Morphometry of the Retrobulbar Human Optic Nerve: Comparison between Conventional Sonography and Ultrafast Magnetic Resonance Sequences

Wolf A. Lagrèze,1 Alexander Lazzaro,1 Matthias Weigel,2 Hans-Christian Hansen,3 Jürgen Hennig,2 and Thorsten A. Bley2

PURPOSE. To compare different methods for quantification of optic nerve and nerve sheath diameter. To apply a novel magnetic resonance protocol using half-Fourier acquired single-shot turbo spin-echo (HASTE) sequences to analyze optic nerve dimensions.

METHODS. Measurements were taken in right eyes of 33 subjects whose median age was 25 years. A-scan ultrasonography was repeated three times in straight gaze. B-scan ultrasonography was repeated three times in straight gaze and abduction. HASTE sequences were applied in straight gaze, analyzed twice by two different radiologists, and completely repeated in a subset of 10 subjects; 95% confidence intervals and coefficients of variation were calculated.

RESULTS. HASTE sequences yielded high contrast between cerebrospinal fluid and optic nerve parenchyma. Acquisition time for each sequence was 1.5 seconds per slice. Optic nerve diameters decreased from 3.23 mm at 5 mm to 2.67 mm at 15 mm behind the eye. Sheath diameters decreased from 5.72 mm to 3.98 mm. A- and B-scan ultrasonography yielded significantly smaller diameters. For HASTE sequences, the coefficients of variation ranged from 2% to 7% and were significantly smaller than those obtained with ultrasonographic measurements (9%–13%).

CONCLUSIONS. The precision of magnetic resonance imaging exceeds that of ultrasonographic methods for determining optic nerve and nerve sheath diameters. HASTE sequences appear particularly appropriate for investigating the retrobulbar optic nerve complex and may be useful in future studies quantifying axonal loss within the optic nerve. (Invest Ophtalmol Vis Sci. 2007;48:1913–1917) DOI:10.1167/iovs.06-0175

Since the introduction of A-scan ultrasonography for measuring optic nerve thickness in 1977,1–3 the diameter of the retrobulbar optic nerve and its sheath has been widely used as a diagnostic parameter in various diseases such as anterior ischemic optic neuropathy, optic neuritis,4 and elevated intracranial pressure.5–9 The diameter and cross-sectional area of the optic nerve have also been shown to correlate with axonal degeneration such as in glaucoma,10–13 demyelination after optic neuritis or multiple sclerosis,14–17 and hereditary optic neuropathies.18,19 Hence, precise documentation of acute swelling or chronic axonal loss in the retrobulbar optic nerve may serve as a useful quantitative diagnostic parameter. It may also serve as a means for future evaluation of neuroprotective strategies.16

To correctly interpret optic nerve measurements, precise normative data are necessary. Accordingly, the retrobulbar optic nerve and its sheath have often been investigated in healthy subjects using methods such as A-scan ultrasonography,20–23 B-scan ultrasonography,6,8,9,24 three-dimensional ultrasonography,25,26 computed tomography,27–29 and magnetic resonance imaging (MRI).30–32 However, these data vary tremendously. Factors contributing to this variation are personal experience, interobserver variability, test–retest variability, and eye movement artifacts occurring during long acquisition times of up to several minutes in certain MRI protocols.5,12,14,15,18,19,30,32–34

The purpose of this study was to measure optic nerve diameters in healthy subjects and to compare our data with those in the literature, motivated by the aforementioned variability of anatomic data presented thus far. We chose A- and B-scan ultrasonography and MRI. In the latter, we applied modified ultrafast half-Fourier acquired single-shot turbo spin-echo sequences (HASTE) published recently by our group.35 This type of T2-weighted spin-echo sequence provides high contrast between optic nerve parenchyma and cerebrospinal fluid and is sensitive enough to show a statistically significant thinning of the optic nerve in 30° abduction compared with straight gaze. Because of the very short acquisition times, this new MRI protocol may be less sensitive to eye motion artifacts, possibly blurring the image.35

METHODS

This study was performed according to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects after explanation of the nature and possible consequences of the study, which had been approved by our institutional Ethics Committee. Thirty-three healthy subjects whose median age was 25 years (range, 22–67 years) were included. Only right eyes were studied. Exclusion criteria were refraction anomalies exceeding 5 D, any optic nerve disease, elevated intraocular pressure, any orbital disease, intracranial abnormalities, and metallic implants or foreign bodies.

