions are shown in Fig. 8d. Note the similarity in the bilateral apparent globe temperatures despite subject-to-subject variability. For the majority but not all patients, the apparent temperature measured with four b-values was significantly higher. Figs. 8e and 8f plot the average difference in globe temperature (T_{peak}) between the eyes, demonstrating that the average globe temperature difference was less than 1°C using both sets of b-values in 18/19 instances (volunteer 8 using three higher b-values).

Apparent temperature in the vitreous was mapped on a series of 5 axial slices. Representative temperature maps from the 3 central slices are provided in figure 9. Some maps demonstrated more uniform temperature, with an approximate -3.5°C temperature gradient from the retina to the lens (see Fig. 9a, inferior and central slices). Other maps demonstrated higher temperatures, with a large radially symmetric increase toward the periphery of the globe (Fig. 9b, central and superior slices only). Often these patterns would alternate in the same patient from scan to scan and even slice to slice but would be relatively similar in the two eyes. This was felt to represent eye motion, which has a greater speed at the periphery of the globe being mapped as an increase in apparent temperature due to elevations in the diffusion coefficient.

Figure 10 shows the results of the linear regression of average apparent eye temperature (T_{peak}) as a function of the proportion of scans with peripheral temperature elevation, representing motion. Volunteer apparent eye temperature varies linearly with number of scans with visible motion, with high correlation ($R^2 = 0.89$ for three b-values). The intercept of the fit estimates posterior chamber temperature in the absence of motion, which is 33.7°C for data acquired using three larger b-values and 32.9°C for data acquired using four lower b-values. The slope of the fit represents the sensitivity of the acquisitions to motion, and is 50% higher (0.06 vs. 0.04) for four b-values compared to three, which is equivalent to the increase in acquisition time with diffusion sensitization present (number of non-zero diffusion weightings; three for four b-value acquisition and two for three b-value acquisition, i.e. 50% increase).

Discussion

The single-slice ROI measurements in the retrospective study of orbital cellulitis showed significantly decreased apparent eye temperature in the contralateral eye as well as significant temperature differences between the eyes in the cases of peri-orbital pathology. The decreased apparent temperature in the contralateral eye might be explained by either decreased eye motion in the setting of peri-orbital swelling, decreased tear film/blinking or decreased contralateral peri-orbital blood flow in the setting of infection (shunting), with a concomitant increase in temperature on the affected side due to inflammation, which overall produces no significant change in ipsilateral apparent temperature and decreased apparent temperature on the contralateral side. The results clearly demonstrate slice-to-slice apparent temperature variation in the cases (which was greater than that seen in controls), which may be due to motion, effects of heterogeneous magnetic field or partial voluming at the edge of the eye. Using the multi-slice histogram averages out these slice-to-slice variations but may also make small temperature changes from being observed, as they become averaged with the effects of motion over multiple slices. Despite these effects, both the significantly decreased T_{mean} in the contralateral eye in the entire cohort, and a significant decrease in apparent temperature distribution in one of the subjects were observed. The significant decreases in apparent T_{min} in both eyes observed in the cases relative to controls may be related to decreased eye motion in patients with peri-orbital cellulitis, as there were also decreases in T_{peak} (-2.1°C), T_{mean} (-2.2°C) and T_{max} (-1.4°C) as well.

Prospective apparent eye temperature measurements in a cohort of healthy volunteers showed significant scan to scan, volunteer to volunteer as well as b-value variability. However, there was much lower variability in eye temperature differences than absolute apparent temperature measurements. This can be understood by the fact that both eyes move together and therefore absolute offsets are reduced in the difference measurement. By correlating the measured (apparent) eye temperature to the number of scans with the pattern of elevated peripheral temperature due to eye motion, the effect of eye motion on temperature was able to be eliminated in the cohort. Apparent eye vitreous temperature was $33.7 \pm 0.4^{\circ}\text{C}$ using three b-values and $32.9 \pm 1.9^{\circ}\text{C}$ using four b-values (-0.8°C temperature offset with four lower compared to three larger b-values).

