Time Course for Measuring Endolymphatic Size in Healthy Volunteers Following Intravenous Administration of Gadoteridol

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Purpose: We developed semi-quantitative methods to measure endolymphatic size on images obtained 4 hours after intravenous administration of single-dose gadolinium-based contrast medium (IV-SD-GBCM) and found little variation in results between observers. We used the methods to measure the size of the endolymph in healthy volunteers at various times after IV-SD-GBCM and attempted to determine the optimal timing for the evaluation.

Methods: In 8 healthy male volunteers, we obtained heavily T2-weighted 3-dimensional fluid-attenuated inversion recovery (hT2W-3D-FLAIR) images1.5,3,4.5, and 6 hours after IV-SD-GBCM as positive perilymph images (PPI) as well as acquiring positive endolymph images (PEI) and magnetic resonance cisternography (MRC). To evaluate the endolymph, we generated 2 kinds of processed images (HYDROPS-Mi2 and HYDROPS2-Mi2) by subtracting PEI or MRC from PPI as previously proposed. We semi-quantitatively measured the ratio of the area of the endolymph (%EL) to that of total lymph on the 2 kinds of generated images for the cochlea and vestibule according to the previously proposed method. We analyzed statistics to evaluate the change in %EL over time and used analysis of variance (ANOVA) for a 2 × 4 repeated-measures design to assess difference in image type. We adopted 5% as a significance level.

Results: The %EL was significantly larger at 1.5 hours after IV-SD-GBCM than at 3, 4.5, and 6 hours in both the cochlea and vestibule for both kinds of generated images. Between 4.5 and 6 hours, the %EL plateaued for both the cochlea and vestibule, and the 2 kinds of generated images did not differ significantly.

Conclusion: A delay of 1.5 hours after IV-SD-GBCM is not sufficient to evaluate endolymphatic size. The %EL plateaus between 4.5 and 6 hours. These data might be valuable for further clinical studies.

Keywords: advanced imaging techniques, endolymphatic hydrops, magnetic resonance imaging, 3D imaging

Introduction

Intratympanic (IT) administration of gadolinium-based contrast media (GBCM) using 3-dimensional fluid-attenuated inversion recovery (3D-FLAIR) has enabled visualization of endolymphatic hydrops in patients with Ménière’s disease.1 As well, the higher sensitivity of heavily T2-weighted 3D-FLAIR (hT2W-3D-FLAIR) sequences to low concentrations of GBCM has permitted visualization of endolymphatic hydrops using intravenous administration (IV) of GBCM.1–3 In both methods, GBCM is distributed mainly in the perilymph and not the endolymph. The endolymphatic space is recognized as the area filled with fluid in which
there is no GBCM distribution. Although the IT administration of GBCM is an off-label use and requires puncture of the tympanic membrane, various institutions have employed this method. On the other hand, recent studies of the relationship between the degree of endolymphatic hydrops and patient symptoms have used the IV administration of single-dose GBCM (IV-SD-GBCM). A previous study in volunteers set the time delay after IV-SD-GBCM at around 4 hours, and a significant rise in perilymph signal beginning 1.5 hours after IV-SD-GBCM in volunteers has been reported. The latter report also showed plateauing of the perilymph signal from 3 to 6 hours after IV-SD-GBCM. However, endolymphatic size over time after IV-SD-GBCM has not been investigated.

Semi-quantitative methods for evaluating the size of the endolymphatic space on images obtained 4 hours after IV-SD-GBCM have been proposed, and results of their use in patients with Ménière’s disease have varied little between observers.

The purpose of the current study was to measure the size of the endolymphatic space in healthy volunteers at various time points after IV-SD-GBCM using the proposed semiquantitative methods and to determine the optimal timing for evaluating the endolymphatic space.

Materials and Methods

The medical ethics committee of our institution approved this study of healthy volunteers, and written informed consent was obtained from all participants.

Subjects

Subjects were 8 healthy male volunteers aged 29 to 53 years (median 37 years) with no history of hearing loss, vertigo, cranial disease, head trauma, renal disease, or heart disease who took no daily medications.

MR imaging

All MR imaging was performed on a 3-tesla scanner (Verio, Siemens, Erlangen, Germany) using a 32-channel array head coil. All volunteers underwent heavily T2-weighted magnetic resonance cisternography (MRC) for anatomical reference of the fluid space and hT2W-3D-FLAIR (positive perilymph image: PPI) with inversion time of 2250 ms according to the clinical protocol of our hospital for evaluating endolymphatic hydrops. We also obtained a positive endolymph image (PEI) with a shorter inversion time (TI) of 2050 ms.

