Magic Angle Enhanced MR Microscopy of Fibrous Structures in Normotensive and Hypertensive Eyes using T2, T2* and T1rho MRI

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Target Audience: Researchers and clinicians with interest in basic and translational applications of magic-angle enhanced MRI to study ocular microstructures and pathophysiology in eye diseases such as ocular hypertension and glaucoma.

Purpose: Sclera is a connective tissue in the outer coat of the eye and is dense, fibrous and viscoelastic. It contains ~90% collagen by weight and its fibrils are organized in a lamellar manner. The sclera acts as the supporting wall of the eye, and the extracellular matrix composition and biomechanical properties may interact with the dynamic ocular environment such as changing intraocular pressures (IOP) [1]. Recent studies suggest an important role of the sclera in eye diseases such as glaucoma and myopia [1, 2, 3]. In particular, ocular hypertension in glaucoma may alter the mechanical behaviors of the sclera, which in turn may damage the retinal and optic nerve fibers nearby and result in vision loss [4]. However, the relative contribution of sclera to the pathogenesis of glaucoma remains incompletely understood. To date, there are limited methods to assess the effects of ocular hypertension on microstructural changes in scleral fibers non-invasively. Although the sclera appears dark in conventional MRI sequences due to short T2/T2*, the magic-angle effect can enhance highly-ordered, collagen-rich tissues with short intrinsic T2/T2* and has been demonstrated extensively in clinical MRI studies of fibrous structures in tendons, ligaments and cartilages [5, 6]. A recent report also demonstrated that magic-angle effect in MRI can be used to improve signal-to-noise and contrast-to-noise ratios when monitoring and differentiating between loaded and unloaded tendons [5]. In this study, we evaluated the feasibility and sensitivity of high-field magic-angle enhanced MRI using gradient-echo (GE), spin-echo (SE) and spin-locking (SL) sequences to detect magnetic tissue property changes on the sclera with and without undergoing ocular hypertensive stress.

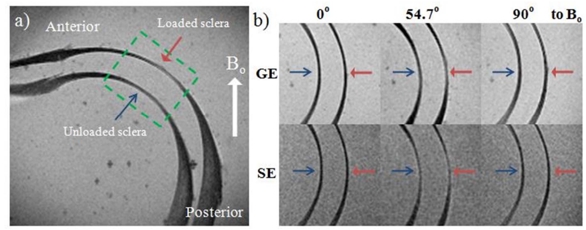
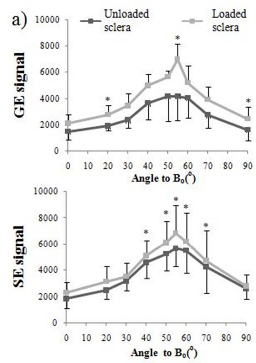
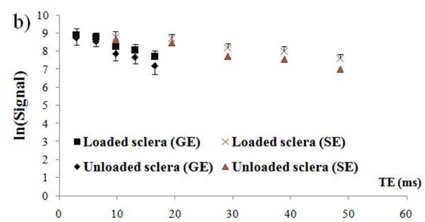


Figure 1. (a) Gradient-echo (GE) image (TE=9.71ms) showing the unloaded (bottom left; blue open arrow) and the loaded (top right; red closed arrow) sclera at magic angle (54.7° to B_o); (b) Zoomed views of green dashed box in panel a using GE and spin-echo (SE) imaging at 0°, 54.7° and 90° to B_o.

Methods: Seven pairs of ovine eyes were extracted and fixed for at least 12 hours in 10% formalin (in PBS) within 24 hours of death. One eye of each ovine was loaded to mimic ocular hypertension in glaucoma and the contralateral eye remained unloaded. For loaded eyes, IOP was set using a gravity perfusion system, cannulated through the anterior chamber for a pressure of 50 mmHg. Unloaded eyes were cannulated with a needle and placed in a reservoir of fixative. The eyes were then washed in PBS and dissected using razors and surgical scissors for anterior sclera. Contralateral eyes (i.e. from the same sheep) were paired up and scanned using a 9.4-Tesla/31-cm Varian/Agilent scanner. GE and SE scans were performed using a custom-made 25mm transmit-receive surface coil. SL scans were performed using a 32mm transmit-receive volume coil. The loaded and unloaded sclera pairs were positioned at different angular orientations from 0° to 90° relative to the static magic field (B_o) inside the scanner using a custom-designed automated rotating positioner [7]. MRI parameters were as follows: (i) GE sequence: TR/TE = 1000/2.93ms; echo space time (EST) = 3.39ms; number of echoes (NE) = 5; (ii) SE sequence: TR/TE = 1000/9.71ms; EST = 9.71ms; NE = 5; (iii) Fast-spin-echo sequence with SL: TR/TE = 1000/9.71ms; on-resonance SL frequency = 500Hz, length of spin lock pulse (TSL) = 10, 20, 30, 40 and 50ms. SL experiment was performed only at 0° and 54.7° (magic angle) relative to B_o.