Phantom experiments allowed determination of the liquid-specific diffusion coefficient temperature calibration factor. In human vitreous, a $+0.7^{\circ}\text{C}$ calibration factor must be applied to the apparent vitreous temperature calculated using equation 1 (which is derived from data from distilled water) to determine the true vitreous temperature. Phantom experiments also demonstrated that there are significant offsets in temperature based on how the diffusion curve is sampled (choice of b-values), with the resulting errors being larger using the four lower b-values. Therefore, true globe temperature in the absence of motion is estimated to be $33.7 + 0.7$ (vitreous calibration factor) $+ 0.1$ (3 higher b-value offset, from table 1) $= 34.5^{\circ}\text{C}$ using the three higher b-value measurement ($b = 0, 500, 1,000 \text{ s/mm}^2$) and $32.9 + 0.7$ (vitreous calibration factor) $+ 1.0$ (4 lower b-value offset, from table 1) $= 34.6^{\circ}\text{C}$ using the four lower b-values ($b = 0, 200, 400, 600 \text{ s/mm}^2$). The difference in estimated eye vitreous temperature using four smaller compared to three larger b-values was similar in-vivo ($32.9 - 33.7 = -0.8^{\circ}\text{C}$) compared to phantom experiments ($20.8 - 21.7 = -0.9^{\circ}\text{C}$),

indicating that apparent temperature offsets due to sampling the diffusion curve are significant, consistent and predictable. Given that eye surface temperature is reported to be 32-35°C and core body temperature was measured to be 36.7°C in this cohort, mean vitreous temperature would be expected to be approximately 34.3-35.9°C (assuming the average of eye surface and core body temperature). Therefore, the estimated vitreous temperatures using diffusion-based thermometry fall within the bounds of expected vitreous temperature. Since the volunteers were asked to keep gazed fixed on a cross on the bore for prolonged periods, their surface eye temperature may be on the lower side of the expected range, due to less blinking than typical. Another possibility is that the eye surface might be slightly on the dryer side due to the use of an in-bore fan, although this was not monitored in this experiment.

One potential limitation of this study is that the vitreous temperature calibration factor was determined at room temperature (21.5°C) rather than body temperature (37°C) due to limitations of the experiment. Prior work by Kozac et al. showed that the CSF calibration factor was independent of temperature over the tested temperature range 32-42°C. It is therefore assumed that the calibration factor is temperature-independent. However, if the calibration factor is not constant, the vitreous would likely become less viscous (and more water-like) at higher temperature; therefore, the calibration factor provided is an upper bound. Although temperature-dependent changes in the vitreous calibration offset might affect the absolute temperature measurement slightly, eye temperature differences are not affected by this calibration factor.

The up to 7.8°C variability (see volunteer number 5) in apparent globe temperature observed, the reduced variability in eye temperature difference, the scan to scan as well as slice-to slice variability, the larger standard deviation of measurement in volunteers with higher average apparent eye temperature, the higher apparent temperature measured with longer scan time (four vs. three b-value acquisitions), the pattern of increased apparent temperature at the periphery of the globe and the ability to regress out the effect all strongly point to motion as having a large effect on apparent temperature measurement in the eye. The absolute apparent individual globe temperatures variations (33.8-41.6°C) caused falsely elevated cohort-wide apparent temperature of +2.4°C when using three b-values (36.1°C compared to 33.7°C) and 4.7°C increase in apparent temperature when using four b-values (37.6°C compared to 32.9°C). Both the fluctuations and elevations in individual apparent globe temperatures as well as the overall increase in cohort-wide apparent temperatures (before correction for motion) are similar to those seen in measurements of core brain temperature measured with diffusion-based thermometry compared to core body temperature. Therefore, the results in the eye emphasize the importance of accounting for CSF motion when making and drawing conclusions from diffusion-based thermometry core brain temperature measurements.

This study suggests that future DBT MRI of the eye should be optimized by minimizing scan time. Instead of encoding three to six diffusion directions as is typically performed for brain imaging, only one direction is needed as diffusion is isotropic in liquids. Another way to accelerate the acquisition may be to reduce the number of b-values sampled from three to two, although this can come at the expense of ADC accuracy²². Schmidt et al. have shown

two b-values of 0 and 600s/mm² work well overall for body tissues; however, larger b-values (>1000 s/mm²) were noted to be needed for tissues with higher diffusivities (such as water)²². Our phantom results showed that three higher b-values of 0, 500 and 1000s/mm² are quite accurate; therefore, one possibility is to use two b-values of 0 and 1000 s/mm². By using a single diffusion direction, a single average and only two b-values, the single diffusion sensitized acquisition can be performed in less than a second, with the motion insensitive b=0 scan performed 10s (one repetition time (TR)) later. The faster acquisition time should be sufficient to obtain temperature maps with much reduced motion sensitivity or could even be used to map motion or flow in different liquids.