We set parameters as previously reported.

Table. Pulse sequence parameters

<table>
<thead>
<tr>
<th>Sequence name</th>
<th>Type</th>
<th>Repetition time (ms)</th>
<th>Echo time (ms)</th>
<th>Inversion time (ms)</th>
<th>Flip angle</th>
<th>Section thickness (mm)</th>
<th>Pixel size (mm)</th>
<th>Number of slices</th>
<th>Number of excitations</th>
<th>Field of view (mm)</th>
<th>Matrix size</th>
<th>Number of excitations</th>
<th>Scan time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR cisternography (MRC)</td>
<td>SPACE with restore pulse</td>
<td>4400</td>
<td>544</td>
<td>90/initial 180</td>
<td>90/initial 120 decrease to constant 120</td>
<td>0.5 x 0.5</td>
<td>104</td>
<td>173</td>
<td>150 x 180</td>
<td>322 x 384</td>
<td>1</td>
<td>0.5 x 0.5</td>
<td>104</td>
</tr>
<tr>
<td>Heavily T2-weighted 3D inversion recovery (PEI)</td>
<td>SPACE with inversion pulse</td>
<td>9000</td>
<td>544</td>
<td>90/initial 180</td>
<td>90/initial 120 decrease to constant 120</td>
<td>0.5 x 0.5</td>
<td>104</td>
<td>173</td>
<td>150 x 180</td>
<td>322 x 384</td>
<td>1</td>
<td>0.5 x 0.5</td>
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3D, 3-dimensional; FLAIR, fluid-attenuated inversion recovery; GRAPPA, generalized autocalibrating partially parallel acquisitions; NA, not applicable; PEI, positive endolymph image; PPI, positive perilymph image; SPACE, sampling perfection with application-optimized contrasts using different flip angle evolutions.
Table details scan parameters. All MRC, PPI, and PEI acquisitions employed an identical field of view, matrix size, and slice thickness to facilitate comparisons. Sets of MRC, PPI, and PEI images were obtained before and at 0.5, 1.5, 3, 4.5, and 6 hours after IV-SD-GBCM.

After the pre-contrast scan, subjects received a single dose (0.2 mL/kg body weight or 0.1 mmol/kg body weight) of gadoteridol (Gd-HP-DO3A: ProHance, Eisai, Tokyo, Japan) by IV administration, after which they were permitted to exit the magnet room and rest during the interval between MR scans without instructions to restrict behavior.

**Image processing**

Before measuring endolymphatic size, we pre-processed images. On the scanner console, we generated HYDROPS (HYbrID of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal) images by subtracting PEI from PPI, and we generated HYDROPS2 (HYbrID of Reversed image Of MR cisternography and positive Perilymph Signal by heavily T2-weighted 3D-FLAIR) images by subtracting MRC multiplied by a constant value of 0.04 from PPI.

The signal intensity values of the perilymph are usually far larger on MRC without inversion pulse than on PPI with inversion pulse, and we determined that this constant value would reduce the original signal intensity value of the perilymph on PPI to approximately half the original value after subtracting the MRC multiplied by the constant value. Before generating HYDROPS2 images, we measured the signal intensity values of the perilymph in the vestibule on PPI and MRC at 4.5 hours in 4 ears of the initial 2 volunteers, drawing a circular region of interest (ROI) on the scanner console to set a constant value to balance the signal intensity values between the PPI and MRC. Based on the results, we determined an average constant value of 0.04.

For the result of subtraction, we allowed negative signal values for both HYDROPS and HYDROPS2 images. Acquisition of source images takes 14 minutes for HYDROPS and 10 minutes for HYDROPS2. In this study, we applied no image motion registration program during subtraction. For the HYDROPS and HYDROPS2 images, a neuroradiologist subjectively confirmed the absence of misregistration artifact, i.e., apparent double contour of the labyrinth.

HYDROPS, HYDROPS2, and MRC images were transferred by CD-ROM to an iMac personal computer (Apple Computer, Inc., Cupertino, CA, USA) with a free DICOM viewer (OsiriX image software, ver. 5.6, 32 bit; downloadable at: http://www.osirix-viewer.com/index.html), which allowed easy pixel-by-pixel multiplication between image series in a few seconds.

We obtained a HYDROPS-Mi2 (HYDROPS image Multiplied with heavily T2-weighted MR cisternography, Image #1 in the present study) image by multiplying the MRC and HYDROPS.

We obtained a HYDROPS2-Mi2 (HYDROPS2 image Multiplied with heavily T2-weighted MR cisternography, Image #2 in the present study) image by multiplying the MRC and HYDROPS2.

