Semi-quantification of Endolymphatic Size on MR Imaging after Intravenous Injection of Single-dose Gadodiamide: Comparison between Two Types of Processing Strategies

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Purpose: Many inner ear disorders, including Ménière’s disease, are believed to be based on endolymphatic hydrops. We evaluated a newly proposed method for semi-quantification of endolymphatic size in patients with suspected endolymphatic hydrops that uses 2 kinds of processed magnetic resonance (MR) images.

Methods: Twenty-four consecutive patients underwent heavily T2-weighted (hT2W) MR cisternography (MRC), hT2W 3-dimensional (3D) fluid-attenuated inversion recovery (FLAIR) with inversion time of 2250 ms (positive perilymph image, PPI), and hT2W–3D-IR with inversion time of 2050 ms (positive endolymph image, PEI) 4 hours after intravenous administration of single-dose gadolinium-based contrast material (IV-SD-GBCM). Two images were generated using 2 new methods to process PPI, PEI, and MRC. Three radiologists contoured the cochlea and vestibule on MRC, copied regions of interest (ROIs) onto the 2 kinds of generated images, and semi-quantitatively measured the size of the endolymph for the cochlea and vestibule by setting a threshold pixel value.

Results: Each observer noted a strong linear correlation between endolymphatic size of both the cochlea and vestibule of the 2 kinds of generated images. The Pearson correlation coefficients (r) were 0.783, 0.734, and 0.800 in the cochlea and 0.924, 0.930, and 0.933 in the vestibule (P < 0.001, for all). In both the cochlea and vestibule, repeated-measures analysis of variance showed no statistically significant difference between observers.

Conclusion: Use of the 2 kinds of generated images generated from MR images obtained 4 hours after IV-SD-GBCM might enable semi-quantification of endolymphatic size with little observer dependency.

Keywords: advanced imaging techniques, magnetic resonance imaging, Ménière’s disease, temporal bone disease, 3D imaging

Introduction

Endolymphatic hydrops is a pathologic anatomical finding in which enlarged endolymphatic volume distends the structures bounding the endolymphatic space.1 It has long been considered the pathologic basis for Ménière’s disease,2 an inner ear disorder characterized by spontaneous attacks of vertigo, fluctuating low frequency hearing loss, aural fullness, and tinnitus. Disease in some patients with inner ear symptoms that do not match the diagnostic guideline of Ménière’s disease is also believed to be based on endolymphatic hydrops.3–6

Endolymphatic hydrops was first visualized in patients with Ménière’s disease by MR imaging us-
Multiplying 3-dimensional (3D) fluid-attenuated inversion recovery (FLAIR) obtained 24 hours after intratympanic (IT) administration of gadolinium-based contrast material (GBCM). However, this use of GBCM is off-label and requires 24 hours of waiting time and puncture of the tympanic membrane. Because some patients are not willing to receive IT administration of GBCM, especially to the ear with normal or better hearing, a method to detect endolympheric hydrops by intravenous (IV) administration of GBCM was explored. Visualization of endolympheric hydrops in patients with Ménière’s disease was reported using heavily T2-weighted 3D-FLAIR (hT2W–3D-FLAIR) and imaging 4 hours after IV administration of single-dose GBCM (IV-SD-GBCM). The image that results from 3D-FLAIR that includes hT2W–3D-FLAIR is called a positive perilymph image (PPI) because the signal of the perilymph increases after IT or IV administration of GBCM, and the signal intensities of both endolymph and surrounding bone show values near zero.

Shortening the inversion time of 3D-FLAIR after IT administration of GBCM was proposed to clarify the boundaries of the endolymphatic space and surrounding bones and rule out partial volume averaging artifact from bones. Optimal shortening of the inversion time in 3D-FLAIR suppresses the signal of perilymph with GBCM distribution to give high signal to endolymph without GBCM distribution (positive endolymph image, PEI). By adjusting inversion time, PPI and PEI based on the hT2W–3D-FLAIR technique could be obtained after IV-SD-GBCM in a similar manner to the acquisition of PPI and PEI after IT administration of GBCM.

Separate visualization of endolymph, perilymph, and bone on a single image has been reported using 3D inversion recovery sequence with "real" reconstruction (3D-real IR) after IT administration of GBCM but not after IV-SD-GBCM, probably because of the lower concentration of GBCM in perilymph. Recently, the fusion of a gray-scale inverted PEI with native gray-scale PPI, that is, subtraction of the PEI from the PPI, has been reported to yield a 3D-real IR-like image even after IV-SD-GBCM. These images, termed "HYDROPS" (HYbriD of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal), facilitate recognition of endolymphatic space by IV-SD-GBCM. However, acquisition of both PPI and PEI requires 30 minutes of scan time for processing. To decrease the duration of HYDROPS imaging, an alternative processing technique was developed that subtracts heavily T2-weighted MR cisterno-
between April and October 2012 at a tertiary referral center. Experienced otorhinolaryngologists determined indication for MR imaging based on the presence of ear symptoms, vertigo, average hearing level on pure tone audiometry, results of various otological tests, and clinical history. Table 1 summarizes patient characteristics and symptoms.