Eye temperature is an interesting physiological parameter as it reflects the combination of heat production by metabolism as well as heat delivery by vasculature and radiative heat loss from the cornea, influenced by the tear film. Eye temperature as a lumped parameter may therefore be found to be important in assessment of prevalent vasculature diseases of the retina (such as diabetic retinopathy²³ with vascular proliferation and macular degeneration with vascular loss), diseases that affect the lacrimal gland and tear film (Sjögren's disease and sarcoidosis), the lacrimal duct or retro-orbital processes such as orbital pseudotumor. Mapping temperature in the contiguous vitreous may allow for functional evaluation of the retina to detect retinal disease earlier, evaluate peripheral retinal lesions not observable with slit lamp examination²⁴⁻²⁷ or monitor treatment²⁸ of the retina once morphological changes have already occurred. Being able to noninvasively measure the temperature of the posterior chamber of the eye may help in further understanding or refining temperatures measured on the surface of the eye.

Conclusion

This study shows that noninvasive measurement of temperature in the posterior chamber of the eye is possible with diffusion-based thermometry MRI. The liquid-specific vitreous temperature offset factor is determined to be +0.7°C and should be used to correct apparent temperatures calculated by DBT MRI in vitreous. Significant (up to 7.8°C) variability in individual apparent eye temperature measurements and 2.4-4.7°C elevations in population mean apparent temperatures can be caused by eye motion. By regressing the effect of motion, average eye vitreous temperature was measured to be 34.5-34.6°C. There is lower variability in eye temperature differences than absolute apparent temperature and using 10 scans, eye temperature differences as small as 0.6°C can be presumed to be pathological. The large variability in individual apparent temperature measurements as well as higher than expected average apparent temperature are similar to those previously reported in core brain temperature measurements using diffusion-based thermometry, suggesting that CSF motion may confound those measurements. Choice of b-value affects the apparent temperature, with a routine clinical diffusion acquisition with 3 larger b-values (b = 0, 500 and 1000 s/mm²) producing a small -0.2°C offset. In subsequent studies using DBT MRI, scan time should be limited relative to the period of motion in the liquid being studied, in part by using a single diffusion direction.

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Fig. 1. ROI-based globe temperature measurement. (a) T2-weighted image showing right pre-septal cellulitis. (b) FLAIR image, (c) $b=0$ diffusion image and (d) ADC. Circular ROIs were drawn in each globe at the level of the lens or optic nerve insertion on the ADC map.

Fig. 2.

Multi-slice histogram-based globe temperature measurement. (a) ADC map is converted to temperature map and the globes are manually segmented on each slice. (b) Histograms from each of five consecutive slices on which the globe is present. Data from the individual slices were combined into a single histogram (c). (d) The envelope of the histogram (solid line) was automatically extracted and fit to an eighth order polynomial (dashed line). The maximum (x) and minimum (o) of the first derivative of the polynomial (dotted line) was used to automatically calculate the minimum ($T_{\min}$) and maximum ($T_{\max}$) of the globe temperature distribution. The peak of the distribution (T_{peak}) as well as the average of $T_{\min}$ and $T_{\max}$ was obtained to calculate T_{mean} .

Fig. 3.

Distilled water and human vitreous phantom results. Scanner reported (a) ADC values using acquisitions with three high b-values (3b: 0, 500, 1000 s/mm^2), four low b-values (4b: 0, 200, 400, 600 s/mm^2) and 16 b-values (i.e. full, $b=1:100:1500\text{s}/\text{mm}^2$). (b) the corresponding apparent temperatures measured in vials containing distilled water and human vitreous using equation 1. (c) Temperatures calculated using ADC value obtained from manual fitting of diffusion data using both full and subsampled diffusion data. (d) Semi-log plot of diffusion signal and the three fits for the vitreous vial. (e) Residuals of the manual fits as function of b-value. (f) Total sum-of-squares (SOS) residuals of each fit for all vials. Three high b-values ($b = 0, 500, 1000 \text{ s}/\text{mm}^2$, i.e. 051) and four low b-values ($b = 0, 200, 400, 600 \text{ s}/\text{mm}^2$, i.e. 0246).