Our aim in multiplying MRC onto HYDROPS and HYDROPS2 images was to set to zero the signal intensity value of bony structures possibly included in the 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 value because of the low signal-to-noise ratio of HYDROPS and HYDROPS2, which would result in the over-estimation of the size of the area of the endolymph.

Acquisition of source images takes 17 min for HYDROPS-Mi2 images and 10 min for HYDROPS2-Mi2 images.

We performed semi-quantitative analysis of endolymphatic size using these HYDROPS-Mi2 (Image #1) and HYDROPS2-Mi2 (Image #2) images according to the previously reported method.

**Image analysis**

A neuroradiologist with 24 years of experience in the field of clinical MR imaging semi-quantitatively evaluated images in 16 ears of 8 volunteers. We separately measured endolymphatic size for the cochlea and vestibule according to previously reported methods.

In brief, the image window level and width were set to 400/1000 before contouring of the cochlea or vestibule on the MRC at each time point. The ROI for the cochlea was drawn on the slice on which the cochlear modiul is visually largest or on the slice with the largest height of the modiul if the modiul is of comparable size on 2 or more slices. When contouring the cochlea on MRC, the POI should be drawn to exclude the modiul.

The ROI for the vestibule should be drawn on the lowest slice on which the lateral semicircular canal ring is visualized more than 240° and should exclude the semicircular canal and ampulla when the ROI for the vestibule is drawn on MRC.

We defined the ROI of the slice of the cochlea to include the middle part of the cochlea and that of the slice of the vestibule to include the middle
part of the vestibule. These ROIs drawn on MRC for each time point 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 number of pixels with negative signal intensity values (i.e., endolymph) in the ROI.

The ratio of the area (%) of endolymphatic space in the whole lymphatic space (%EL) was defined as: \[ \text{%EL} = \left( \frac{\text{number of negative pixels for endolymph in the ROI}}{\text{number of total pixels in the ROI}} \right) \times 100. \]

In our recent volunteer study,\(^1\) we observed significant enhancement of the perilymph at 1.5, 3, 4.5, and 6 hours after IV-SD-GBCM. Therefore, we generated and evaluated Images \#1 and \#2 at these time points.

**Statistical analysis**

To evaluate the change in the estimated area ratio of endolymph (%EL) over time after IV-SD-GBCM and the difference in image type in this ratio, we performed an analysis of variance (ANOVA) for a 2 × 4 repeated-measures design and a planned trend analysis. Factors were the 2 types of formed images (Images \#1 and \#2) and 4 time points after IV-SD-GBCM (1.5, 3, 4.5, and 6 hours). Here, if the null hypothesis in Mauchly’s test of sphericity was rejected, we used the Greenhouse-Geisser epsilon, Huynh-Feldt epsilon, and lower-bound epsilon to adjust degrees of freedom of the F test statistics. We also performed pairwise comparison among those means of estimated %EL by the Bonferroni adjustment.

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

**Results**

Figure 1 shows examples of Images \#1 and \#2 at each time point.

Figure 2 shows the means (with standard deviations) of estimated %EL in cochlear images. Repeated-measures ANOVA showed a statistically significant difference in estimated %EL among the times after IV-SD-GBCM (\(P < 0.001\) for the Greenhouse-Geisser epsilon, for the Huynh-Feldt epsilon, and for the lower-bound epsilon) and statistically significant linear and quadratic trends of time after IV-SD-GBCM (\(P < 0.001\)). However, there was no statistically significant difference between the 2 types of formed images (\(P = 0.356\)), but there was significant interaction between type of formed image and time after IV-SD-GBCM.

**Fig. 1.** A 53-year-old healthy male volunteer. (a) Slice for evaluation of cochlear endolymphatic size. The size of the black area in the cochlea (long arrows) is largest in the images obtained 1.5 hours after intravenous administration of single-dose gadolinium-based contrast medium (IV-SD-GBCM). The black area (short arrow) extends to the perilymph of the scala tympani in the images obtained 1.5 hours after IV-SD-GBCM. Therefore, endolymphatic size is overestimated on the images obtained at 1.5 hours after IV-SD-GBCM. (b) Slice for evaluation of vestibular endolymphatic size. The size of the black area (short arrow) corresponding to the posterior ampulla can be recognized at all times. Therefore, endolymphatic size is thought to be overestimated on the images obtained at 1.5 hours after IV-SD-GBCM.
\[ P = 0.005 \text{ for the Greenhouse-Geisser epsilon,} \]
\[ P = 0.003 \text{ for the Huynh-Feldt epsilon, and} \]
\[ P = 0.027 \text{ for the lower-bound epsilon) and a statistically significant linear trend of the interaction} \]
\[ (P = 0.002). \] Thus, the estimated %EL of endolymph was significantly higher at 1.5 hours than at 3, 4.5, and 6 hours. “Image \#1,” HYDROPS-Mi2 (HYDROPS image Multiplied with heavily T2-weighted magnetic resonance [MR] cisternography); “Image \#2,” HYDROPS2-Mi2 (HYDROPS2 image Multiplied with heavily T2-weighted MR cisternography).

