Volume Quantification of Endolymph after Intravenous Administration of a Single Dose of Gadolinium Contrast Agent: Comparison of 18- versus 8-minute Imaging Protocols

Shinji NAGANAWA*, Toshio OHASHI, Mai KANOU, Kayao KUNO, Michihiko SONE, and Mitsuru IKEDA

1Department of Radiology, Nagoya University Graduate School of Medicine
65 Tsurumai-cho, Shouwa-ku, Nagoya 466–8550, Japan
2Department of Radiology, Kamiida Daiichi General Hospital
3Department of Otorhinolaryngology, Kamiida Daiichi General Hospital
4Department of Otorhinolaryngology, Nagoya University Graduate School of Medicine
5Department of Radiological and Medical Laboratory Sciences, Nagoya University Graduate School of Medicine

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Purpose: We measured the volume of the endolymphatic space by extending a previously proposed less observer-dependent method of area quantification and compared volume measurements obtained using long (18 min, Image A) and short (8 min, Image B) scan times.

Methods: We performed MR imaging of 40 ears in 20 patients with clinically suspected endolymphatic hydrops 4 hours after intravenous administration of single-dose gadolinium-based contrast material (IV-SD-GBCM). Two observers separately measured the ratio of the volume of the endolymph to that of total lymph in the cochlea and vestibule by extending the area ratio measurement method previously reported (Image A and B). The correlation between the values by Image A and B was calculated.

Results: We observed a strong linear correlation between Images A and B in the cochlear images; the Pearson’s correlation coefficient ($r$) was 0.928 for Observer A and 0.926 for Observer B ($P < 0.001$, for all). A strong linear correlation was also observed in the vestibular images; the Pearson’s correlation coefficient ($r$) was 0.962 for Observer A and 0.968 for Observer B ($P < 0.001$, for all).

Conclusion: Measurement of endolymphatic volume after IV-SD-GBCM may be feasible using an MR imaging protocol with a reduced scan time of 8 min. This method might facilitate greater use of endolymphatic hydrops imaging in clinical applications.

Keywords: endolymphatic hydrops, magnetic resonance imaging, temporal bone disease, volume quantification

Introduction

Magnetic resonance (MR) imaging has been used to evaluate endolymphatic hydrops (EH) in patients with suspected Ménière’s disease. Imaging of EH was initially attempted after intratympanic (IT) administration of gadolinium-based contrast material (GBCM), and an imaging method utilizing intravenous (IV) administration of a double dose of GBCM was then developed to decrease invasiveness. More recently, an IV method has been utilized that requires only a single dose of GBCM. Multiplication of $T_2$-weighted MR cisternography on HYDROPS (HYbriD of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal) or HYDROPS2 (HYbriD of Reversed image Of MR cisternography and posi-
tive Perilymph Signal by heavily T₂-weighted 3D-FLAIR) images increased the contrast-to-noise ratio (CNR) more than 200-fold. A less observer-dependent method of area quantification was then proposed to image EH after IV-GBCM using HYDROPS-Mi2 (HYDROPS-Multiplied with heavily T₂-weighted MR cisternography) and HYDROPS2-Mi2 (HYDROPS²-Multiplied with heavily T₂-weighted MR cisternography). The high CNR obtained by HYDROPS-Mi2 and HYDROPS2-Mi2 enabled a dramatic reduction of scan time with similar results of area measurement to that obtained by the conventional protocol with lengthy scan time.

A grading scale for EH imaging was proposed that employed a semi-quantitative evaluation of the area of endolymph in a single slice to grade the degree of EH. Most reported studies have utilized this evaluation of the area of endolymph. The presentation of volumetric images of endolymphatic hydrops has been tried in imaging after IT administration of GBCM and after IV-SD-GBCM, but images were susceptible to subtle changes in the threshold setting. Quantitative measurement of the volume of endolymph by setting a signal intensity threshold has not been reported mainly because the CNR between peri- and endolymph is insufficient to set an appropriate threshold.

In this study, we measured the volume of the endolymphatic space by extending the previously proposed less observer-dependent method of area quantification and compared the measurements obtained using long (18 min) and short (8 min) scan times.

Materials and Methods

Patients

We evaluated 40 ears in 20 patients (5 men, 15 women; aged 41 to 80 years, median 64 years) who underwent MR examination between April 1 2013 through January 31 2014 to assess clinically suspected endolymphatic hydrops. Experienced otolaryngologists determined the indication for MR examination. The differential diagnosis of Ménière’s disease was based on the guidelines of the American Academy of Ophthalmology and Otolaryngology–Head and Neck Surgery (AAO-HNS). All patients with suspected EH except those with contraindication for MR or GBCM and those who refused MR examination underwent the MR evaluation of endolymphatic hydrops. A medical ethics committee approved this retrospective study with a waiver for informed consent.

