TECHNICAL NOTE

Imaging of Ménière's Disease by Subtraction of MR Cisternography from Positive Perilymph Image

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To visualize endolymph, perilymph, and bone separately in a single image after intravenous injection of single-dose gadodiamide, we generated a HYDROPS2 image (subtraction of MR cisternography from heavily T₂-weighted 3-dimensional fluid-attenuated inversion recovery image) in 12 patients with suspected Ménière's disease. The contrast-to-noise ratio of endo- and perilymph did not differ significantly between the HYDROPS2 and previously reported HYDROPS (hybrid of reversed image of positive endolymph signal and native image of positive perilymph Signal) images, and scan time was 40% shorter for the HYDROPS2 than HYDROPS.

Keywords: *intravenous, magnetic resonance imaging, Ménière's disease, 3D imaging*

Introduction

Endolymphatic hydrops in patients with Ménière's disease was first visualized by magnetic resonance (MR) imaging using 3-dimensional (3D) fluid-attenuated inversion recovery (FLAIR) after intratympanic (IT) administration of gadolinium-based contrast material (GBCM).¹ Researchers from multiple institutions have reported some correlation of endolymphatic hydrops visualized on MR images and clinical tests,^{2–4} but one report failed to show significant correlation between endolymphatic hydrops and caloric test.⁵ Thus, correlation between endolymphatic hydrops and clinical findings remains under investigation. The IT administration of GBCM is off-label use and requires 24 hours of waiting time and puncture of the tympanic membrane, so the development of a method to detect endolymphatic hydrops by intravenous (IV) injection of GBCM was explored. Visualization of endolymphatic hydrops in patients with Ménière's disease is reported using heavily T₂-weighted 3D-FLAIR (hT₂W-3D-FLAIR) and imaging 4 hours after IV injection of single-dose GBCM (IV-SD-GBCM).⁶ On 3D-FLAIR including hT₂W-3D-FLAIR images, perilymph signal increases after administration of GBCM, and signal intensities of

both endolymphatic space and surrounding bone show values near zero (positive perilymph image, PPI). To clarify the boundaries of endolymphatic space and surrounding bones and rule out partial volume averaging artifact from bones, shortening of the inversion time of 3D-FLAIR after IT administration of GBCM was proposed.⁷ Optimal shortening of 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).⁷ Similar to acquisition of PPI and PEI after IT administration of GBCM, PPI and PEI could be obtained after IV-SD-GBCM based on the hT₂W-3D-FLAIR technique by adjusting inversion time.⁸

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^{9,10} but not after IV-SD-GBCM, probably because of lower GBCM concentration in 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 (HYbrid of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal) facilitate recognition of endolymph space by IV-SD-GBCM but require scan time of 30 min to obtain both PPI and PEI for

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processing.¹¹ Furthermore, occasional failure of PEI to visualize small endolymph space in the cochlea, probably due to low signal-to-noise ratio (SNR) and blurring,⁸ might be a risk for underestimating the size of endolymphatic space. To overcome these problems with HYDROPS, we sought to develop an alternative processing technique by subtracting heavily T₂-weighted MR cisternography from PPI to achieve images with similar contrast to HYDROPS images using a shorter scan time. We named the resulting image “HYDROPS2” (HYbrid of Reversed image Of MR cisternography and positive Perilymph Signal by heavily T₂-weighted 3D-FLAIR). In this study, we adjusted the technique for HYDROPS2 processing to obtain images with similar contrast to HYDROPS images and compared image contrast and results of endolymphatic hydrops grading between HYDROPS and HYDROPS2 in patients with suspected Ménière’s disease.