All patients underwent MR scanning 4 hours after single-dose (0.2 mL/kg or 0.1 mmol/kg body weight) IV administration of gadolinium-diethylene-triamine pentaacetic acid-bis (methylamide) (gadodiamide: Gd-DTPA-BMA; Omniscan, Daiichi-Sankyo Co. Ltd., Tokyo, Japan) to evaluate the degree of endolymphatic hydrops. The estimated glomerular filtration rate (eGFR) of all patients exceeded 60 mL/min/1.73 m².

**MR imaging**

All MR imaging was performed on a 3.0-tesla unit (MAGNETOM® Verio, Siemens, Erlangen, Germany) using a 32-channel array head coil. All patients underwent heavily T2-weighted MRC for anatomical reference of total lymph fluid, hT₂W–3D-FLAIR with inversion time of 2250 ms (PPI), and hT₂W–3D-IR with inversion time of 2050 ms (PEI) according to the clinical protocol of our hospital for evaluating endolymphatic hydrops. Parameters were set as previously reported. Detailed scan parameters for MRC follow.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Sex</th>
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<th>Left ear</th>
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<td>56</td>
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<td>cochlear MD</td>
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<td>2</td>
<td>F</td>
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<td>3</td>
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<tr>
<td>24</td>
<td>F</td>
<td>25</td>
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ALHL, acute low-tone hearing loss; EH, endolymphatic hydrops; HL, hearing loss; IBSNHL, idiopathic bilateral sensorineural hearing loss; MD, Ménière’s disease; SD, SNHL, sensorineural hearing loss
USA) with a free DICOM viewer (OsiriX image software, ver. 3.0.2. 32 bit; downloadable at http://www.osirix-viewer.com/index.html), which allowed easy pixel-by-pixel multiplication between the image series in a few seconds. The HYDROPS-Mi2 image (Image #1) was obtained by multiplying the MRC and HYDROPS images. The HYDROPS2-Mi2 image (Image #2) was obtained by multiplying the MRC and HYDROPS2 images. Figure 1 is a conceptual diagram of the image processing. The aim of multiplying the MRC image onto the HYDROPS and HYDROPS2 images was to set to zero the signal intensity value of bony structures possibly included in the region of interest (ROI), i.e., osseous spiral lamina, interscalar septum and bony wall of the labyrinth. Without multiplication, such bony structures might show non-zero negative signal intensity values due to the low signal-to-noise ratio (SNR) of the HYDROPS and HYDROPS2 images, which would result in overestimation of the size of the area of endolymph.

**Image analysis**

Three radiologists, with 24 years’ experience in neuroradiology and 3 and 2 years’ experience in radiology, independently evaluated the images. Each observer manually contoured the cochlea and vestibule separately to set up an ROI on the MRC after receiving the following instructions:

“Before starting the contouring of the cochlea or vestibule on MRC, set the image window level and width to 400/1000.

“For the cochlear ROI, select the slice on which the cochlear modiolus is visually largest. If the size of the modiolus is comparable on 2 or more slices, choose the slice with the largest height of the modiolus. When contouring the cochlea on MRC, exclude the modiolus when drawing the ROI.

“For the vestibular ROI, select the lowest slice where the lateral semicircular canal ring is visualized more than 240°, and exclude the semicircular canal and ampulla when drawing the ROI for the vestibule on MRC.”

Reviewers were also shown an example of ROI setting before starting the contouring (Fig. 2). The ROI of the cochlear slice was defined to select the middle part of the cochlea, and the ROI of the vestibular slice, to select the middle of the vestibule. These ROIs drawn on MRC were copied and pasted onto Images #1 and #2. We then used the histogram function of OsiriX to measure the numbers of all pixels in the ROI and the numbers of pixels with negative signal intensity values (i.e., endolymph) in the ROI.

The ratio of the area (%) of endolymphatic space in the entire lymphatic space (%EL) was defined as:

\[ \%EL = \frac{\text{number of negative pixels for the endolymph in the ROI}}{\text{total number of pixels in the ROI}} \times 100 \]

**Statistical analysis**

We investigated the relationship between the %EL in Images #1 and #2 by linear regression analysis and evaluated interobserver and image type difference in the %EL using analysis of variance (ANOVA) for a 2×3 repeated-measures design on the %EL for 48 ears. Factors were the 2 types of generated images (Images #1 and #2) and 3 observers. If the null hypothesis in Mauchly’s test of sphericity was rejected, the adjustments to degrees of freedom of the F test statistics were done using the Greenhouse-Geisser epsilon, Huynh-Feldt epsilon, and lower-bound epsilon.

