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Original Article

Magnetic Resonance 3D Measurement of the Endolymphatic Space in 100 Control Human Subjects

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Three Dimensional-magnetic resonance imaging of the inner ear endolymphatic space was performed in 100 control human subjects. Ear endolymphatic space was visualized using contrast-enhanced magnetic resonance imaging with intravenous gadolinium injection. The images were acquired on a 3-tesla magnetic resonance scanner using a 32-channel array head coil for all patients. The ear endolymphatic space and total fluid space volumes of the inner ear, cochlea, and vestibule were measured, and the ear endolymphatic space in the cochlea and vestibule was classified into four categories. The cochlea categories were: c-1, no ear endolymphatic space; c-2, ear endolymphatic space visualized only until the upper turn; c-3, ear endolymphatic space visualized from the upper turn to the second turn; and c-4, ear endolymphatic space visualized up to the basal turn. The vestibule categories were: v-1, no ear endolymphatic space; v-2, ear endolymphatic space visualized only in the utriculus; v-3, ear endolymphatic space visualized in the utriculus and sacculus separately; and v-4, ear endolymphatic space visualized in the utriculus and sacculus together. The mean TFS volumes of the inner ear, cochlea, and vestibule were 282.1 ± 33.2 µL, 112.9 ± 15.9 µL, and 69.1 ± 9.9 µL, respectively, and that of the ampulla of the posterior semicircular canal was 7.8 ± 1.7 µL. The mean ear endolymphatic space/total fluid space volume ratio in the cochlea was 10.3 ± 6.7% and that in the vestibule was 17.3 ± 12.2%. This ratio in the cochlea was between the results of categories c-1 and c-2 and that in the vestibule between those of categories v-2 and v-3. Two subjects had ear endolymphatic space extending from the vestibule to the posterior non-ampullated crus of the lateral semicircular canal. These findings can be applied as standard reference values for further research.

KEYWORDS: Control participants, endolymphatic space, inner ear MRI, normal value, volumetric measurement

INTRODUCTION

All individuals have an endolymphatic space (ELS) in the inner ear. When the ELS increases beyond its normal size, it can be detected as an extended ELS. In 1938, endolymphatic hydrops (ELH) was first demonstrated by Hallpike and Cairns[1] and Yamakawa,[2] and it was only possible to show the presence of hydrops in post-mortem temporal bone specimens. The presence of ELH in patients with Meniere's disease (MD) is generally accepted as a hallmark of this disease. The first report of the visualization of ELH in living patients with MD using 3-dimensional magnetic resonance (3D-MR) imaging was published by Nakashima et al[3] in 2007.

The purpose of this study was to quantitatively measure the volume of the inner ear ELS in subjects without vertiginous or cochlear symptoms and to determine the normal value of the ELS using three-dimensional (3-D) inner ear magnetic resonance imaging (MRI).

MATERIALS AND METHODS

Subjects

One hundred subjects without vertiginous or cochlear symptoms were included in this study. Subjects with vertigo, hearing loss, middle or inner ear diseases, cranial disease, head trauma, renal disease, or heart disease were excluded. The enrolled subjects had no history of gadolinium allergy. This study was approved by the Medical Ethics Committee of Nara Medical University Hospital

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(certificate number: 0889). Written informed consent was obtained from all subjects, and this study was performed in compliance with the Declaration of Helsinki.

Pre-Processing

The area of the ELS was first confirmed using our workstation (Virtual Place; AZE, Ltd., Tokyo, Japan) (Figure 1). Because ELS voxels have negative signal values and the perilymph space voxels have positive signal values, positive perilymph images (PPI) and positive endolymph images (PEI) were transferred, and PEI images were subtracted from the PPI images using the fusion program included with the multi-volume software in our workstation. The borderline between the gray and green areas of the color bar in our subtracted image was consistent with the value of zero in our program (Figure 1). Additionally, our subtracted image was consistent with the "PPI-PEI" image that was prepared during the MRI examination. In this process, areas of intensity lower than gray were categorized as the ELS.