Materials and Methods

Patients

The study included 12 patients with clinically suspected Ménière’s disease (4 men, 8 women, aged 17 to 76 years) who underwent MR scanning 4 hours after single-dose (0.2 mL/kg or 0.1 mmol/kg body weight) IV administration of gadolinium-diethylenetriamine pentaacetic acid-bis (methylamide) (gadodiamide, Gd-DTPA-BMA; Omniscan, Daiichi-Sankyo Co. Ltd., Tokyo, Japan) to evaluate the degree of endolymphatic hydrops. All patients had an estimated glomerular filtration rate (eGFR) value exceeding 60 mL/min/1.73 m². Each eGFR was calculated using an equation reported by the Japanese Society of Nephrology for estimating GFR in Japanese patients based on serum creatinine level (Cr): $eGFR (mL/min/1.73 m^2) = 194 \times Cr^{-1.094} \times Age^{-0.287}$ (if female, $\times 0.739$). Experienced otorhinolaryngologists made the clinical diagnosis of Ménière’s disease based on the guidelines of the American Academy of Ophthalmology and Otolaryngology—Head and Neck Surgery (AAO-HNS).¹²

MR imaging

All MR imaging was performed using a 3-tesla unit (Verio, Siemens, Erlangen, Germany) with 32-channel array head coil. According to the clinical protocol of our hospital for the evaluation of endolymphatic hydrops, the 12 patients underwent heavily T₂-weighted MR cisternography (MRC) for anatomical reference of total lymph fluid, hT₂W-3D-FLAIR with 2250-ms inversion time

(PPI), and hT₂W-3D-inversion recovery with 2050-ms inversion time (PEI) 4 hours after receiving IV-SD-GBCM. Parameters were set as previously reported.⁸

Detailed scan parameters for MRC were: heavily T₂-weighted MRC images using variable flip angle 3D turbo spin echo technique (SPACE: sampling perfection with application-optimized contrasts by using different flip angle evolutions); repetition time (TR), 4400 ms; echo time (TE), 544 ms; initial re-focusing 180° flip angle rapidly decreased to constant 120° flip angle for the turbo-spin-echo refocusing echo train; echo-train length, 173 with restore magnetization pulse (fast recovery pulse); matrix size, 322 × 384; 96 axial slices of 1.0-mm-thickness covering the labyrinth; field of view (FOV), 15 × 18 cm; generalized autocalibrating partially parallel acquisition (GRAPPA) parallel imaging technique; acceleration factor, 2; number of excitations (NEX), 1.8; and scan time, 2.9 min.

Detailed scan parameters of hT₂W-3D-FLAIR for PPI were: SPACE sequence; TR, 9000 ms; TE, 544 ms; inversion time, 2250 ms; frequency-selective fat-suppression pre-pulse; initial refocusing 180° flip angle rapidly decreased to constant 120° flip angle for turbo-spin-echo refocusing echo train; echo-train length, 173; matrix size, 322 × 384; and 104 axial slices of 1.0-mm thickness covering the labyrinth; FOV, 15 × 18-cm; acquired using GRAPPA parallel imaging technique with acceleration factor of 2, 4 excitations, and scan time of 14.5 min.

For PEI, inversion time was 2050 ms. To simplify comparison, we used identical FOV, matrix size, and slice thickness for MR cisternography, PPI, and PEI.

Usually, signal intensity values of perilymph are far larger on MRC without inversion pulse than PPI with inversion pulse. Before generating HYDROPS2 images, we measured signal intensity values of perilymph in the vestibule on PPI and MRC in 2 patients, drawing a circular region of interest (ROI) on the scanner console to set up the constant value to balance the signal intensity values between PPI and MRC. We determined a constant value that would reduce the original signal intensity value of the perilymph on PPI to approximately half the original value after the subtraction of MRC multiplied by the constant value. The subtraction should yield similar absolute signal intensity value of positive perilymph and negative endolymph on processed images. Based on results in the 4 ears of the 2 patients, the average constant value was 0.05 (range, 0.04 to 0.06). Therefore, we generated HYDROPS2 images on the scanner console by

subtracting the MRC multiplied by 0.05 from PPI and generated HYDROPS images by subtracting PEI from PPI. The HYDROPS and HYDROPS2 images generated for all 12 patients were saved and transferred to a PACS server. For the result of subtraction, negative signal value was allowed. Acquisition of source images takes approximately 30 min for HYDROPS images and approximately 18 min for HYDROPS2 images. During subtraction, we applied no image registration program in this study.