c)

TE(ms)	2.93	6.32	9.71	13.1	16.49
GE	p<0.05	p<0.01	p<0.05	p<0.05	p<0.05
TE(ms)	9.71	19.42	29.13	38.84	48.55
SE	p<0.05	p<0.01	p<0.01	p<0.05	p<0.05

Figure 2. (a) Plots of gradient-echo (GE) and spin-echo (SE) signals (both at TE=9.71ms) in unloaded and loaded sclera at 9 angles from 0° to 90° to B_o. (two-tailed paired t-tests between loaded and unloaded sclera: *$p<0.05$); (b) GE and SE signal decays (in natural log scale) of unloaded and loaded sclera at different TE; (c) Results of two-tailed paired t-tests of GE and SE signals between contralateral loaded and unloaded sclera for different TE at magic angle(54.7°).

Results: Figure 1 qualitatively shows the magic-angle enhacement in GE and SE images at 54.7° to B_o relative to 0° and 90° in both loaded (red closed arrows) and unloaded (blue open arrows) sclera. Quantitatively, the GE and SE signal intensities were generally higher in loaded sclera than unloaded sclera (Figure 2), with larger differences near the magic angle at 54.7° to B_o. Figure 3 shows the % signal difference in loaded sclera relative to unloaded sclera at magic angle using GE, SE and SL sequences. Larger GE and SE signal differences between loaded and unloaded sclera were observed with increasing TE. At the same TE at 9.71ms, GE sequence appears to give better contrast between loaded and unloaded sclera than SE sequence ($p<0.05$). Magic angle enhancement was also observed in SL signals relative to 0° for each TSL (not shown). However, a trend of magic-angle effect on T1rho was observed only in loaded sclera ($p=0.09$) at TSL=0 - 10ms and was not apparent in unloaded sclera ($p>0.1$) under the same MRI settings. The % difference in SL signals between loaded and unloaded sclera ranged from 20% to 30% across TSL.

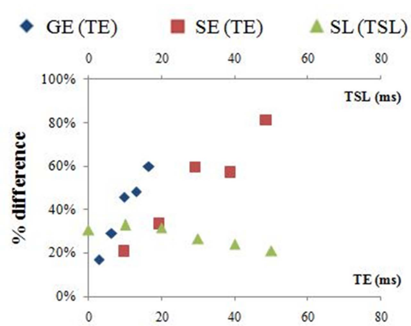


Figure 3. % difference of GE, SE and SL signals in loaded sclera relative to unloaded sclera at magic angle (54.7° to B_o). GE and SE % signal differences were plotted against TE (primary x-axis) and SL % signal difference was plotted against TSL (secondary x-axis).

Discussion and Conclusion: Our results demonstrated that the magic-angle effect enhanced the visibility of scleral tissues in the eye and may help differentiate between unloaded and loaded sclera under ocular hypertensive stress. The GE and SE signal decays in Figure 2 reflect T2 and T2* lengthening in loaded sclera in the eye similar to a previous report on loaded body tendon at the same magnetic field strength [5]. Such T2/T2* lengthening might be due to microscopic realignment of the collagen fibers when the scleral tissue experienced the tensile stress, separating fiber protons further apart and diminishing the spin-dephasing of neighboring protons. Based on the results in Figure 3, stronger image contrasts between loaded and unloaded sclera may be obtained with higher TE at magic angle, or with GE sequence over SE sequence at similar TE provided that image signal-to-noise is sufficient. Recent studies suggest that T2/T2* relaxation may be more sensitive to collagen depletion whereas T1rho may be more sensitive to depletion of other structural proteins such as proteoglycans [8]. Further studies are currently ongoing to elucidate the magic angle effect on T1rho in loaded and unloaded sclera. If confirmed, it may provide additional information from different biological sources of microstructural changes in scleral fibers under ocular hypertension collateral to T2 and T2* signals.

In conclusion, magic-angle enhanced MRI is a feasible methodology to detect and enhance changes in magnetic tissue properties in the sclera under both normotensive and hypertensive conditions in the eye. Such technique may open up new areas on non-invasive assessments of biomechanical and biochemical properties of scleral fiber distribution, deformation and remodeling in the eye, and may potentiate future studies on longitudinal monitoring of functional microstructures in diseases involving the corneoscleral shell such as glaucoma, myopia and aging.

References: [1] Rada J.A., Exp Eye Res, 2006; [2] Pijanka J.K., IOVS, 2012; [3] Sigal I. A., IOVS 2005; [4] Morrison J.C., J Glaucoma 2005; [5] Mountain K.M., Mag Res Med, 2011; [6] Bolbos R.I, Osteo Cart., 2009; [7] Mershon C., ISMRM, 2013; [8] Du J., Mag Res Med, 2013.