Fig. 4. Retrospective measurement of apparent globe temperature using the single-slice ROI method in 6 patients with per-orbital pathology (cases) and 11 age-matched controls. Individual globe temperature in (a) controls, (b) cases, average globe temperature in (c) controls, (d) cases as well as (e) individual and (f) average globe temperature differences.

Fig. 5.

ROI-based apparent temperature measurements on all slices of each globe in patients with peri-orbital eye pathology. The eye on the side of the pathology (ipsilateral) is denoted in red.

Fig. 6. Histogram-based multi-slice apparent temperature measurements in patients with eye pathology as well as age-matched controls. Globe apparent temperature distribution characteristic temperatures in (a) controls and (b) in cases with eye pathology. Globe temperature distribution differences (ipsilateral-contralateral eye) in cases is plotted in (c).

Fig. 7. Globe apparent temperature distributions in patient 4, (a) ipsilateral and (b) contralateral to peri-orbital cellulitis. Note the higher globe temperature on the side of (ipsilateral to) infection.

Fig. 8.

Prospective apparent globe temperature measurements in 10 volunteers. (a) Characteristic globe temperatures in 24 consecutive measurements using three larger b-values. Globe temperature measured 10 times using (b) four lower b-values and (c) three higher b-values in 10 volunteers. (d) Average T_{peak} comparison for both eyes using the two techniques. Average right-left globe T_{peak} difference using (e) four lower b-values and (f) three larger b-values.

Fig. 9.

In vivo apparent eye temperature maps on the three central-most eye slices (2-inferior, 3-central and 4-superior) in the same volunteer in two consecutive acquisitions (R = right eye, L = left eye). (a) All slices without peripheral increased temperature, i.e. no motion and (b) with apparent temperature elevation at the periphery of the globe on the central and superior slice. This variability is felt to be due to eye motion. Note the gradual decrease in globe temperature from the retina to lens in (a), inferior and central slices.

Fig. 10.

Mean apparent globe temperature (T_{peak}) plotted as a function of percent of scans with visible motion in studies acquired using (a) three b-values and (b) four b-values. Results of linear regression of temperature as a function of motion are provided in the inlays.

Table 1.

Apparent temperatures of vitreous and water phantoms, used to calculate the vitreous offset (calibration) temperature and the offsets due to choice of b-value (from data plotted in figure 3).

b-values	Vitreous T_a (°C)	Water T_a (°C)	$T_{\text{offset,vit}}$ ($T_{\text{vit}} - T_{\text{water}}$) (°C)	p-value
From scanner-provided ADC				
Full (16 b-values)	21.79 ± 0.05	22.53 ± 0.22	$-0.74 \pm 0.06^{**}$	1.9E-4
3 b-values	21.70 ± 0.36	22.30 ± 0.25	$-0.60 \pm 0.38^{**}$	4.2E-5
Error (3b estimate-full)	-0.09 (p=0.67)	-0.24^{**} (p=0.008)	0.14 (p=0.55)	
4 b-values	20.82 ± 0.25	22.09 ± 0.15	$-1.27 \pm 0.30^{**}$	4.0E-11
Error (4b estimate-full)	-0.97^{**} (p=6.5E-4)	-0.44^{**} (p=2.1E-4)	-0.53^* (p=0.03)	
From manual fit ADC				
Full (16b) manual fit	21.32 ± 0.03	22.15 ± 0.14	$-0.83 \pm 0.03^{**}$	4.3E-4
Scanner offset (scanner 16b-full manual fit)	0.48^{**} (p=1.2E-4)	0.39^{**} (p=0.004)	0.2 (p=0.09)	
3b manual fit	21.067 ± 0.007	22.01 ± 0.03	$-0.94 \pm 0.03^{**}$	2.4E-4
Error (syn3b – full manual fit)	$-0.25 \pm 0.03^{**}$ (p=0.004)	$-0.14 \pm 0.03^*$ (p=0.01)	-0.11^* (p=0.02)	
4b manual fit	20.63 ± 0.04	21.75 ± 0.02	$-1.12 \pm 0.06^{**}$	9.0E-4
Error (syn4b-full manual fit)	$-0.69 \pm 0.06^{**}$ (p=0.002)	$-0.40 \pm 0.05^{**}$ (p=0.005)	$-0.30 \pm 0.09^*$ (p=0.03)	

* p<0.05

** p<0.01, T_a =apparent temperature

Table 2.

