溫差測試與垂直半規管之快速擺頭檢查
對梅尼爾氏症內淋巴水腫的反應不同，可作為互補檢查

Vertical Head Impulse and Caloric Are Complementary but React Opposite to Meniere’s Disease Hydrops

Munehisa Fukushima, MD, PhD; Ryohei Oya, MD; Kengo Nozaki, MD; Hirotaka Eguchi, MD; Shiro Akahani, MD, PhD; Hidenori Inohara, MD, PhD; Noriaki Takeda, MD, PhD

Commentary

快速擺頭檢查 (Head Impulse test, HIT) 與溫差測試 (caloric test) 皆以前庭眼反射 (vestibulo-ocular reflex, VOR) 為其作用機轉，然兩者使用的前庭刺激不同，快速擺頭檢查測試高頻率反應 (2000-4000°/s²)，溫差檢查測試低頻率反應 (0.001-0.003 赫茲)。兩檢查最常測試水平半規管 (semicircular canal, SC) 功能，但影像快速擺頭檢查 (video HIT, vHIT) 的問世後，垂直半規管亦可測試。本文比較梅尼爾氏症 (Meniere’s disease, MD) 病患的影像快速擺頭檢查和溫差測試，且根據核磁共振影像計算內淋巴水腫 (endolymphatic hydrops, EH) 佔據前庭部分的體積比例，來分析兩前庭檢查結果與此比例的相關性。

本研究一共納入 90 位經診斷為單側確定性梅尼爾氏症 (definite unilateral MD) 患者，其中男性 30 位，女性 60 位，多數病例集中在梅尼爾氏症分期第一期 (n=38) 及第三期 (n=37)，在計劃進行的三個月內，每人接受了數次影像快速擺頭檢查和溫差測試。作者以半規管麻痺 (canal paresis, CP) 爲主要分析參數，發現影像快速擺頭測試的結果中，後半規管 CP 比率遠高於水平半規管 (44.4%：13.3%)，代表梅尼爾氏症對後半規管影響大於水平半規管，故推論單以溫差測試不足以檢測梅尼爾氏症之半規管功能變化，而兩檢查可互補來檢測梅尼爾氏症患者垂直及水平半規管的功能。另一方面，影像快速擺頭檢查和溫差測試測出水平半規管 CP 的結果有統計上相關性，但患者實際有 CP 的比例在兩檢查中卻相差很大 (13.3%：45.1%)，根據統計分析結果，推論出對於半規管麻醉的檢測，影像快速擺頭檢查具有高特異性 (high specificity) 但是低敏度 (low sensitivity)，而溫差測試則正好相反，為一敏感度高但特異性較差的檢查。對於這個推論，作者的解釋是，頂帽 (cupula) 偏移的大小與耳毛細胞 (hair cell) 受刺激程度成正相關，在半規管內淋巴水腫環境下，以高速轉頭刺激或溫差刺激造成的淋巴液流動可能對於推動頂帽使之偏移的效率不同；作者推測在內淋巴水腫時，溫差造成的內淋巴液流動，或因膜性迷路 (membranous labyrinth) 面積擴大造成單位面積推動頂帽力量減少，或因膜性迷路面積擴大在內淋巴腔形成液體對流而影響內淋巴液的沿管流動；兩者皆減少了頂帽移動的幅度，造成半規管麻痺在溫差測試有較多的偽陽性。這個理論也解釋了為何以核磁共振影像計算內淋巴水腫佔前庭部分的體積比例，會與溫差測試測出半規管麻痺比例有關，而與影像快速擺頭檢測中半規管麻痺比例無關。

本文以檢查的數據進行統計為主要研究方法，在某些結果的比較上感覺無法直觀，需要分析方能取得數據的意義。然而作者也提出了合理自圓的解釋，算是一篇嚴謹且撰本數足夠的臨床報告，最後的結論是，因為梅尼爾氏症的後半規管功能異常率高，故應執行垂直半規管的影像快速擺頭檢查，但因影像快速擺頭檢查對於水平半規管的檢驗可能敏感度不足，建議以目前常用的溫差測試互補之。