Image analysis

For quantitative evaluation, we measured CNR between peri- and endolymph on HYDROPS and HYDROPS2 images. To reduce partial volume averaging effect, we measured CNR in the vestibule, where endolymphatic space is usually larger than in the cochlea. A circular region of interest (ROI) of 1.2-mm diameter was manually placed on the PACS viewer (Rapideye, Toshiba Medical Systems, Tokyo, Japan). We referred to MRC to set ROIs on the PPI image. We set the ROI for vestibular endolymph in the center of the area of low signal in the utricle of the vestibule on the PPI image at the slice level of the superior vestibular nerve, and we set the ROI for vestibular perilymph in the area of high signal surrounding the utricle on the PPI image. If endolymph occupied the entire vestibule, we set the ROI in the area of high signal in the lateral semicircular canal. Noise level was defined as the standard deviation (STD) of air signal in the lower corner of the image, and we set a circular ROI of 10-mm diameter for noise. ROIs were copied from PPI onto HYDROPS and HYDROPS2 images. CNR was defined as the difference in signal intensity value between peri- and endolymph divided by the STD of the air signal. We compared average CNR between HYDROPS and HYDROPS2 using Student's *t*-test. $P < 0.05$ was considered statistically significant difference.

In the present study, we estimated noise in the area of air, although we applied parallel imaging. Use of parallel imaging and multi-channel phased array coil causes uneven noise distribution across the image.¹³ However, in the present study, we measured CNR to compare it between HYDROPS and HYDROPS2 images in each subject. We estimated signal in the inner ear and noise in the area of air in the lower corner of the image in the identical place in each subject, places that differed little among subjects. Though our CNR measurement was not ideal, we believe it was reasonably appropriate for our study purpose.

For qualitative analysis, 2 neuroradiologists with 5- and 22-years' experience in inner ear MR imag-

ing independently evaluated images on a PACS viewer. Reviewers knew patients had clinically suspected Ménière's disease. They evaluated the vestibule and cochlea separately. First, they reviewed either the HYDROPS or HYDROPS2 image and graded endolymphatic hydrops as none, mild, or significant for the cochlea and vestibule according to previously proposed criteria.¹⁴ Then, after more than 2 weeks, they reviewed and graded endolymphatic hydrops in the other image. Review order of patients was randomized. The presence of misregistration artifact for HYDROPS and HYDROPS2 images was scored on a positive or negative basis. Apparent double contour of the labyrinth was considered positive for misregistration. In both review sessions, MRC images were used as maps of the total lymph fluid anatomy. Reviewers resolved any discrepancy in grading by consensus after discussion. We used Wilcoxon signed-ranks test to compare grades of endolymphatic hydrops between HYDROPS and HYDROPS2 images. $P < 0.05$ was considered statistically significant difference. Image window width was set at 200 and window level, at 50.

Our institutional medical ethics committee approved this retrospective study, and informed consent was waived.

Results

In the quantitative analysis, the average CNR $\pm$ STD of the HYDROPS image was 100.1 ± 29.2 and of the HYDROPS2 image, 91.1 ± 33.6 . The difference between the 2 types of image was not significant.

In the qualitative analysis, grading scores of endolymphatic hydrops did not differ significantly by HYDROPS and HYDROPS2 image for either the cochlea or vestibule (Figs. 1, 2). For the cochlea, the hydrops grade was higher by HYDROPS2 than HYDROPS in 2 ears; in no ear was the grade by HYDROPS2 lower than that by HYDROPS. For the vestibule, the grade of hydrops was higher by HYDROPS2 than HYDROPS in one ear; in no ear was the grade by HYDROPS2 lower than that by HYDROPS.