MR imaging

All MR imaging was performed using a 3-tesla unit (Skyra, Siemens, Erlangen, Germany) with a 32-channel array head coil. MR scanning was performed 4 hours after single-dose IV administration (0.2 mL/kg body weight or 0.1 mmol/kg body weight) of gadoteridol (Gd-HP-DO3A; ProHance, Eisai, 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.

According to the hospital’s clinical protocol for the evaluation of endolymphatic hydrops, patients underwent heavily T₂-weighted (hT₂W) MR cisternography (MRC) for anatomical reference of total lymph fluid and hT₂W 3-dimensional (3D) fluid-attenuated inversion recovery (FLAIR) with a 2250-ms inversion time (positive perilymph image, PPI) 4 hours after receiving IV-SD-GBCM. We set parameters as previously reported and obtained a PPI (15 min), MRC (3 min), and a PPI with fewer excitations (PPI short, 5 min). We obtained the PPI short as a back-up for the full PPI (15 min), which might be susceptible to patient motion from the lengthy scan time.

Table details the scan parameters.

Image processing

We generated 2 kinds of HYDROPS2-Mi2 images–Image A (total scan time, 18 min), (PPI − 0.04 × MRC) × MRC and Image B (total scan time, 8 min), (PPI short − 0.04 × MRC) × MRC.

Multiplication by the MRC was used to boost the contrast-to-noise ratio between the endo- and perilymph while suppressing and stabilizing the background signal of bone and air. We employed a constant value of 0.04 according to a recent study and generated HYDROPS2 images on the scanner console. We allowed negative signal values for the subtraction and applied no image registration program during this step.

We then transferred MR images to a Mac Book Pro personal computer (Apple Computer, Inc., Cupertino, CA, USA) with a free DICOM viewer (OsiriX image software, ver. 5.8 32 bit; downloadable at http://www.osirix-viewer.com/index.html), which allowed easy pixel-by-pixel multiplication between the image series.

Volume measurement

We estimated voxels with a negative value as endolymph. In 40 ears, we measured the percentage of the volume of endolymphatic space in the total lymphatic space (%EL) for the cochlea and vestibule semi-quantitatively on Images A and B ac-

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Two radiological technologists (with 9 and 12 years' experience in MR imaging) contoured the 2 ROIs around the cochlea and vestibule on MRC slices according to the instructions described below and example images (Fig. 1). Seven to 9 slices were contoured for the cochlea and 5 to 7 slices for the vestibule.

### Table. Pulse sequence parameters

| Sequence name             | Type                        | Repetition time (ms) | Echo time (ms) | Inversion time (ms) | Flip angle (degrees) | Section thickness (mm) | Pixel size (mm) | Number of slices | Echo train length | Field of view (mm) | Matrix size | Number of excitations | Scan time (minutes) |
|---------------------------|-----------------------------|---------------------|----------------|---------------------|----------------------|-----------------------|------------------|------------------|------------------|------------------|------------|----------------------|---------------------|
| MR cisternography (MRC)  | SPACE with restore pulse    | 4400                | 544            | NA                 | 90/ initial 180      | 0.5 × 0.5             | 104              | 173              | 165 × 196        | 324 × 384         | 1.8        | 3                     |
| Heavily T₂ weighted 3D-FLAIR (PPI) | SPACE with inversion pulse | 9000                | 544            | 2250               | 90/ initial 180      | 0.5 × 0.5             | 104              | 173              | 165 × 196        | 324 × 384         | 4          | 15                    |
| Heavily T₂ weighted 3D-FLAIR (PPI short) | SPACE with inversion pulse | 9000                | 544            | 2250               | 90/ initial 180      | 0.5 × 0.5             | 104              | 173              | 165 × 196        | 324 × 384         | 1.4        | 5                     |

FLAIR, fluid-attenuated inversion recovery; Generalized auto-calibrating partially parallel acquisition (GRAPPA) × 2 for all sequences; PPI, positive perilymph image; SPACE, sampling perfection with application-optimized contrasts using different flip angle evolutions

All sequences utilize frequency selective fat suppression pre-pulse.

Each 3-dimensional (3D) slab is set in an identical axial orientation.

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**Fig. 1.** An example of an image of magnetic resonance cisternography (MRC) with region of interest (ROI) settings for the cochlea (a) and vestibule (b). Seven to 9 slices were contoured for the cochlea and 5 to 7 slices for the vestibule.