關鍵詞：快速擺頭檢查，梅尼爾氏症，前庭眼反射，內淋巴水腫，後半規管

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Vertical Head Impulse and Caloric Are Complementary but React Opposite to Meniere’s Disease Hydrops

Munehisa Fukushima, MD, PhD; Ryohei Oya, MD; Kengo Nozaki, MD; Hirotaka Eguchi, MD; Shiro Akahani, MD, PhD; Hidenori Inohara, MD, PhD; Noriaki Takeda, MD, PhD

Objective/Hypothesis: Meniere’s disease (MD) patients can show normal head impulses despite poor caloric test results. This study aimed to investigate the discrepancy in the vestibulo-ocular reflex (VOR) in MD patients and whether endolymphatic hydrops (EH) influence the VOR.

Study Design: Prospective, cross-sectional observational study.

Methods: Ninety MD patients were enrolled. Neuro-otological testing, including a video head impulse test (vHIT) of all semicircular canals (SCs), and gadolinium-enhanced inner ear magnetic resonance imaging were performed. The vestibular EH volume was quantitatively evaluated by processing magnetic resonance images.

Results: Abnormal vHIT results in MD patients were found most frequently in the posterior (44.4%) SCs, followed by the horizontal (13.3%) and anterior (10%) SCs. Canal paresis (CP) was assessed using the vHIT and the caloric test, and results were not significant when vHIT responses were assessed as CP only using the horizontal SC. The difference in the vestibular EH between the presence and absence of CP was not significant if assessed using the vHIT (P = .5591), but it was statistically different if assessed using the caloric test (P = .0467).

Conclusions: The contradictory reaction of VOR in MD patients may result from the high specificity but low sensitivity of CP in the horizontal vHIT. EH volume in the vestibule affects the caloric response but does not affect the vHIT response.

Key Words: Head impulse test, Meniere’s disease, vestibulo-ocular reflex, endolymphatic hydrops, posterior semicircular canal.

Level of Evidence: 2b

INTRODUCTION

The head impulse test (HIT) and caloric test are reliable clinical tests that are used to assess vestibular function in various disorders, including Meniere’s disease (MD). These two tests are based on the vestibulo-ocular reflex (VOR) of the horizontal semicircular canal (SC) in response to different frequencies of angular acceleration applied to the cupula, which constitute a large part of the difference between stimulation characteristics in the two tests; a high frequency (2000–4000°/s²) is generated by a head impulse, and a low frequency (0.001–0.003 Hz) is generated by caloric stimuli. Two different angular acceleration stimuli are used, and the sensitivity to detect canal paresis (CP) is usually lower in HIT than in the caloric test. High-speed video measures the eye movement response to head impulses, but video HIT (vHIT) can provide an objective analysis of individual SCs including vertical SCs. Detecting vertical SC dysfunction is a great advantage of vHIT, and it is different from both HIT and the caloric test.

MD is a common inner ear disease that is characterized by episodic vertigo, fluctuating sensorineural hearing loss, and tinnitus. MD patients can have normal head impulses despite poor or absent caloric results. This difference between the results of HIT and caloric testing in MD patients has been reported. However, MD patients have been evaluated mainly using VOR responses of horizontal SC in previous studies, and the VOR responses of vertical SCs in MD patients have not been examined in detail. Thus, it is necessary to examine VOR findings of vertical SCs in MD patients.

MD pathology was reported to be endolymphatic hydrops (EH) in the inner ear, and EH is suggested to be related to dissociation of the VOR responses in vivo visualization of EH using 3 T magnetic resonance imaging (MRI) 4 hours after intravenous administration of single-dose gadolinium is routinely performed. In this study, we prospectively investigated vHIT findings of all SCs and caloric responses in MD patients. We also measured the volume ratio of the vestibular part of EH by...
processing MRI semiquantitatively and analyzed whether vestibular EH affects VOR responses delivered by two different tests.