FIG. 2. Means (± standard deviation) of the estimated ratio of the endolymph to that of total lymph (%EL) for 1.5, 3, 4.5, and 6 hours after intravenous administration of single-dose gadolinium-based contrast medium (IV-SD-GBCM) in 2 types of formed images in 16 cochleas of 8 volunteers. The %EL is significantly larger at 1.5 hours than at 3, 4.5, and 6 hours. Figure 3 shows the means (with standard deviations [SD]) of estimated %EL in vestibular images. Repeated-measures ANOVA showed a statistically significant difference in the estimated %EL among the times after IV-SD-GBCM (\( P < 0.001 \)) and statistically significant linear (\( P < 0.001 \)), quadratic (\( P < 0.001 \)), and cubic (\( P = 0.001 \)) trends of time after IV-SD-GBCM. Further, there was a statistically significant difference between the 2 types of formed images (\( P = 0.003 \)), a statistically significant linear trend of type of formed image (\( P = 0.003 \)), a statistically significant interaction between type of formed image and time after IV-SD-GBCM (\( P = 0.003 \) for the Greenhouse-Geisser epsilon, \( P = 0.002 \) for the Huynh-Feldt epsilon, and \( P = 0.012 \) for the lower-bound epsilon in the cochlear image), and statistically significant linear (\( P = 0.006 \)) and quadratic (\( P = 0.008 \)) trends of the interaction. Thus, the estimated %EL of the endolymph was significantly higher at 1.5 hours after IV-SD-GBCM than other times (these are also statistically significant \( P < 0.001 \) from the pairwise comparison), almost the same after 4.5 hours, and showed no significant difference between the 2 types of formed images.

FIG. 3. Means (± standard deviation) of the estimated ratio of the endolymph to that of total lymph (%EL) for 1.5, 3, 4.5, and 6 hours after intravenous administration of single-dose gadolinium-based contrast medium (IV-SD-GBCM) in 2 types of formed images in 16 vestibules of 8 volunteers. The %EL is significantly larger at 1.5 hours than at 3, 4.5, and 6 hours. Image \#1, HYDROPS-Mi2 (HYDROPS image Multiplied with heavily T2-weighted magnetic resonance [MR] cisternography); Image \#2, HYDROPS2-Mi2 (HYDROPS2 image Multiplied with heavily T2-weighted MR cisternography).

Discussion

In evaluating endolymphatic size, weak enhancement of the perilymph on PPI results in poor contrast between the perilymph and endolymph. Weak enhancement of the perilymph on PPI also results in poor suppression of the perilymph on PEI. Poor suppression of the perilymph on PEI results in overestimation of %EL in Image \#1. Regarding the time course of perilymph enhancement in healthy volunteers, one previous study reported the strongest enhancement of labyrinthine lymph fluid 4 hours after IV-SD-GBCM among 0, 2, 4, and 6 hours after IV-SD-GBCM.\(^{18}\)

Another recent volunteer study\(^{19}\) showed significant perilymph enhancement beginning 1.5 hours after IV-SD-GBCM but significantly weaker enhancement at 1.5 hours than at 3, 4.5, and 6 hours.
after IV-SD-GBCM, with no significant difference among 3, 4.5, and 6 hours. Significantly weaker enhancement of the perilymph at 1.5 hours or poor suppression of the perilymph on PEI might have yielded the larger %EL in Image \#1 than Image \#2.

Separate visualization of the 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 lower GBCM concentration in the perilymph. Recently, the fusion of gray-scale inverted PEI with native gray-scale PPI, that is, subtraction of PEI from PPI, has been reported to yield a 3D-real IR-like image even after IV-SD-GBCM. These HYDROPS images facilitate recognition of endolymphatic space by IV-SD-GBCM but require long scan time to obtain both PPI and PEI for processing. An alternative processing technique, HYDROPS2, subtracts heavily T2-weighted MRC from PPI to achieve images with similar contrast to HYDROPS in less scan time.