Sonographic measurements were taken by an experienced and specifically trained technician with the subjects in supine position and with the use of state-of-the-art equipment. We intended to cut the nerve approximately 5 mm behind the eye. For A-scan ultrasonography (Ophthascan S mini A; Biophysics Medical, Clermont-Ferront, France),
the probe was placed onto the temporal sclera with the subject looking straight ahead after application of topical anesthesia. The device was set to 80 dB in the orbit mode, and quantification was performed off-line. Diameters of the optic nerve and its sheath were documented three times. For B-scan ultrasonography (Ultrscan Digital B 4000; Alcon, Irvine, CA), subjects were instructed to close their right eyes and to keep their left eyes either looking straight ahead or fixating a target 30° to the right to induce right eye abduction. The probe was placed on the eyelid covered with sonographic coupling gel. Diameters of the optic nerve and its sheath were again documented off-line three times at 80 dB.

On the same day, subjects were investigated with a 3T magnetic resonance scanner (Magnetom Trio; Siemens, Erlangen, Germany) that uses an eight-channel phased-array head coil. Subjects were instructed to fixate on a target inside the scanner, with the right eye in straight gaze. As published previously in more detail, an ultrafast $T_2$-weighted HASTE sequence was applied with the following characteristics: half-Fourier acquisition in single-shot turbo spin-echo (HASTE); TR, 1500 ms; TE, 146 ms; number of excitations 1; bandwidth, 195 Hz/pixel; fast sync pulses (duration, 1 ms); FOV, $23 \times 18$ cm$^2$; matrix, $512 \times 367$; nominal spatial resolution, $0.45 \times 0.49$ mm$^2$; slice thickness, 3 mm. The images were then interpolated to a matrix size of $2048 \times 1468$, leading to a pixel size of $0.11 \times 0.12$ mm$^2$. In these HASTE images, cerebrospinal fluid (CSF) yielded a high, white signal and the optic nerve a low, dark signal. Voxels containing CSF and optic nerve or CSF and adjacent tissue showed a defined gray shade proportional to their fractional contents of CSF and tissue (partial volume effect of MRI). Hence, quantification of the optic nerve and CSF sheath diameter was facilitated by the high-contrast differences in the nerve compared with its surroundings. As a result, measurement accuracy was then limited to the reproducibility of the region of interest (ROI). Three slices perpendicular to the optic nerve were acquired in each subject. They were placed at 5, 10, and 15 mm behind the globe. The exact imaging time was documented for each image.