**MATERIALS AND METHODS**

**Patients**

Between April 2017 and January 2018, 90 patients with definite unilateral MD were enrolled into this study. The present study was approved by the ethics committee of Kansai Rosai Hospital (certificate number: 16C053e). All patients were fully informed about the execution and goals of the study and provided informed consent to participate in this study. All patients underwent neuro-otological testing and MRI within 3 months after consulting our institution. They were followed up for at least 6 months, and multiple vHIT tests were performed.

**Functional Examination**

**Auditory evaluation.** Hearing function was measured using pure-tone audiometry (PTA) and evaluated based on the four-tone average formulated by \((a + b + c + d)/4\) (where \(a, b, c,\) and \(d\) are hearing levels at 0.5, 1, 2, and 4 kHz, respectively) according to the modified 1995 American Academy of Otolaryngology–Head and Neck Surgery criteria.

**Vestibular evaluation.** Video head impulse test and caloric test. Three-dimensional vHIT was conducted to assess the VOR in each semicircular canal plane using a lightweight Video-oculography device (ICS Impulse; GN Otometrics, Taastrup, Denmark) with an integrated, digital, high-speed camera designed for quantitative HIT testing. Experienced otologists performed brief, abrupt, and unpredictable head rotations on patients, and at least 20 impulses with peak velocity ranges of 100 to 250/s were collected from each canal. Individual VOR gains were automatically calculated using the device software (OTOsuite vestibular software, version 4.00, build 1286; GN Otometrics). Individual VOR gains were calculated as the ratio of the area under the entire eye velocity response divided by the area under the entire head velocity stimulus. It was assumed that the normal VOR gains were 0.8 or more for horizontal canals and 0.7 or more for vertical canals. We consider patients whose VOR gains were less than these cutoffs to have CP when the catch-up saccades (CUS) with larger amplitudes compared with those of the head movements were detected simultaneously. For the caloric test, the patient’s head was placed at a 30° angle, and the external auditory canal was irrigated with 20 mL of cold water at 30°C followed by 20 mL of hot water at 44°C for 10 seconds after confirming the integrity of the tympanic membrane. The induced nystagmus was recorded using electronystagmography in a dark, open-eye situation, and a maximum slow-phase velocity (max-SPEV) of nystagmus was measured following each irrigation. The percentage of canal paresis (CP%) was calculated using Jongkees’ formula, in which 0% indicated the absence of right–left differences and 100% indicated complete CP. A CP% of > 25% was defined as caloric weakness. A max-SPEV of < 10 per second on the treated side was defined as no response.

**MRI.** MR imaging was performed as previously described. Briefly, a standard dose (0.2 mL/kg) of intravenous gadoteridol (ProHance; Eisai Co., Ltd., Tokyo, Japan) was administered, and 4 hours later, MRI was performed using a 3 T MRI unit (Magnetom Verio; Siemens, Erlangen, Germany) equipped with a receive-only, 32-channel phased-array coil. All patients underwent heavily T2-weighted (hT2W) magnetic resonance cisternography (MRC) and T2-weighted magnetic resonance imaging (MRI). Functional Examination of total lymph fluid, and hT2W three-dimensional fluid-attenuated inversion recovery with inversion times of 2,250 and 2,050 ms. HYDROPS imaging (Fig. 1, center) was used to detect EH; the details of the sequence parameters were described previously.

**EH image evaluation.** The HYDROPS-Mi2 image (Fig. 1, right) was obtained by multiplying the MRC and HYDROPS images using a Digital Imaging and Communications in Medicine viewer OsiriX (version 9.0; Pixmeo SARL, Berne, Switzerland). Experienced otologists, who were blinded to the clinical progress of patients, manually placed regions of interest (ROI) contouring of the vestibule on the MRC, and then they were copied to the HYDROPS-Mi2 image. Using the OsiriX histogram function, we measured the total number of all pixels in the ROI and the number of pixels with negative signal intensity values, which represents vestibular EH, in the ROI. The volume ratio of vestibular EH (v-EH%) was calculated based on the ratio defined as the number of negative pixels for EH in the ROI divided by the total number of pixels in the ROI.