No misregistration artifact was noticed in any ear.

Table summarizes the patients, results of endolymphatic hydrops grading for the cochlea and vestibule, and results of CNR measurement.

Discussion

The development of the HYDROPS2 image has

Fig. 1. A 72-year-old woman with bilateral Ménière's disease. **(a)** Heavily T_2 -weighted magnetic resonance cisternography (MRC) of the left inner ear. **(b)** Corresponding positive endolymph image (PEI) obtained by heavily T_2 -weighted (hT_2W) 3-dimensional (3D) inversion recovery sequence with inversion time of 2050 ms. Note the significantly dilated cochlear endolymph (short arrows) and vestibular endolymph (long arrows) show bright signal. **(c)** Corresponding positive perilymph image (PPI) obtained by hT_2W 3D fluid-attenuated inversion recovery (FLAIR) sequence with inversion time of 2250 ms. Filling defects are noted at the corresponding locations of high signal on PEI. The boundaries between cochlear endolymph (short arrows) and bone and between vestibular endolymph (long arrows) and bone are unclear. **(d)** Corresponding HYDROPS (HYbrid of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal) image obtained by subtracting the PEI image from the PPI image. Note that perilymph, endolymph, and bone show different signal. Perilymph shows positive signal (white on image); endolymph shows negative signal (black on image); and bone shows zero signal (gray on image). Short arrows indicate significantly dilated cochlear endolymph, and long arrows indicate significantly dilated vestibular endolymph. **(e)** Corresponding HYDROPS2 (HYbrid of Reversed image Of MR cisternography and positive Perilymph Signal by heavily T_2 -weighted 3-dimensional fluid-attenuated inversion recovery) image obtained by the subtraction of MRC image multiplied by 0.05 from PPI image. Significantly dilated cochlear endolymph (short arrows) and vestibular endolymph (long arrows) are visualized with similar contrast as that of the HYDROPS image.

enabled the recognition of endolymphatic space on a single kind of image with similar contrast to that of the HYDROPS image in shorter scan time, even after clinically feasible IV-SD-GBCM. On both image types, perilymph signal is positive, endolymph signal is negative, and surrounding bone signal is zero. Image contrast resembles that of 3D-real IR images obtained after IT-GBCM. Acquisition time for source images is approximately 40% shorter for HYDROPS2 than HYDROPS images. Both PEI and PPI employ inversion recovery pulse, so the signal-to-noise ratios of PEI and PPI are usually

lower than the SNR of MRC without inversion recovery pulse. During the generation of the HYDROPS image, simple subtraction of PEI with low SNR from PPI further increases noise. In the present study, we performed subtraction of MRC with an attenuation value of 0.05 to generate a HYDROPS2 image. Subtraction of the attenuated MRC with high SNR from PPI for HYDROPS2 might improve noise management. So, HYDROPS2 images obtained in a shorter scan time could maintain a similar level of CNR as that of HYDROPS images.

Fig. 2. A 76-year-old man with bilateral Ménière's disease. **(a)** A HYDROPS (HYbrid of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal) image of the right inner ear. "Mild" endolymphatic hydrops of the cochlea (short arrows) and significant endolymphatic hydrops of the vestibule (long arrows) are visualized. **(b)** Corresponding HYDROPS2 (HYbrid of Reversed image Of MR cisternography and positive Perilymph Signal by heavily T₂-weighted 3-dimensional fluid-attenuated inversion recovery) image. Note that the cochlear endolymph (short arrows) is visualized slightly larger on the HYDROPS2 image than the HYDROPS image **(a)**. On the HYDROPS2 image, cochlear endolymphatic hydrops is graded as "significant." Endolymphatic hydrops of the vestibule is graded "significant" on HYDROPS2, which is the same grade as HYDROPS.