We used SPSS 17 software (SPSS Inc., Chicago, Illinois, USA) for all statistical analyses and adopted 5% as the significance level for statistical testing.

The medical ethics committee of our institution approved this retrospective study, and informed consent was waived.

**Results**

No misregistration artifact from motion was noted in any ear. Table 2 shows the mean %EL of the cochlea and vestibule on Images #1 and #2 for the 3 observers.

Figure 3a shows the relationship between the %EL in the 2 types of generated images for the cochlea, and Fig. 3b shows that for the vestibule. A strong linear correlation was observed between the %EL in the 2 types of generated images for each observer; the Pearson’s correlation coefficients (r) were 0.783, 0.734, and 0.800 for the cochlea and 0.924, 0.930, and 0.933 for the vestibule (P<0.001, for all). Further, the linear regression lines for the 3 observers were almost identical. All the linear regression lines intersected the vertical axis at positive values of %EL on Image #2 and at the 0% of %EL on Image #1.

For both the cochlea and vestibule, repeated-measures ANOVA showed significant difference between the area ratio means in the 2 types of generated images (P<0.001). However, the difference among observers was not significant (P=0.235 for Greenhouse-Geisser epsilon, 0.234 for Huynh-Feldt epsilon, 0.230 for lower-bound epsilon in the cochlear image; P=0.600 for Greenhouse-Geisser epsilon, 0.607 for Huynh-Feldt epsilon, 0.488 for lower-bound epsilon in the vestibular image), and there was no statistically significant interaction be-
Fig. 1. Conceptual diagram of image processing. Multiplication of magnetic resonance cisternography (MRC) boosts the contrast-to-noise ratio. All images are acquired 4 hours after intravenous administration of single-dose gadolinium-based contrast material (IV-SD-GBCM). (a) HYDROPS image is formed by the subtraction of the PEI (positive endolymph image) from the PPI (positive perilymph image). HYDROPS-Mi2 (Image #1) is formed by the multiplication of the HYDROPS image and MRC. (b) HYDROPS2 image is formed by the subtraction of MRC multiplied by 0.05 from the PPI. HYDROPS2-Mi2 (Image #2) is formed by the multiplication of HYDROPS2 and MRC. Note that the background signal of HYDROPS-Mi2 and HYDROPS2-Mi2 is far more uniform than HYDROPS and HYDROPS2. HYDROPS, HYbrid of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal; HYDROPS2, HYbrid Of Reversed image Of MR cisternography and positive Perilymph Signal by heavily T2-weighted 3D-FLAIR; HYDROPS-Mi2, HYDROPS image Multiplied with heavily T2-weighted MR cisternography; HYDROPS2-Mi2, HYDROPS2 image Multiplied with heavily T2-weighted MR cisternography.
Fig. 2. An example of the setting of region of interest (ROI) on magnetic resonance cisternography (MRC). The window level and width of the MRC was set as 400/1000. (a) At the mid-modiolar slice, the cochlea is contoured excluding the modiolus. (b) At the lowest slice that visualizes more than 240° of the lateral semicircular canal ring, the vestibule is contoured excluding the ampulla and semicircular canal. To measure the size of the endolymph, ROIs on MRC are copied onto HYDROPS-Mi2 (Image #1) (c) and HYDROPS2-Mi2 (Image #2) (d). Pixels with negative signal values in the ROIs are defined as endolymph. HYDROPS-Mi2, HYDROPS image Multiplied with heavily T2-weighted MR cisternography; HYDROPS2-Mi2, HYDROPS2 image Multiplied with heavily T2-weighted MR cisternography.

Table 2. Mean %EL in the cochlea and vestibule by 3 observers for 2 kinds of generated image

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<tr>
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<th>Cochlear %EL</th>
<th>Vestibular %EL</th>
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<tr>
<td></td>
<td>HYDROPS-Mi2</td>
<td>HYDROPS-Mi2</td>
</tr>
<tr>
<td></td>
<td>(Image #1)</td>
<td>(Image #2)</td>
</tr>
<tr>
<td>Observer A</td>
<td>13.3 ± 16.5</td>
<td>22.7 ± 17.4</td>
</tr>
<tr>
<td>Observer B</td>
<td>14.4 ± 16.1</td>
<td>24.3 ± 17.3</td>
</tr>
<tr>
<td>Observer C</td>
<td>12.6 ± 15.7</td>
<td>24.4 ± 18.8</td>
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</table>