**Statistical Analysis**

All data were assessed statistically using JMP version 13.2.0 (SAS Institute, Cary, NC). The Wilcoxon rank sum test was used to compare the values of mean VOR gain between the affected and intact sides. Welch’s t test was used to compare the difference of v-EH% and max-SPEV between presence and absence of CP. The 2 × 2 contingency table was analyzed using the Fisher exact probability test. The sensitivity and specificity were calculated for each table. P values < .05 were considered significant.

![Fig. 1](image-url). An example of magnetic resonance image processing. Left: magnetic resonance cisternography (MRC) image for the anatomical reference of total lymph fluid. Center: HYDROPS image. The black area represents endolymphatic hydrops, and the white area represents the perilymphatic space in the vestibule. Right: HYDROPS-Mi2 image, which was obtained by multiplying the MRC and HYDROPS. All three images are the same left inner ear of an Meniere’s disease patient. A dotted line shaped like a pentagon surrounds the vestibule and semicircular canals.
RESULTS

The patient population consisted of 30 males and 60 females, with ages ranging from 13 to 86 years (average = 56.6 years). The disease stage was based on hearing function. Stages I, II, III, and IV correlated with four-tone averages of the worst audiograms (<25, 25–40, 41–70, and >70, respectively) in the 6 months before treatment. In this study cohort, there were 38 patients at stage I (average PTA, 15.0 dB; left-to-right ratio of affected ears, 18:20), 10 patients at stage II (average PTA, 31.9 dB; left-to-right ratio of affected ears, 7:3), 37 patients at stage III (average PTA, 55.9 dB; left-to-right ratio of affected ears, 17:20), and five patients at stage IV (average PTA, 75.8 dB; left-to-right ratio of affected ears, 3:2). Figure 2 shows representative vHIT findings of all SCs in one MD patient demonstrated using the ICS Impulse device. Horizontal and posterior SCs showed reduction of VOR gain accompanied by a large CUS on the affected side. Fifty-one of 90 MD patients (56.7%) were assessed as having CP using three-dimensional vHIT, and 37 of 82 MD patients (45.1%) were assessed as having CP using caloric tests.

The distribution of CP assessed using the vHIT findings and the comparison of VOR gain values in individual
SCs are shown in Figure 3. There were 12 patients with CP in the horizontal SC, 40 with CP in the posterior SC, and nine with CP in the anterior SC (Fig. 3a). The values of the median VOR gain comparing the affected side to the intact side were 0.665 to 0.915 in the horizontal SC ($P = .0003$), 0.615 to 0.68 in the posterior SC ($P = .0325$), and 0.67 to 0.58 in the anterior SC ($P = .7907$; Fig. 3b). The distribution of the vestibular EH (v-EH%) volume ratio ranged from 3.2% to 64.1% (median = 18.1%).

Table I shows $2 \times 2$ contingency with the association between CP assessed using vHIT and the caloric test. The first section of Table I summarizes the vHIT responses assessed as CP in all SCs ($P = .6572$). The second section summarizes the vHIT responses assessed as CP only using the posterior SC ($P = 1.0000$). The third section summarizes the vHIT responses assessed as CP only using the horizontal SC ($P = .0191$). The difference between the presence or absence of CP in max-SPEV and in v-EH% is shown in Figure 4. The values of the mean max-SPEV when CP was compared with non-CP were 19.0 ± 2.4 to 19.8 ± 1.6 if assessed using vertical vHIT in the posterior SC ($P = .7820$) (Fig. 4a) and 11.3 ± 0.9 to 26.1 ± 1.9 if assessed using the caloric test ($P < .0001$). The values of mean v-EH% when CP was compared with non-CP were 19.7 ± 1.3 to 18.1 ± 2.3 if assessed using vHIT ($P = .5591$) (Fig. 4b) and 22.1 ± 2.2 to 16.8 ± 1.3 if assessed using the caloric test ($P = .0467$) (Fig. 4c).