Grades of endolymphatic hydrops for both the cochlea and vestibule did not differ significantly between HYDROPS and HYDROPS2 images, and grades were not lower on HYDROPS2 than HYDROPS images in any ear. Therefore, the sensitivity of the HYDROPS2 image to detect endolymphatic hydrops might be higher or at least similar to that of the HYDROPS image, though we lack histological confirmation for the grades of endolymphatic hydrops in the present study. Histological confirmation of endolymphatic hydrops is impossible in living human patients. Endolymphatic hydrops may be overestimated by HYDROPS2 and underestimated by HYDROPS. It is still necessary to validate the grading by HYDROPS and HYDROPS2 in a larger patient population by correlating patient symptoms and results of clinical ontological tests with imaging results.

The HYDROPS2 image has some potential limitations. In the present study, we observed no ear with poor contrast enhancement of the perilymph, which might occur by improper injection of contrast material, too early scan timing, and low permeability of the blood-perilymph barrier by unknown etiology. Lower-than-usual perilymph signal on PPI in the case of poor contrast enhancement might result in overestimation of endolymph size on HYDROPS2 images. Therefore, image interpretation should include PPI as well as

HYDROPS2 images to prevent misdiagnosis in the clinical setting. In cases with poor perilymph enhancement, it might be necessary to reduce the constant value from 0.05; this value was considered appropriate in this study because the HYDROPS2 image preserved positive signal of perilymph in all ears.

Although we noted no significant motion, motion could also cause image misregistration. However, reducing scan time from 30 min for HYDROPS image to 18 min for HYDROPS2 should reduce the chance of significant motion during scanning.

This preliminary study is also limited because we did not include normal subjects, so we cannot conclude that HYDROPS2 images improve recognition of endolymphatic space in patients without endolymphatic hydrops. Therefore, further study is necessary to determine if the HYDROPS2 image can replace the HYDROPS image.

Conclusions

The subtraction of MRC from PPI facilitated recognition of endolymph space on images obtained after IV-SD-GBCM in shorter scan time than that for the previously proposed method. Further clinical study is warranted for the routine use of this subtracted HYDROPS2 image.

Table. Summary of patients, endolymphatic hydrops grading and contrast-to-noise measurements

Patient [#]	sex	age	side	HYDROPS			HYDROPS2		
				Grading score			Grading score		
				cochlea	vestibule	CNR	cochlea	vestibule	CNR
1	M	63	R	2	0	28.9	2	0	73.3
			L	1	1	77.2	1	1	98.3
2	F	63	R	1	1	115.6	1	2	158.0
			L	1	1	163.3	1	1	194.0
3	F	58	R	2	0	123.3	2	0	126.7
			L	0	1	83.3	0	1	89.2
4	F	72	R	2	2	126.7	2	2	90.0
			L	2	2	137.8	2	2	80.0
5	F	52	R	2	2	117.5	2	2	61.7
			L	1	2	102.5	1	2	63.3
6	F	37	R	2	2	95.0	2	2	70.0
			L	2	1	137.5	2	1	70.0
7	F	33	R	2	2	93.3	2	2	61.4
			L	1	2	91.1	1	2	42.9
8	F	17	R	2	2	98.8	2	2	82.0
			L	0	2	78.8	0	2	88.0
9	F	52	R	2	2	87.8	2	2	100.0
			L	1	2	93.3	2	2	122.0
10	M	47	R	2	2	90.0	2	2	68.0
			L	2	2	125.7	2	2	72.0
11	M	76	R	1	2	58.9	2	2	66.7
			L	2	2	121.1	2	2	115.0
12	M	70	R	2	2	64.4	2	2	86.7
			L	1	1	90.0	1	1	106.7
Average		53				100.1			91.1
STD		23				29.2			33.6
				*n.s.	**n.s.	***n.s.	*n.s.	**n.s.	***n.s.

CNR; contrast-to-noise ratio, n.s.; no significant difference

Grading score: 2, significant endolymphatic hydrops; 1, mild endolymphatic hydrops; 0, no hydrops

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 image

STD; Standard deviation

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