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Intratympanic Iodine Contrast Injection Diffuses Across the Round Window Membrane Allowing for Perilymphatic CT Volume Acquisition Imaging

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Abstract

Hypothesis—Whether the RWM is permeable to iodine-based contrast agents (IBCA) is unknown; therefore, our goal was to determine if IBCAs could diffuse through the RWM using CT volume acquisition imaging.

Introduction—Imaging of hydrops in the living human ear has attracted recent interest. Intratympanic (IT) injection has shown gadolinium's ability to diffuse through the round window membrane (RWM), enhancing the perilymphatic space.

Methods—Four unfixed human cadaver temporal bones underwent intratympanic IBCA injection using three sequentially studied methods. The first method was direct IT injection. The second method used direct RWM visualization via tympanomeatal flap for IBCA-soaked absorbable gelatin pledget placement. In the third method, the middle ear was filled with contrast after flap elevation. Volume acquisition CT images were obtained immediately post-exposure, and at 1, 6, and 24 hour intervals. Post-processing was accomplished using color ramping and subtraction imaging.

Results—Following the third method, positive RWM and perilymphatic enhancement were seen with endolymph sparing. Gray scale and color ramp multiplanar reconstructions displayed increased signal within the cochlea compared to pre-contrast imaging. The cochlea was measured for attenuation differences compared to pure water, revealing a pre-injection average of $-1,103$ HU and a post-injection average of 338 HU. Subtraction imaging shows enhancement remaining within the cochlear space, Eustachian tube, middle ear epithelial lining, and mastoid.

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Conclusions—Iohexol iodine contrast is able to diffuse across the RWM. Volume acquisition CT imaging was able to detect perilymphatic enhancement at 0.5mm slice thickness. The clinical application of IBCA IT injection appears promising but requires further safety studies.

Keywords

Iodine; contrast; intratympanic; round window; round window membrane; perilymph; endolymph; computed tomography; CT

Introduction

Magnetic resonance imaging (MRI) is currently used to detect abnormalities of the membranous labyrinthine structures, including endolymphatic hydrops in Menière disease (MD). Both intravenous and intratympanic (IT) injection mechanisms utilizing gadolinium-based contrast agents (GBCA) have been developed(1). IT injection has shown gadolinium's ability to diffuse through the round window membrane (RWM), enhancing the perilymphatic space without causing enhancement of the endolymph. IV injection has demonstrated decreased contrast to noise ratios, resulting in lower image quality compared to IT injection(2). However, limitations to MRI inner ear imaging include tradeoffs between data acquisition time and resolution, with resolution decreasing as data acquisition time is reduced, partial volume averaging, and possible motion artifact.

Computed tomography membranous labyrinthine imaging has been rarely studied(3), with no current data surrounding IT injection of iodine-based contrast agents (IBCA). While the RWM has been shown to allow diffusion of corticosteroids, gentamicin, and GBCAs(1), it is unknown if the membrane is permeable to IBCAs. Therefore, the goal of our study was to determine if IBCAs can diffuse through the RWM and imaged with CT volume acquisition protocols.

Methods

Specimens

Four unfixed adult human cadaver temporal bones were acquired from the Maryland State Anatomy Board within one day of harvest for approved study. All soft-tissue was left intact and bones were utilized as received from the Board. Each bone was labeled with fine anatomy pins for identification on CT. This study utilizing cadaveric specimens from the Maryland State Anatomy Board is exempt from IRB review at our institution.