r, Pearson’s correlation coefficient
%EL, ratio (%) of the area of endolymphatic space in the entire lymphatic space
HYDROPS-Mi2, HYDROPS image Multiplied with heavily T2-weighted magnetic resonance (MR) cisternography, Image #1 in the present study
HYDROPS2-Mi2, HYDROPS2 image Multiplied with heavily T2-weighted MR cisternography, Image #2 in the present study
HYDROPS, HYbriD of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal
HYDROPS2, HYbriD of Reversed image Of MR cisternography and positive Perilymph Signal by heavily T2-weighted 3D-FLAIR
Fig. 3. Linear regression analysis between the ratio of the area of the endolymphatic space in the entire lymphatic space (%EL) of the cochlea (a) and vestibule (b) on HYDROPS-Mi2 (Image #1) and HYDROPS2-Mi2 (Image #2) for the 3 observers. For all observers, the correlation between Image #1 and #2 was strong. Note that all regression lines intersect the vertical axis at positive values of Image #2, whereas many datapoints of Image #1 showed 0% of EL% in the cochlea and vestibule (Fig. 3). In the previously reported MR imaging study obtained after IT administration of GBCM, the normal values of %EL were 8 to 26% in the cochlea and 20 to 41% in the vestibule. In the previous histological study, the %EL in control subjects was 9 to 12% in the cochlea and 22 to 26% in the vestibule. These results suggest that there should be some non-zero %EL values even in healthy condition. Therefore, we can speculate that Image #1 tends to underestimate the values of %EL, probably as a result of the blurring effect of small endolymph on PEI.

A subjective 3-step scale was introduced to grade endolymphatic hydrops in both the cochlea and vestibule on MR images. Then, a 4-step scale was proposed based on the 3-step scale. However, neither grading system specifies the slice level to use for evaluation or defines how to manage cases with nonuniform distribution of endolymphatic hydrops in each cochlear turn.

A quantitative method is proposed to measure endolymph size manually on 3D-FLAIR images obtained after IT administration of GBCM. In this method, the cochlear ducts in each cochlear turn are manually traced on a 3D-FLAIR image at the mid-modiolar level. However, borders between the cochlear endolymph and surrounding bone are unclear on 3D-FLAIR, so the manual tracing of the area of endolymph is susceptible to observer bias. Contouring cochlear ducts in each turn is also time-consuming. Another study proposed a grading method in which the labyrinth was segmented into 7 parts, the presence of contrast enhancement of perilymph on 3D-FLAIR obtained after IT administration of GBCM was noted for each part, and the parts showing enhancement were counted. The points correlated well with patient symptoms, and interobserver variability was small. However, endolymphatic size cannot be directly evaluated by counting the number of parts with perilymph enhancement after IT administration of GBCM. Absence of enhancement in perilymph does not neces-
sarily indicate the presence of endolymphatic hydrops. Distribution of GBCM in the perilymph might be impaired due to poor penetration of the round window membrane. Furthermore, less uniform distribution of GBCM in the cochlea by IT than IV administration is reported. Just counting the number of sites with perilymphatic enhancement after IT administration of GBCM might not be sufficiently robust as an evaluation method for endolymphatic hydrops. The method proposed in the present study allowed the separate and simultaneous direct measurement of the %EL of the cochlea and vestibule in the ears of both sides, was less invasive, and showed little interobserver variability.

Our study is limited because we included no healthy subjects and no patients with definite Ménière’s disease. However, the wide variety of %EL either in the cochlea or vestibule enabled us to fulfill our study purposes. Evaluation was performed by the area ratio of endolymph in the total lymph in a slice and not by the volume ratio of endolymph in the total lymph volume. Volume might be evaluated by measuring the area on all slices, but this is quite time-consuming. In the present study, we chose a practical and clinically applicable method. No histological confirmation regarding the size of endolymphatic space was obtained, so we cannot firmly decide whether Image #1 or #2 provided better results compared to the truth. Neither can we rule out the possibility that the multiplication of MRC might have altered the shape of the endolymphatic space. It is virtually impossible to obtain histological specimens in benign conditions like endolymphatic hydrops. The present study suggested the possibility of slight underestimation of Image #1. Further study comparing the %EL on MR images, patient symptoms, and otological tests would be necessary in a larger number of patients to establish the quantitative assessment of endolymphatic hydrops on MR.

Although we noted no significant motion, motion could also cause image misregistration. However, reducing scan time from 33 min for Image #1 to 18 min for Image #2 should reduce the chance of significant motion.

Conclusions

HYDROPS-MI2 (Images #1) and HYDROPS2-MI2 (Images #2) might enable semi-quantification of endolymphatic size with small observer dependency even by less invasive IV-SD-GBCM. Correlation of Images #1 and #2 was strong, but Image #1 seemed to underestimate the %EL more than Image #2.

Acknowledgements

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References

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Semi-quantification of Endolymphatic Size