The multiplication of heavily T2-weighted MRC and HYDROPS, which we have termed HYDROPS-Mi2, has been reported to increase the contrast-to-noise ratio (CNR) between the endolymph and perilymph. HYDROPS-Mi2 images showed a more than 200-fold increase in CNR, and the background signal became quite uniform. MRC can be used as a “CNR booster.” On HYDROPS-Mi2 images, pixel values of the endolymph are negative, and those of the perilymph are positive. The absolute values of the endo- and perilymph are quite large due to the multiplication of MRC. Air and bone near the labyrinth show zero pixel values on HYDROPS-Mi2. MRC can also be multiplied as a CNR booster for HYDROPS2 images, and we have termed the generated image HYDROPS2-Mi2.

In the present study, the measured size of the endolymphatic space is significantly larger at 1.5 hours than at 3, 4.5, and 6 hours after IV-SD-GBCM. Measured values at 1.5 hours are surprisingly large for healthy subjects and unrealistic. In most volunteers, sufficient enhancement has not been achieved on the source images (PPI) obtained at 1.5 hours in the cochlear and vestibular perilymph. Therefore, the %EL was overestimated.

The subjective evaluation of the course of endolymphatic size over time after IV-SD-GBCM in patients with suspected Ménière’s disease demonstrated no significant differences in grades of endolymphatic hydrops between 3.5 and 4 hours or between 4 and 4.5 hours after IV-SD-GBCM. No study has compared the semi-quantitative values of endolymphatic size at multiple time points after IV-SD-GBCM. Our present study results indicate that measured values of endolymphatic size are stable from 3 to 6 hours in the cochlea and from 4.5 to 6 hours in the vestibule.

We observed statistically significant interaction between type of formed image and time after IV-SD-GBCM for both the cochlea and vestibule. As the graphs in Figs. 2 and 3 demonstrate, this means that there is a trend for the plotted lines of Images \#1 and \#2 to cross each other at a certain time point. The time of crossing in the cochlea is between 3 and 4.5 hours and in the vestibule, around 4.5 hours. Thus, we can speculate that the measured %EL value at around 4.5 hours would be similar between Images \#1 and \#2. Acquisition takes longer for Image \#1 than \#2. Use of the value of Image \#2 instead of that of Image \#1 could shorten examination time. Further clinical study is necessary if the measured %EL is comparable between Images \#1 and \#2 even in patients with endolymphatic hydrops.

Currently, most clinical studies wait 4 hours after IV-SD-GBCM before initiating the MR scan. The typical protocol takes approximately 40 min including patient set-up and localizing scan. Therefore, our current finding of 4.5 hours as the optimal waiting time would give additional confidence to ongoing clinical studies. However, serial data in patients with suspected endolymphatic hydrops is still needed to confirm optimal timing.

One study utilizing the IT method reported the normal range (mean ± 1.96 SD) of %EL as 8 to 26% in the cochlea and 20 to 41% in the vestibule for 45- to 55-year-old volunteers, and another study reported the normal range as 10.2 to 25.8% in the cochlea and 13.3 to 40.7% in the vestibule in 20- to 30-year-old volunteers. Mean values of our present results at 4.5 hours were 11.2% (Image \#1) and 11.6% (Image \#2) in the cochlea and 23.1% (Image \#1) and 22.3% (Image \#2) in the vestibule, values within the normal range shown utilizing the IT method. Although these previous measurements by the IT method were performed by manual tracing on 3D-FLAIR images, these previous results suggest that the measured results of the present study are reasonable. However, one ear was larger than this range in the cochlea on both Images \#1 and \#2, and 3 ears were larger than this range in the vestibule on both Images \#1 and \#2. Even in asymptomatic volunteers, enlargement of the endolymphatic space is sometimes seen, a finding consistent with results of a reported histological study performed in asymptomatic ears with endolymphatic hydrops. As previously suggested, there
may be a population with asymptomatic endolymphatic hydrops.30

Our study has some limitations. We included a small number of only male volunteers within a limited age range. Age or gender dependency of endolymphatic size might be of interest for future research. Evaluation was done in area on a single slice not in volume. Further study with volumetric measurement should be conducted in the future. Most previous studies in patients employed gadodiamide as the GBCM; in the present study, we employed gadoteridol. No study has directly compared these 2 kinds of GBCM. However, a study that uses these 2 kinds of GBCM in different patients suggested that the contrast effect of the two might be similar in the perilymph.3

In conclusion, a time delay of 1.5 hours after IV-SD-GBCM is not sufficient to evaluate endolymphatic size. Measured size plateaus between 4.5 and 6 hours. At 4.5 to 6 hours, values do not differ between Images 1 and 2 in both the cochlea and vestibule. These data might be valuable for further clinical studies in inner ear pathology.

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