Intratympanic Injection

External auditory canals were cleaned and temporal bones were secured to Styrofoam bases to prevent movement. Bones were positioned with the external auditory meati facing superiorly, perpendicular to the scanner table. Neurotology faculty (J.C.) performed intratympanic iohexol (Omnipaque™ 350; GE Healthcare, Mickleton, NJ) infusion using three sequentially studied methods. In the first, analogous to the method for clinical intratympanic injections, a 25-ga 1.5cm needle was used. One ventilation hole was made posterosuperior to the umbo with a second hole made inferior to the first for injection. A

total of 200µl was injected into the middle ear space under direct microscope visualization. All four temporal bones were treated in the same manner. In the second method, a tympanomeatal flap was elevated with a curved knife for direct visualization of the round window membrane. A small, approximately 3mm² Gelfoam® (Pfizer, New York, NY) pledget was placed directly adjacent to the RWM. IBCA was injected with a 25-ga 1.5cm needle to soak the pledget. In the third method, a tympanomeatal flap was elevated, and the middle ear was infused with approximately 1cc of contrast, purposefully overfilling the middle ear and leaving a reservoir of contrast solution in the external auditory canal (EAC) to assure continuous RWM exposure despite slow losses through the Eustachian tube. A visual check assured continued presence of the solution over the RW niche 14 hours after filling. The temporal bones were left refrigerated overnight and imaged 17 hours later.

Imaging

All temporal bones were scanned on a Toshiba Aquilion™ ONE CT imaging system, a dynamic volume CT scanner with a 320-row detector array. Collimation settings were for 0.5 mm thickness with a slice interval of 0.25mm, generating 640 slices per rotation. Tube potential was set at 120 kilovolts and current was 300 milliamperes. The calibrated field of view was small at 109.7mm, and the scan range for volume was 120mm. Data were acquired as a volume acquisition, with a rotation time of 0.75s. Data were filtered using Toshiba's bone detection algorithm for internal auditory canal imaging studies.

The four temporal bones underwent pre-injection imaging <30 minutes prior to contrast instillation. Once IBCA exposure was completed, immediate scanning took place sequentially from first specimen injected to last specimen injected. The first post-contrast injection was acquired 15 minutes after exposure. The second image acquisition occurred 1 hour after pledget placement. Six hours following the pledget, a 6-hour post-contrast scan was obtained. Finally, 24-hours following first IT injection, and 17 hours after direct middle ear space contrast injection, the final scans were acquired.

Software

OsiriX 6.5.2 was used to view DICOM files and produce multiplanar 3D reconstructions. Digital subtraction images were produced in MATLAB® R2014A from 3D reconstructions. Windowing of the relevant inner ear structures led to area selection for quantitative estimation of average attenuation. Mean Hounsfield unit (HU) attenuation values were measured with UltraVisual (Emageon) software. Image enhancement for visualization was accomplished with UltraVisual Color Ramp; the color enhancements of visualization did not affect quantitative estimation of attenuation values.

Results

Four unfixed cadaver temporal bones were utilized for the CT imaging protocol. One ventilation hole was made posterosuperior to the umbo with a second made inferior to the first, yielding contrast visible within the middle ear space, with almost immediate drainage down the Eustachian tube. The 15-minute post-injection CT scan did not show RWM or perilymphatic space enhancement.

The second method, an elevated tympanomeatal flap, allowed direct visualization of the RWM. The 3mm² pledget sphere was successfully placed directly abutting the RWM. Soaking the pledget with IBCA allowed direct contact of the medium with the membrane. Imaging one hour following IBCA-soaked sphere placement did not demonstrate RWM enhancement. Of four pledget spheres placed, two detached from the RWM onto the middle ear floor space. Without direct RWM contact, no enhancement was seen within the cochlea.

The third method, tympanomeatal flap elevation with middle ear IBCA filling, yielded positive RWM and perilymphatic enhancement with endolymph sparing. Both the gray scale (Figure 1) and color ramp (Figure 2) multiplanar reconstructions display increased attenuation within the scala tympani compared to pre-contrast imaging. Compared to pre-injection imaging, there are visibly noticeable areas of enhancement within the basal cochlear turn. The total cochlear area on axial imaging was measured for attenuation differences compared to pure water, revealing a pre-injection average of -1,142 HU and a post-injection average of 340 HU (Figure 3). The RWM is also visible, with increased enhancement and attenuation value following contrast instillation. Subtraction imaging shows enhancement remaining within the cochlear space (Figure 4).