Outer diameters of the optic nerve and its sheath were determined by a board-certified radiologist on a radiologic work station (J-Vision; Tiani, Vienna, Austria) by placement of circles around their outlines so that the best possible fit was achieved. These measurements were repeated in a blinded fashion by a second radiologist. In addition, a subset of 10 subjects was reevaluated 3 months later in a second round in a blinded fashion by a second radiologist. In addition, a subset of 10 subjects was reevaluated 3 months later in a second round and 4.09 mm, respectively. Mean diameters of the optic nerve and its sheath were obtained in the B-scan mode. In straight gaze, the optic nerve diameters were 2.67 mm at a position 5 mm behind the eye and dropped to 2.67 mm at a position 15 mm behind the eye. The same applied to its sheath, with diameters declining from 5.72 to 3.98 mm, respectively. Compared with MRI readings, ultrasonography consistently yielded smaller diameters. In the A-scan mode, diameters were 2.31 mm for the retrobulbar optic nerve and 4.08 mm for the sheath. Slightly larger diameters of the optic nerve and its sheath were obtained in the B-scan mode. In straight gaze, the optic nerve diameters were 2.60 mm and 4.16 mm for the sheath, and in abduction they were 2.60 mm and 4.09 mm, respectively. Mean diameters of the optic nerve and sheath obtained with all three methods (A-scan, B-scan, MRI) differed statistically significant ($P < 0.05$) and were normally distributed. In comparisons of straight gaze and abduction, the nerve and sheath diameters obtained with B-scan ultrasonography did not differ significantly.
TABLE 1. Diameters of the Optic Nerve and Its Sheath Measured with Different Methods at Various Positions behind the Eye

<table>
<thead>
<tr>
<th>Method</th>
<th>Structure</th>
<th>Mean (mm)</th>
<th>CI95 (mm)</th>
<th>Mean</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Nerve</td>
<td>3.23</td>
<td>3.14-3.32</td>
<td>4.89*</td>
<td>4.18†</td>
</tr>
<tr>
<td></td>
<td>middle</td>
<td>2.94</td>
<td>2.82-3.05</td>
<td>4.91*</td>
<td>4.56‡</td>
</tr>
<tr>
<td></td>
<td>posterior</td>
<td>2.67</td>
<td>2.57-2.77</td>
<td>2.67*</td>
<td>6.54‡</td>
</tr>
<tr>
<td>Sheath</td>
<td>anterior</td>
<td>5.72</td>
<td>5.51-5.93</td>
<td>2.59*</td>
<td>2.91†</td>
</tr>
<tr>
<td></td>
<td>middle</td>
<td>4.53</td>
<td>4.34-4.72</td>
<td>2.42*</td>
<td>4.00‡</td>
</tr>
<tr>
<td></td>
<td>posterior</td>
<td>3.98</td>
<td>3.80-4.16</td>
<td>6.37*</td>
<td>6.72‡</td>
</tr>
<tr>
<td>A-scan</td>
<td>Nerve</td>
<td>2.51</td>
<td>2.17-2.44</td>
<td>12.78*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sheath</td>
<td>4.08</td>
<td>3.85-4.33</td>
<td>9.45</td>
<td></td>
</tr>
<tr>
<td>B-scan</td>
<td>straight gaze</td>
<td>2.60</td>
<td>2.46-2.74</td>
<td>8.36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sheath</td>
<td>4.16</td>
<td>3.95-4.37</td>
<td>7.57</td>
<td></td>
</tr>
<tr>
<td>B-scan</td>
<td>abduction</td>
<td>2.60</td>
<td>2.43-2.77</td>
<td>7.98</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sheath</td>
<td>4.09</td>
<td>3.89-4.30</td>
<td>6.87</td>
<td></td>
</tr>
</tbody>
</table>

CI95, 95% confidence interval; CV, coefficient of variation.

*Repetition of diameter measurements from the same MR images by a second radiologist.
†Repetition of the entire MRI procedure.

When a second radiologist remeasured the optic nerve diameters in the original scans, the CVs among readers ranged between 4% anteriorly and 7% posteriorly. For the sheath they varied between 5% and 7%, respectively. When the whole MRI procedure was repeated in a subset of subjects, the CVs were similar and ranged between 5% and 6% for the nerve and between 2% and 6% for the sheath. A-scan ultrasonography yielded CVs of 13% for the nerve and 9% for its sheath. B-scan ultrasonography was slightly more precise with CVs of approximately 8% for both the nerve and the sheath. CVs for A-scan and B-scan ultrasonography did not differ significantly (P > 0.05). However, CVs for MRI were significantly lower than those for the ultrasonographic methods (P < 0.001).