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According to the previously reported threshold-based method, two radiological technologists (with 9 and 12 years' experience in MR imaging) contoured the 2 ROIs around the cochlea and vestibule on MRC slices according to the instructions described below and example images (Fig. 1). Seven to 9 slices were contoured for the cochlea and 5 to 7 slices for the vestibule.

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**Fig. 1.** An example of an image of magnetic resonance cisternography (MRC) with region of interest (ROI) settings for the cochlea (a) and vestibule (b). Seven to 9 slices were contoured for the cochlea and 5 to 7 slices for the vestibule.
basal turn connects with the vestibule, the border of the ROI should be drawn at the posterior edge of the osseous spiral lamina.

3. On the MRC, the vestibular ROI should exclude the semicircular canals and ampullas. Where the basal turn of the cochlea connects with the vestibule, the border of the ROI should be drawn at the posterior edge of the osseous spiral lamina.

The 2 observers reviewed example images when drawing the ROIs. The ROIs drawn on the MRC were copied and pasted onto Images A and B. We used the histogram function of OsiriX to count the number of all voxels within the ROI and the number of voxels with a negative signal intensity value (i.e., endolymph) within the ROI.

The ratio of the volume (%) of endolymphatic space in the entire lymphatic space (%EL) was defined as: \[
%\text{EL} = \frac{\text{sum of the number of negative voxels for the endolymph in the ROI of all slices divided by the total number of voxels in the ROIs of all slices}}{\times 100}.
\]

Statistical analysis

We used Pearson’s correlation coefficient to evaluate the correlation between volume ratios from the 2 pairs of processed images and assess the correlation between the volume ratios by the 2 observers. We employed the York method to calculate a linear regression line.

Results

Figure 2 shows the relationship between the volume ratios from Images A and B. We observed a strong linear correlation in the cochlea. The Pearson’s correlation coefficient \(r\) was 0.928 for Observer 1 and 0.926 for Observer 2 (\(P < 0.001\), for all), and the estimated slope coefficient and intercept (± standard error) of the linear regression line were 1.002 ± 0.062 and 1.957 ± 1.490 for Observer 1 and 1.012 ± 0.064 and 1.909 ± 1.467 for Observer 2. We also observed a strong linear correlation in the vestibule. The Pearson correlation coefficient \(r\) was 0.962 for Observer 1 and 0.968 for Observer 2 (\(P < 0.001\), for all); and the estimated slope coefficient and intercept (± standard error) of the linear regression line were 0.950 ± 0.043 and 0.792 ± 1.334 for Observer 1 and 0.963 ± 0.040 and 0.393 ± 1.303 for Observer 2.

Fig. 2. Scattergrams of the volume ratios from Images A and B by Observer 1 (a, cochlea; b, vestibule) and those by Observer 2 (c, cochlea; d, vestibule).
The Pearson’s correlation coefficients (r) between the volume ratios by the 2 observers were 0.998 for the cochlea and 0.984 for the vestibule in Images A and 0.998 for cochlea and 0.981 for the vestibule in Images B.

Figure 3 shows representative images of MRC.

Discussion

In the present study, we observed a strong linear correlation of the ratio of endolymphatic volume between Images A and B of both the cochlea and the vestibule by multiple observers. This result may indicate the feasibility of replacing the 18- with the 8-min scan to measure the volume ratio of endolymphatic space, The CNR compensation by multiplication of the HYDROPS2 images with the MRC might have allowed the accurate volume measurement even with noisy images obtained in shorter scan time.13

A recent study showed strong correlation of area measurements by HYDROPS2-Mi2 utilizing 17-min (4 excitations for PPI) and 10-min (2 excitations for PPI short) scan times.14 In the present study, we further reduced the number of excitations to 1.4, reducing the scan time for PPI short to 5 min (scan time for HYDROPS2-Mi2, 8 min). Even with this further reduction in scan time, the results of volume measurement showed a strong correlation with those from the longer scan time of 18 min. Reduction of scan time to 8 min would further support the clinical feasibility of MR imaging of EH.

Our study has several limitations. It is retrospective, and so there may be some bias in patient selection. In addition, we did not randomize the order of scan acquisition from MRC, PPI, and PPI short. The time interval between MRC was always shorter for PPI than PPI short, which may have created a difference in subtraction errors in Images A and B due to misregistration between scans. Use of an automatic rigid body registration program might help reduce subtraction errors. Further, though the correlation between Images A and B is strong, we do not know which value is more accurate because there is no gold standard for measuring endolymphatic volume. Finally, although the ROI setting on the MRC for volume measurement is faster compared to the contouring of each endolymphatic space and total lymph space on HYDROPS2 images, it still requires approximately 15 min per patient. This might be a problem for a wide clinical application of volume quantification. An automatic bias-free segmentation method should be developed in the future.4

Conclusions

Use of an MR imaging protocol with a reduced scan time of 8 min might be feasible to measure endolymphatic volume after IV-SD-GBCM and thereby promote further application of EH imaging in the clinical setting.