Discussion

The ability to resolve intricate details of the inner ear is continually advancing. Currently, MRI is the most explored imaging modality for presumed hydrops. However, MRI has limitations including acquisition time to resolution ratios, volume averaging, motion artifact, and cost. We have demonstrated that iodine-based contrast agent has the ability to diffuse through the round window membrane, selectively enter the perilymphatic space, and be detected by CT. There is no evidence of contrast enhancement within the endolymphatic compartment.

While visibly evident, we sought to determine if contrast was within the perilymphatic space with objective data using a filtering algorithm. Differences of >1400HU are seen between pre- and post-contrast images in all four cochlear specimens. Bone marrow was used as an internal control for attenuation values, with HU measurements measuring within 30HU between pre- and post-contrast imaging. Color ramp enhancement displayed increased density within the cochlea and on the RWM. Subtraction images were produced from 3D multiplanar reconstructions, displaying differences between the pre- and post-contrast injection images. The scala tympani and vestibuli have evidence of increased enhancement compared to the scala media on the subtraction image. Enhancement can also be seen lining the middle ear space, Eustachian tube, and RWM. Mastoid air cells are also display enhancement due to their direct communication with the middle ear. A combination of measured attenuation values, color ramp enhancement, and subtraction imaging show IBCA IT injection is a viable modality to image the inner ear. Additionally, CT was able to resolve the round window and inner ear compartments. The ability to resolve the compartments is important to determine if endolymphatic hydrops is present.

Various MRI sequences and protocols have been used to study the inner ear following intratympanic injection(2). Nakashima et al. devised a grading system using three-

dimensional (3D) real inversion recovery imaging utilizing a ratio of the area of endolymphatic space to the vestibular fluid space (peri- plus endolymphatic spaces)(4,5). They demonstrated patients without endolymphatic hydrops have a ratio of $\frac{1}{3}$ or less, mild hydrops has a ratio of $\frac{1}{3}$ to $\frac{1}{2}$, and $>\frac{1}{2}$ established significant hydrops. 3D-real inversion-recovery turbo spin-echo showed visualization of each cochlear compartment was possible using a 32-channel head coil at 3T(6). Fang et al. utilized 3D sampling perfection with application-optimized contrast using different flip angle evolutions FLAIR to report a scoring system of perilymphatic space appearance(7). Advances in MRI technology including 32-channel head coils allows resolution as small as $0.4 \times 0.4 \times 0.8$ mm; however, resolution and time are inversely related, with longer scans needed to acquire this level of detail. As many as fifteen minutes are needed to image the inner ear at this resolution, adding potential for motion artifact or degradation and decreased signal-to-noise ratios due to parallel imaging techniques(8,9). We were able to achieve 0.5mm slice thickness resolution in 0.75s total scanning time. Bykowski et al. utilizing 3-inch surface coil for 3T FLAIR MRI imaging showed 0.375×0.375 mm in-plane FLAIR resolution at approximately five minutes imaging time, but highlighted a pitfall regarding overestimation of vestibular endolymphatic distention due to partial volume averaging(2). Finally, one study comparing IT to IV GBCA injection found IT to provide superior perilymphatic enhancement(10).

While there are robust data for MRI imaging of the inner ear spaces, sparse data for CT imaging exist. Yamane et al. used 3D CT to measure the vestibular aqueduct from lateral outside and inside views in Menière patients(11). They concluded obliterated vestibular aqueducts were specific to MD, but did not show any other shape to disease correlations. Estimated vestibular aqueduct function was significantly abnormal in MD patients compared to healthy ears. The same group studied 3D cone beam CT MICS (membranous image between the vestibular cecum of the cochlea and saccule), showing the MICS patterns were significantly different than either healthy ears or non-affected ears in MD patients(3). Finally, Wu et al. reconstructed the membranous labyrinths of normal and endolymphatic hydrops (EH) affected guinea pigs using micro-CT after staining with osmium tetroxide(12). They concluded volume and geometrical dilation changes occur mainly in the ampullae, utricles, and saccules of EH animals, without significant change in the semicircular canals. To our knowledge, there are no studies to date accessing IBCAs ability to diffuse through the round window membrane or whether CT with IT contrast injection is effective at membranous labyrinth imaging.