We used the method described by Naganawa et al[4] for using MR as a tool for imaging ELH. MR imaging measurements were performed 4 hours after intravenous administration of a single dose of Gd-diethylenetriaminepentaacetic acid bis-methylamide (0.2 mL/kg or 0.1 mmol/kg body weight; Magnescope, Guerbet, Tokyo, Japan). Imaging was performed on a 3T MR imaging unit (Magnetom Verio; Siemens, Erlangen, Germany) using a 32-channel array head coil. Special sequences for the differentiation of endolymphatic and perilymphatic fluid were adopted, as proposed by Naganawa et al[4] All subjects underwent the following: heavily T2-weighted (hT2W) MR cisternography (MRC) for anatomical total lymph fluid reference; hT2W 3-D fluid-attenuated inversion recovery sequences with an inversion time of 2250 ms, resulting in PPI; and hT2W 3-D inversion recovery with an inversion time of 2050 ms, resulting in PEI. The detailed scan parameters for hT2W MRC were as follows: variable refocus flip angle 3-D-turbo spin-echo (sampling perfection with application-optimized contrasts using different flip angle evolutions [SPACE]); repetition time (TR), 4400 ms; echo time (TE), 544 ms; constant flip angle mode; matrix size, 322 × 384; slices per slab, 104; slice thickness, 1.0 mm; field of view, 150.9 × 180.0 mm; and bandwidth, 434 Hz/pixel.

Image Fusion Method and Magnetic Resonance Imaging Evaluation

This technique was used to evaluate the MR imaging data using the inner ear total fluid space (TFS; SPACE sequence) and ELS (PPI-PEI) images reconstructed using a specialized workstation (Figure 1).[5] Briefly, the inner ear fluid space was manually separated from the surrounding structures using the object extraction function and cutting tool of the workstation. A high-quality 3D image was then semi-automatically constructed using both anatomical and tissue information to fuse 3D inner ear fluid space and 3D ELS images. Components of the inner ear were identified by the border between the inner ear and the peripheral side of the acoustic nerve, between the end of the cochlea and the vestibule, between the three ampullae of the semi-circular canals (SCCs) and the vestibule, and between the distal side of the common crus and the vestibule, using anatomical drawings.[6] The volumes of the inner ear ELS and TFS were measured, and their ratio was calculated using the aforementioned multi-volume software. The volumes of the cochlea, vestibule, and SCCs were also measured.

Statistical Analysis

Values are presented as mean ± standard deviation. Volumetric measurements and ratios were compared using 1-way analysis of variance (ANOVA) to compare multiple groups, followed by pairwise comparisons with Tukey's post hoc test and unpaired Student's *t*-tests for comparing two groups. Statistical analyses were performed using the StatMate software (version 5.01; ATOMS, Tokyo, Japan). Statistical significance was set at $P < .05$.