**DISCUSSION**

Apart from our recent pilot study, this is the first systematic application of HASTE sequences to investigate the dimensions of the orbital optic nerve. HASTE clearly demonstrated a narrowing of the nerve and its sheath as they approached the orbital apex. In addition to the high contrast between CSF and nerve parenchyma, the main advantage of HASTE sequences was their unprecedented short acquisition time of 1.5 seconds, which reduced blur created by uncontrolled eye movements. Small coefficients of variation indicated high precision and reproducibility.

Our data confirm most previous MRI measurements of the optic nerve and its sheath. We found almost exactly the same mean diameters as Lam et al., who applied fat-suppressed T2-weighted fast-spin-echo MR sequences in coronal slice orientation at 1.5 T. However, these sequences did not attain the spatial resolution necessary to detect the thinning of the nerve induced by lateral gaze. For technical reasons, their acquisition times were much longer (2-3 minutes). Ozgen et al. measured the width of only the optic nerve sheath in the middle portion of the optic nerve and found a mean diameter of 4.4 mm, concurring with our data. They applied T1-weighted imaging with a spatial resolution of 507 μm. In a more recent publication, however, optic nerve readings deviated from our measurements by +0.7 mm along the course of the optic nerve in three cadaveric eyes and in 23 living subjects. We explain this difference by the suboptimal delineation of CSF from the optic nerve because the T1 pulse sequences chosen depict the CSF and the optic nerve as hypointense and dark, necessitating contrast enhanced post hoc by standard imaging software. The pixel resolution in that study ranged between 195 and 312 μm, two to three times lower than in our protocol, in which the quantifiable resolution was 110 μm × 120 μm. The width of the nerve sheath was not reported.

In preparing for this study, we tested several sequences, mainly with pronounced T2 contrast. The three-dimensional CISS (constructive interference in steady state) and balanced SSFP (steady state in free precession) sequences demonstrated less tissue contrast and were more susceptible to artifacts such as banding artifacts of the eyeball. Longer acquisition times, attributed, for example, to signal averaging, resulted in increased susceptibility to artifacts and might have resulted in degraded spatial resolution. Furthermore, the HASTE sequence did not exhibit any T1-weighting compared with conventional TSE, which results in a considerable signal loss for CSF. We are aware that we have not compared our MRI data with sequences obtained from other protocols, but we assume that ultrafast HASTE sequences are a good compromise between visible image quality and detail resolution for exact quantification of the optic nerve diameter. Because it is a single-shot sequence, it is less sensitive to artifacts resulting from motion, such as eye or head movement and jitting of the eye resulting from continuous fixation on the marker in the scanner. We were primarily interested in delineating the optic nerve from its surrounding fluid; therefore, HASTE sequences optimized for T2 contrast were sufficient. However, if the whole eye ball is to be imaged, other protocols should be used, such as those devised by Bert et al., who applied T1-weighted protocols. These, however, require longer acquisition times of approximately 4 minutes and yield a spatial resolution of approximately 250 μm, with the eye taped shut and covered with water-soaked gauze.

One potential problem of HASTE sequences is image blur in the phase-encoding direction. This may occur in TSE and HASTE sequences, if the echo train duration for sampling the k-space is noticeably higher than the T2 relaxation time. Given that T2 depends on the tissue, this type of blurring is tissue specific and is not an overall image characteristic. Blurring is commonly attributed to HASTE sequences because they use long echo trains, which means that the respective train durations are considerably higher than the T2 relaxation times of most body tissues. However, our optic nerve measurements were based on the diameter of the CSF sheath and had very long relaxation times of approximately 1500 ms at 3 T. The echo train duration of our HASTE sequence was 1500 ms and, thus, was equal to T2 relaxation times of CSF. Hence, a good point spread function occurs in CSF, without blurring in the
phase-encoding direction, enabling precise measurements for the inner and outer diameters of the CSF sheath. In HASTE images, other tissues may be blurred; however, in the present study, their respective signals had almost vanished because of the high TE and, hence, did not affect quantification. In fact, we took advantage of this high contrast between bright CSF and dark adjacent tissues. Common clinical TSE protocols have echo train durations of approximately 150 ms, whereas tissues under observation have T2 relaxation times shorter than 100 ms. Therefore, such routine TSE sequences have worse point spread functions for CSF than HASTE sequences.