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References

1. Pyykkö I, Zou J, Poe D, Nakashima T, Naganawa S. Magnetic resonance imaging of the inner ear in Meniere’s disease. Otolaryngol Clin North Am 2010; 43:1059–1080.
2. Pyykkö I, Nakashima T, Yoshida T, Zou J, Naganawa S. Meniere’s disease: a reappraisal supported by a variable latency of symptoms and the MRI visualisation of endolymphatic hydrops. BMJ Open 2013; 3(2).
3. Nakashima T, Naganawa S, Sugiura M, et al. Visualization of endolymphatic hydrops in patients with Meniere’s disease. Laryngoscope 2007; 117:415–420.
4. Naganawa S, Nakashima T. Visualization of endolymphatic hydrops with MR imaging in patients with Ménière’s disease and related pathologies: current status of its methods and clinical significance. Jpn J Radiol 2014; 32:191–204.
5. Tagaya M, Teranishi M, Naganawa S, et al. 3 Tesla magnetic resonance imaging obtained 4 hours after intravenous gadolinium injection in patients with sudden deafness. Acta Otolaryngol 2010; 130:665–669.
6. Nakashima T, Naganawa S, Teranishi M, et al. Endolymphatic hydrops revealed by intravenous gadolinium injection in patients with Ménière’s disease. Acta Otolaryngol 2010; 130:338–343.
7. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Visualization of endolymphatic hydrops in Ménière’s disease after intravenous administration of single-dose gadodiamide at 1.5T. Magn Reson Med Sci 2013; 12:137–139.
8. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Three-dimensional visualization of endolymphatic hydrops after intravenous administration of single-dose gadodiamide. Magn Reson Med Sci 2013; 12:147–151.
9. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Visualization of endolymphatic hydrops in Ménière’s disease after single-dose intravenous gadolinium-based contrast medium: timing of optimal enhancement. Magn Reson Med Sci 2012; 11:43–51.
10. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Visualization of endolymphatic hydrops in Ménière’s disease with single-dose intravenous gadolinium-based contrast media using heavily T2-weighted 3D-FLAIR. Magn Reson Med Sci 2010; 9:237–242.
11. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T. Imaging of Ménière’s disease after intravenous administration of single-dose gadodiamide: utility of multiplication of MR cisternography and HYDROPS image. Magn Reson Med Sci 2013; 12:63–68.
12. Naganawa S, Suzuki K, Yamazaki M, Sakurai Y. Serial scans in healthy volunteers following intravenous administration of gadoteridol: time course of contrast enhancement in various cranial fluid spaces. Magn Reson Med Sci 2014; 13:7–13.
13. Naganawa S, Suzuki K, Nakamichi R, et al. Semi-quantification of endolymphatic size on MR imaging after intravenous injection of single-dose gadodiamide: comparison between two types of processing strategies. Magn Reson Med Sci 2013; 12:261–269.
14. Naganawa S, Kawai H, Ikeda M, Sone M, Nakashima T. Imaging of endolymphatic hydrops in 10 minutes: a new strategy to reduce scan time to one third. Magn Reson Med Sci 2014 Dec 15. [Epub ahead of print]
15. Nakashima T, Naganawa S, Pyykko I, et al. Grading of endolymphatic hydrops using magnetic resonance imaging. Acta Otolaryngol Suppl 2009; (560):5–8.
16. Katayama N, Yamamoto M, Teranishi M, et al. Relationship between endolymphatic hydrops and vestibular-evoked myogenic potential. Acta Otolaryngol 2010; 130:917–923.
17. Gürkov R, Flatz W, Louza J, Strupp M, Ertl-Wagner B, Krause E. In vivo visualized endolymphatic hydrops and inner ear functions in patients with electrocochleographically confirmed Ménière’s disease. Otol Neurotol 2012; 33:1040–1045.
18. Naganawa S, Ishihara S, Iwano S, Sone M, Nakashima T. Three-dimensional (3D) visualization of endolymphatic hydrops after intratympanic injection of Gd-DTPA: optimization of a 3D-real inversion-recovery turbo spin-echo (TSE) sequence and application of a 32-channel head coil at 3T. J Magn Reson Imaging 2010; 31:210–214.