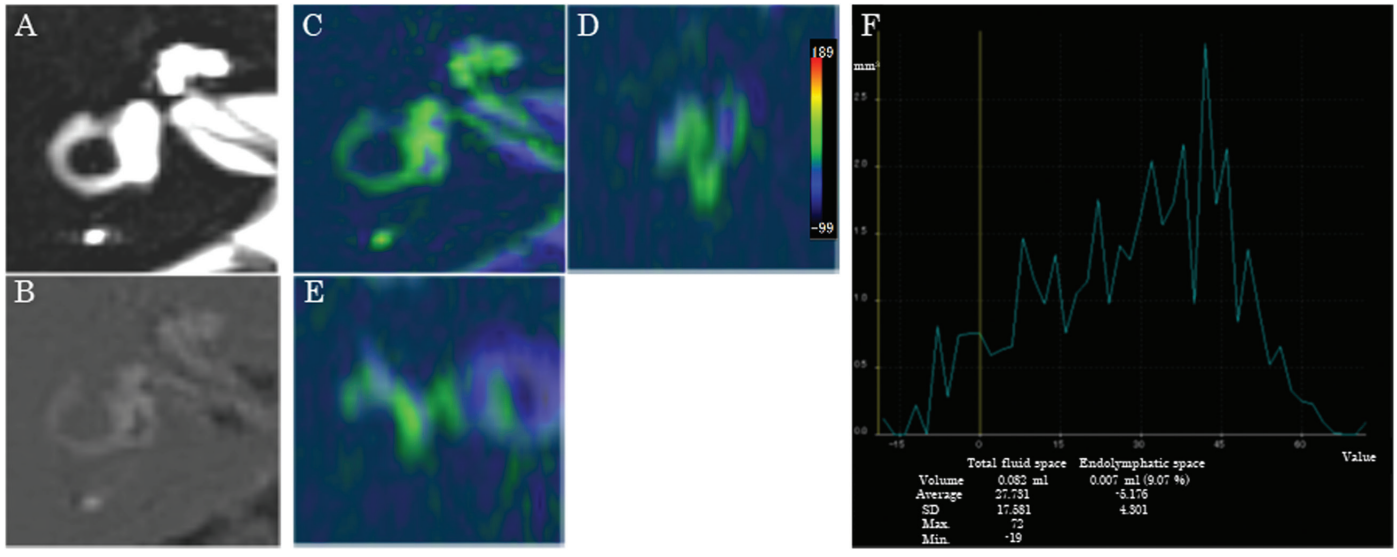

Figure 1. Reconstruction procedure for color rendering and fusion of 3D images of the inner ear fluid space and the ELS. (A) Image of the inner ear fluid space and (B) image of the ELS. (C) Fusion images: axial view of the inner ear. (D) Fusion images: sagittal images of the inner ear. (E) Fusion images: coronal view of the inner ear. (F) Actual graph for the measurement of the volume of the total inner ear fluid space and the ELS. The image of the total inner ear fluid space obtained using the T2-SPACE sequence was fused with the image of the ELS by subtracting the positive endolymph image from the positive perilymph image. The gray area on the color bar indicates a value of zero on the graph (yellow line). A negative value indicates the volume of the ELS. ELS, endolymphatic space.

Table 1. Characteristics of the Subjects (n = 100)

Total number of subjects	100
Age range, years	20-83
Mean age, years	57.8
Subjects under the age of 60	43
Subjects over the age of 60	57
Male	51
Female	49

RESULTS

A total of 100 subjects (200 ears) aged 20-83 years (mean age: 57.8 years) were enrolled in this study. Fifty-seven subjects were aged ≥60 years, and 51 were men (Table 1).

The results of the volumetric measurement of the inner ear fluid space are shown in Table 2. The ELS volume of inner ear, cochlea, vestibule, and SCCs were 39.2 ± 22.0 μL, 11.8 ± 8.3 μL, 12.2 ± 7.5 μL, and 15.2 ± 12.3 μL, respectively. The TFS of the ampulla of the posterior semicircular canal (PSC) was 7.8 ± 1.7 μL. Twenty-one subjects aged <60 years had significantly larger TFS and ELS/TFS volume ratio in the inner ear and significantly larger ELS/TFS volume ratio in the vestibule and SCCs than the 28 subjects aged ≥60 years.

The ELS images were grouped into 4 categories in the cochlea and vestibule (Table 3). In the cochlea, there were no cases in which the ELS was present only in the second turn. The mean cochlear ELS/TFS volume ratio was 10.3 ± 6.7%, and this value fell between categories c-1 and c-2 (Fig. 2). In the vestibule, the ELS/TFS volume ratio in the utriculus (category v-2) was 12.3 ± 4.7%, and when the ELS/TFS volume ratio in the sacculus was added (category v-3), the ratio was 19.9 ± 7.6%. There were no cases in which the ELS was present only in the sacculus. The mean vestibular ELS/TFS volume ratio was 17.3 ± 12.2%, and this value fell between the categories v-3 and v-4 (Figure 2).

The extended ELS of the ampulla of the posterior SCC was observed in 30 of 98 ears, and the extended ELS of the non-ampullated lateral SCC was observed in 3 of 98 ears.

Table 3. Variations of Endolymphatic Space in Cochlea and Vestibule

Cochlea	
Category c-1	No ELS
Category c-2	ELS visualized only in the upper turn
Category c-3	ELS visualized from the upper turn to the second turn
Category c-4	ELS visualized up to the basal turn
Vestibule	
Category v-1	No ELS
Category v-2	ELS visualized only in the utriculus
Category v-3	ELS visualized in utriculus and sacculus separately
Category v-4	ELS visualized in utriculus and sacculus together

ELS, endolymphatic space.

DISCUSSION

Zou et al[7] reported the separate visualization of endolymph and perilymph spaces in living humans using MR imaging. In 2010, Naganawa et al[8] first described a 3-D reconstructed model of ELH in the inner ear, and Gürkov et al[9] reported the volumetric measurement of ELH in patients with MD. Morita et al[10] reported that the mean utricular and saccular volumes were 10.65 and 2.42 μL, respectively. This volume in our v-3 category was 14.1 ± 5.5 μL (ratio 19.9 ± 7.6%).