Several histomorphometric studies have focused on the composition of optic nerve tissue in normal, healthy human nerves30,38,39 and in glaucomatous human nerves.40,41 However, only Karim et al.30 examined differences in tissue composition along the entire intraorbital course of the nerve. Indeed, they found a relative decrease in connective tissue volume compared with an unchanged volume of axonal tissue as the nerve extended from the eye toward the orbital apex. These findings are based on Masson trichrome-stained sections from 2 to 16 mm behind the globe, showing that the percentage of connective tissue decreased from 30% behind the globe to 20% in the orbital apex while the percentage of axonal tissue remained constant.

Although our MRI measurements and those reported in the literature yield consistent diameters, sonographic measurements of the optic nerve and its sheath vary greatly. With A-scan ultrasonography, retrobulbar optic nerve diameters have been quantified as 2.8 to 3.1 mm,4,2 3.5 ± 0.5 mm,4,2 2.8 to 3.4 mm,21 or 3.6 mm.44 For the sheath, diameters of 3.8 to 5.5 mm24 and 4.0 to 5.3 mm21 have been reported. The present measurements range below those reported in the other studies and in our own MRI study. With B-scan ultrasonography, the literature reports optic nerve diameters of 1.9 ± 0.1 mm,20 2.86 ± 0.46 mm,10 and 3.0 mm ± 0.3 mm.8 Sheath diameters of 4.8 ± 0.6 mm,20 2.9 to 4.3 mm,6,7 4.5 mm,45 and 2.4 to 4.7 mm24 have been published. Factors contributing to this tremendous variation are differences in examiner experience, uncertainty in finding the right cutting plane along the nerve, limited spatial resolution, and the inability to achieve perpendicular ultrasonic penetration of the optic nerve.75

The spectrum of methods for retrobulbar imaging has changed over the years from sonography to more precise MRI. This is likely a logical consequence of the rapid developments in MR technology. However, one has to be aware that this trend has led to higher costs and logistic complexity. Ultrasound and MRI have their own advantages and disadvantages. Nevertheless, in our study, MRI yielded higher precision. The low variance and short data acquisition time documented herein indicate that HASTE sequences may be particularly practical compared with other MRI sequences in evaluating the optic nerve and its sheath.

References


In Materials and Methods, in the fourth paragraph of the “Image Acquisition” section, the eighth sentence should read, “These sectors were named according to their locations as temporal (T; 311–40°), superotemporal (ST; 41–80°), superonasal (SN; 81–120°), nasal (N; 121–230°), inferonasal (IN; 231–270°), and inferotemporal (IT; 271–310°).”

In the “Statistical Analysis” section, the equation should read:

\[
t = \frac{(\mathbf{r}_{AB} - \mathbf{r}_{AC}) \cdot \sqrt{[(N - 1) \cdot (1 + \mathbf{r}_{BC})/\{(2(N - 1)/(N - 3)\}] \cdot |\mathbf{R}|}}{\sqrt{[(\mathbf{r}_{AB} + \mathbf{r}_{AC})/2] \cdot [(1 - \mathbf{r}_{BC})^3]}}
\]

where \(\mathbf{R} = (1 - \mathbf{r}_{AB}^2 - \mathbf{r}_{AC}^2 - \mathbf{r}_{BC}^2) + (2 \cdot \mathbf{r}_{AB} \cdot \mathbf{r}_{AC} \cdot \mathbf{r}_{BC})\), and \(N\) is the sample size.