Retrospective apparent eye temperature measurement results.

	ROI (SS)	Multi-Slice Histogram			
		T _{min}	T _{peak}	T _{mean}	T _{max}
Controls (n=11)					
T _R (°C)	37.6±2.0	34.3±2.0	37.7±2.3	37.8±2.5	41.2±3.2
T _L (°C)	37.3±2.0	34.2±1.7	37.4±1.9	37.4±2.0	40.5±2.5
T _{R-L} (°C)	0.38±0.60	0.1±0.9	0.3±0.9	0.4±1.0	0.6±1.4
p-value (T _{R-L})	0.07	0.67	0.27	0.25	0.19
T _c (°C)	37.4±2.1	34.3±1.8	37.5±2.2	37.6±2.2	40.9±2.8
T _{thresh}	41.6	37.9	41.9	42.0	46.4
T _{thresh}	1.6	1.9	2.1	2.4	3.4
Cases	n=6	n=5			
T _{ipsi} (°C)	37.3±2.5 (p=0.95)	31.6±1.5 ** (p=0.007)	35.5±1.1 (p=0.06)	35.8±1.4 (p=0.10)	39.9±3.2 (p=0.53)
T _{contra} (°C)	34.9±1.5 * (p=0.02)	30.8±1.2 ** (p<0.001)	35.8±3.6 (p=0.18)	35.0±2.2 * (p=0.03)	39.2±3.7 (p=0.29)
T _{I-C} (°C)	2.5±1.2 ** (p<0.001)	0.79±2.3 (p=0.46)	-0.3±3.1 (p=0.57)	0.8±1.5 (p=0.60)	0.72±1.1 (p=0.92)
p-value (T _{I-C})	0.02 *	0.53	0.86	0.38	0.25

T_C (combined temperature) = T_R+T_L/2.*
p<0.05**
p< 0.01T_{thresh} (abnormal temperature threshold) = average normal temperature + 2*standard deviation of normal temperatureT_{thresh} (abnormal ocular temperature difference threshold) = mean ocular temperature difference + 2*standard deviation of normal ocular temperature difference

Table 3.

Globe vitreous histogram characteristic apparent temperature results in 10 asymptomatic volunteers (n=10 measurements/volunteer).

		$T_{\min}$	T_{peak}	T_{mean}	T_{max}
3 b-values (b = 0, 500, 1000s/mm ²)	T_a (°C)	32.7 ± 1.0	36.1 ± 1.7	36.1 ± 1.7	39.5 ± 2.4
	$T_{R,L}$ (°C) (p-value)	0.4 ± 0.5 (0.04 [*])	0.3 ± 0.5 (0.09)	0.3 ± 0.5 (0.11)	0.2 ± 0.7 (0.63)
	T_{Thresh} (°C)	34.7	39.5	39.5	44.3
	T_{Thresh} (°C)	1.4	1.3	1.3	1.6
4 b-values (b = 0, 200, 400, 600 s/mm ²)	T_a (°C)	34.3 ± 1.4	37.6 ± 2.0	37.6 ± 2.0	40.8 ± 2.8
	$T_{R,L}$ (°C) (p-value)	0.2 ± 0.9 (0.49)	0.0 ± 0.4 (0.67)	0.1 ± 0.5 (0.63)	0.0 ± 0.3 (0.93)
	T_{Thresh} (°C)	37.1	41.6	41.6	46.4
	T_{Thresh} (°C)	2.0	0.8	1.1	0.6
	T_{4b-3b} (°C) (p-value)	1.7 (0.003 ^{**})	1.5 (0.02 [*])	1.5 (0.01 [*])	1.3 (0.03 [*])

*
p<0.05

**
p< 0.01, T_a = apparent temperature

T_{thresh} (abnormal temperature threshold) = average normal apparent temperature + 2*standard deviation of normal apparent temperature

T_{thresh} (abnormal ocular temperature difference threshold) = mean ocular temperature difference + 2*standard deviation of normal ocular temperature difference

Volunteer oral $T_{\text{pre}} = 36.7 \pm 0.1^\circ\text{C}$, $T_{\text{post}} = 36.8 \pm 0.1^\circ\text{C}$, $T_{\text{oral}} = 0.1^\circ\text{C}$,* (p=0.01)

No difference between T_{peak} and T_{mean} using 4b-values (p=0.81) or 3b-values (p=0.68)