Our method allowed measuring the volume of the ELS to assess the degree and severity of ELH. We described the ELS volumetric measurements in subjects without vertiginous or cochlear symptoms, as the purpose of this study was to determine the normal range of the ELS distribution. Liu et al[11] reported cochlear ELS/TFS ratios and vestibular cross-section ratios. The mean ELS ratio in the cochlea was 17.1% and that in the vestibule was 30.5% in 20 healthy volunteers. In the present study, the mean ELS/TFS volume ratio in the cochlea was 10.3 ± 6.7% and that in the vestibule was 17.3 ± 12.2% in all subjects. This cochlear ratio was equivalent to the results of our categories c-1 and c-2, while the vestibular ratio was equivalent to that in our categories v-2 and v-3. On MRI, this value means that the ELS in the cochlea was invisible or slightly visible. In the vestibule, this value means that the ELS in the utriculus was clearly visible and that in the sacculus was hardly visible or slightly visible (Figure 3).

An extended ELS of the ampulla of the posterior SCC and the non-ampullated lateral SCC was observed in the present study. Some studies have shown that the extended ELS of non-ampullated lateral SCC indicates herniation of the hydropic membranous labyrinth from the vestibule, possibly from the sacculus, into the posterior crus of the lateral SCC in patients with MD.[12,13] However, our subjects did not present vertiginous or cochlear symptoms. Fukushima et al[14] reported a relationship between the progression of vertical semicircular canal dysfunction and increased vestibular endolymphatic hydrops in patients with early stage MD.

Table 2. Volumetric Measurement of Components in the Inner Ear

	Inner Ear		Cochlea		Vestibule		SCCs		Ampulla of PSC
	TFS (μL)	ELS/TFS ratio (%)	TFS (μL)	ELS/TFS ratio (%)	TFS (μL)	ELS/TFS ratio (%)	TFS (μL)	ELS/TFS ratio (%)	TFS (μL)
All cases	282.1 ± 33.2	13.7 ± 7.8	112.9 ± 15.9	10.3 ± 6.7	69.1 ± 9.9	17.3 ± 12.2	101.3 ± 20.2	12.3 ± 12.2	7.8 ± 1.7
Subjects under the age of 60	293.4 ± 29.3	16.2 ± 9.1	116.0 ± 16.4	10.4 ± 7.1	69.8 ± 10.7	21.7 ± 12.1	107.8 ± 16.4	18.6 ± 14.0	7.7 ± 1.5
	**	**	-	-	-	**	-	**	-
Subjects over the age of 60	273.7 ± 33.7	11.8 ± 6.2	110.6 ± 15.2	10.2 ± 6.4	68.5 ± 9.2	14.0 ± 6.9	96.5 ± 21.6	11.8 ± 9.8	7.9 ± 1.9

ELS, endolymphatic space; PSC, posterior semicircular canal; SCCs, semicircular canals; TFS, total fluid space.
Values are presented as the mean ± standard deviation. Unpaired Student's *t*-test **significant difference ($P < .01$).