Through experimentation, we determined IT injection with prolonged round window abutment of contrast material is not straightforward. Direct IT injection with one ventilation hole and one injection hole can accurately fill the middle ear space, but loss of contrast agent was noted through the Eustachian tube on immediate post-injection imaging. Subsequent tympanomeatal flap creation with pledget placement directly on the RWM showed accurate placement on CT imaging. However, we were uncertain how much contrast would be directly available for diffusion. Finally, it was decided to utilize the flap corridor for direct injection of Icc contrast. Imaging 18 hours later revealed iodine contrast could diffuse through the RWM and cause perilymphatic enhancement. Otolaryngologists might benefit from these trials during clinical IT gentamicin or corticosteroid injection. Sometimes symptom relief is unsuccessful and it is difficult to assess if the drug had sufficient contact

time with the RWM. This can be due to patient positioning, where solution can drain out the Eustachian tube because the patient is rotated too far to the contralateral injection side(13).

Our study has limitations inherent to human cadaver studies. While cadaver temporal bones were fresh, within one day of harvest, and unfixed, structures might degrade or otherwise not mimic *in vivo* physiology. IBCAs crossed the RWM, but determining if a component of this diffusion is active diffusion requiring energy remains unknown. The first method used mimics clinical application with direct needle IT injection while the final method utilized an elevated tympanomeatal flap with contrast injection. Much of the contrast flowed out the Eustachian tube on one-hour imaging following method one, thus the data showing RWM contrast diffusion was seen only after method three. Future directions include moving this model to animals.

Conclusions

Our study indicates that an iodine-based contrast agent is able to diffuse across the round window membrane. CT imaging with volume acquisition was able to detect perilymphatic enhancement at 0.5mm slice thickness. The borders between the endolymphatic scala media and perilymphatic scala tympani/vestibuli were clearly visible. This technique could be used for inner ear membranous labyrinth imaging in research on disorders such as Menière disease. Advantages over MRI imaging include decreased acquisition time, decreased possibility of motion artifacts, decreased cost, ability for high-quality resolution with accurate bone/soft tissue differentiation, and ability to produce crisp subtraction imaging from fast acquisition time. The clinical application of IBCA IT injection appears promising and necessitates further study.

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Figure 1.

A human cadaver temporal bone represented as a multiplanar reconstruction of the volume acquisition CT. TOP ROW: Contains from left to right axial, oblique, and coronal sections pre-contrast injection. BOTTOM ROW: Post-contrast images with analogous sections as top row. Of note, the post-contrast imaging displays attenuation and enhancement within the cochlea. The Eustachian tube, middle ear epithelial lining, and mastoid air cells also contain contrast.

Figure 2.

The images represent the same multiplanar CT slices as Figure 1, with color ramping for density mapping. The top row is pre-contrast and the bottom row is post-contrast injection.

Figure 3.

These images represent a 3.0×3.0cm view of the middle and inner ear. TOP ROW: Axial pre-contrast imaging with attenuation measured as average Hounsfield units (HU) within the cochlea. The attenuation averaged to -1,103 HU. BOTTOM ROW: Axial post-contrast imaging with average cochlear attenuation being 338 HU. Attenuation was also measured at the same spot within the bone marrow. The pre-contrast marrow measured 1,869HU with the post-contrast measuring 1,840HU. The Eustachian tube measured an average of 35 HU in 0.44cm² pre-contrast and an average of 3,157 HU in 0.42cm² post-contrast.

Figure 4.

The post-contrast data was subtracted from the pre-contrast data, yielding this image. The cochlea can be seen with the small arrows and arrowhead. The small arrows point to the enhancing perilymphatic space while the small arrowhead shows the endolymph. The Eustachian tube (large arrow), mastoid air cells (large arrowhead), and middle ear epithelial lining have contrast media causing attenuation. EAC: external auditory canal, ME: middle ear.