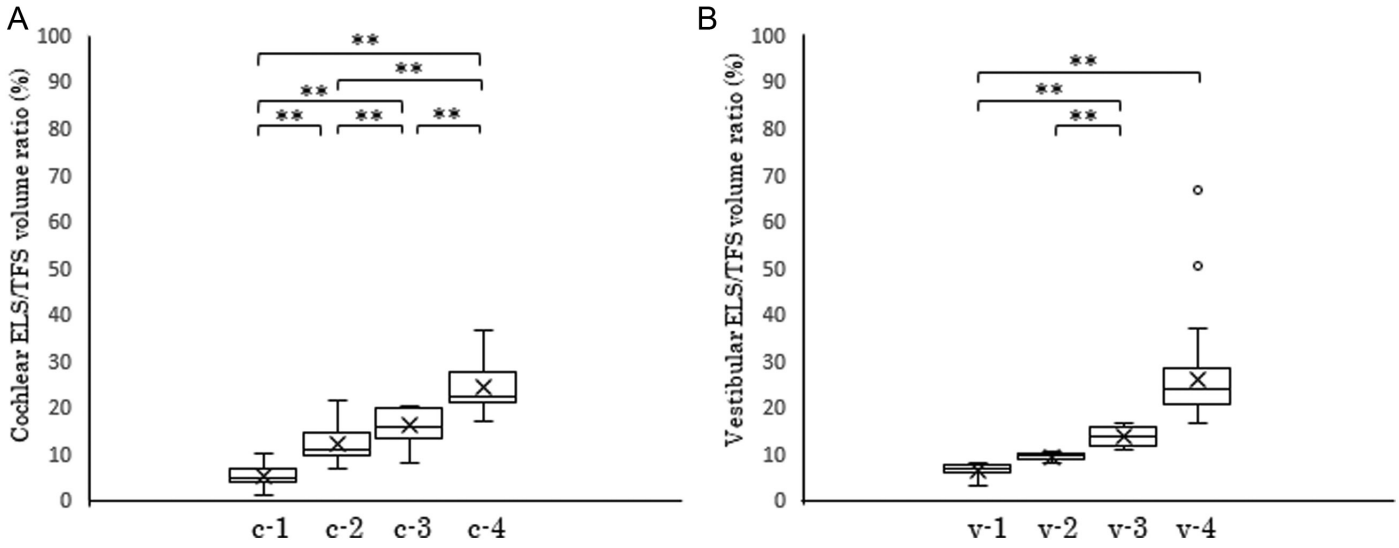

Figure 2. Severity of cochlear and vestibular ELS/TFS volume ratio. (A) Severity of cochlear ELS/TFS volume ratio (%): c-1: 5.5 ± 2.2, c-2: 12.2 ± 3.8, c-3: 15.9 ± 3.6, and c-4: 24.2 ± 5.9. (B) Severity of vestibular ELS/TFS volume ratio (%): v-1: 7.6 ± 2.1, v-2: 12.3 ± 4.7, v-3: 19.9 ± 7.6, and v-4: 24.2 ± 14.3. ELS, endolymphatic space; TFS, total fluid space. Values are presented as mean ± standard deviation. One-way ANOVA and Tukey's test. **Significant difference ($P < .01$).

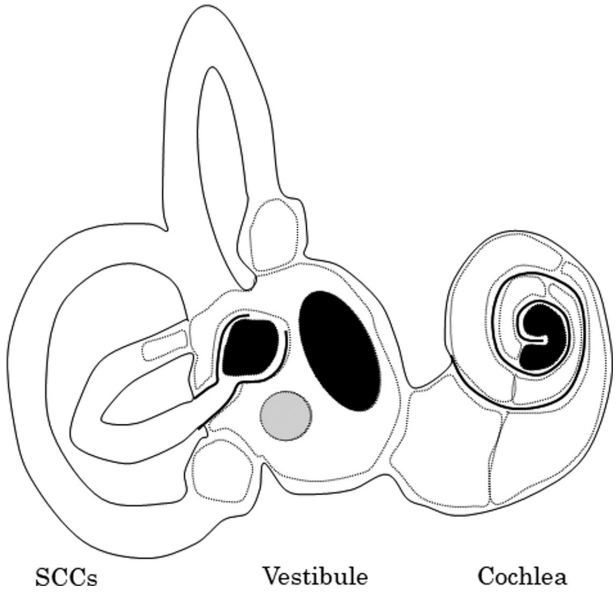

Figure 3. ELS normal values. Cochlea: the ELS was hardly visible or very small. Vestibule: the utricular ELS was clearly visible, while the saccular ELS was hardly visible or very small. SCCs: the ELS of the ampulla of the lateral SCC was clearly visible, while the ELS of the membranous duct was not visible. ELS, endolymphatic space; SCCs, semicircular canals.

This study has several limitations. First, it was difficult to visualize the ELS in the ampulla of the anterior and lateral SCCs. It was also difficult to remove these SCCs together, and the ELS within these SCC ampullae was too small to be visualized separately using MR imaging. Second, no ELS was observed visually, and the results of categories c-1 or v-1 were not equal to zero. Third, we could not follow up the changes over time in each case, and the process of ELS development remains unclear. Further studies are required to determine the relationship between ELH and the clinical and functional aspects of MD and other diseases to demonstrate the importance of ELS and improve our understanding of these diseases.

CONCLUSION

Quantitative volumetric measurement of inner ear ELS in control human subjects was performed in the present study. A 3-D image was constructed semi-automatically using both anatomical and tissue information by fusing 3-D images of the inner ear fluid space and 3-D ELS. The mean ELS/TFS ratio in the cochlea was 10.3% and that in the vestibule was 17.3%. The ELS in the cochlea and vestibule was classified into four categories. This ratio in the cochlea was situated between the results of our categories c-1 and c-2 and that in the vestibule between the results of our categories v-2 and v-3.

Data Availability Statement: The data generated and analyzed for this study are available from the corresponding author upon reasonable request.

Ethics Committee Approval: This study was approved by the Medical Ethics Committee of Nara Medical University Hospital (certificate number: 0889).

Informed Consent: Written informed consent was obtained from all subjects, and this study was performed in compliance with the Declaration of Helsinki.

Peer Review: Externally peer-reviewed.

Author Contributions: T.K. and T.I. designed the research. H.I. and T.S. performed the research. H.I. analyzed the data and wrote the paper.

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Conflict of Interest: The authors have no conflict of interest to declare.

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