**DISCUSSION**

In the present study, we investigated vHIT of all SCs and caloric findings in MD patients. As shown in Figures 2 and 3a, abnormal vHIT findings in MD patients were observed most frequently in the posterior SC (40 out of 90, 44.4%) followed by the horizontal SC and the anterior SC. Over 40% of the MD patients had posterior SC dysfunction, whereas only 12 out of 90 MD patients (13.3%) had horizontal SC dysfunction. Caloric weakness was detected in 37 out of 82 MD patients (45.1%) in this study group. The sensitivity of detecting CP is usually lower in HIT than in the caloric test, and it was reported that the vHIT reached 100% sensitivity only when the caloric deficit was higher than 62.5%. It is assumed that MD patients have posterior SC dysfunction more frequently than 44.4%. CP% and max-SPEV are conventional caloric parameters to estimate vestibular function in MD patients, and they have been widely used. However, the caloric test is not sufficient to assess vestibular function of MD patients, because the SC dysfunction of MD patients is most frequently located in the posterior SC. It was similarly reported that the VOR gain reduction in MD patients was most frequently located in the posterior SC of the symptomatic ear. This also suggests the importance of evaluating the posterior SC in MD patients. It is necessary to examine both vHIT of the posterior SC and caloric results in MD patients. For MD symptoms, posterior SC disorder might cause a subjective sensation of dizziness rather than rotatory vertigo when vertigo attacks occur. As shown in Figure 3b, the difference in the VOR gain between the affected and intact sides was significant in horizontal and posterior SCs. The value of VOR gain was bilaterally lower than the normal value of 0.7 in the posterior SC. This may be a result of the progression of bilateral hypofunction in the posterior SCs.
SC during the chronic course of MD. Additionally, the cutoff values of healthy subjects were investigated and shown to be 0.68 for the right posterior SC and 0.58 for the left posterior SC. Based on that reference value, our results for the intact ear are within normal range.

Recently, it was reported that MD patients have a normal horizontal vHIT but weak caloric test results. This contradictory reaction of the VOR response to different angular accelerations in MD patients had been reported (vestibular weakness: 35% in head impulse and 59.8% in caloric tests) and is sometimes inversely used to distinguish MD from other disorders. Table I shows 2 x 2 contingency with the association between CP assessed using vHIT and the caloric test. If the vHIT responses were assessed as CP using all SCs or using only the posterior SC, the association was not statistically significant, as shown in the first and second sections of Table I. If the vHIT responses were assessed as CP using only the horizontal SC, as shown in the third section of Table I, the association became statistically significant, and the specificity also increased and the sensitivity decreased compared with using the other tests. This indicates that the contradictory reaction of VOR in MD patients may result from the high specificity but low sensitivity of CP using horizontal vHIT, although the agreement between both tests was not high in any combination of SCs, as previously described. We additionally separated the distribution of max-SPEV from presence of CP assessed using the two tests. The CP group that was assessed using the caloric test showed a reduction in the max-SPEV, whereas the CP group assessed by vertical vHIT using the posterior SC showed almost the same mean value (Fig. 4a). Based on the results of the above analysis, we conclude that the vHIT of the posterior SC and the caloric test assessing the respective SC functions are complementary to each other for evaluating vestibular function in MD patients.

The pathology of MD was reported to be EH in 1938, and EH is now widely recognized as a typical marker of MD. EH was most frequently observed in the cochlea, followed by the saccule, the utricle, the ampullae, and the three SCs in MD patients. Although EH is not

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*P = .6572, not statistically significant; sensitivity, 0.595; specificity, 0.467
†P = 1.0000, not statistically significant; sensitivity, 0.459; specificity, 0.556
‡P = .0191, statistically significant; sensitivity, 0.243; specificity, 0.956
CP = canal paresis; vHIT = video head impulse test; SC = semicircular canal.

Fig. 4. (a) Comparison of maximum slow-phase velocity (max-SPEV) between canal paresis (CP) and non-CP patients assessed using a vertical video head impulse test (vHIT) of the posterior semicircular canal. Comparison of the volume ratio of vestibular EH (v-EH%) between CP and non-CP assessed by (b) vHIT and (c) the caloric test. Dotted lines in the graph indicate the mean value for each group. *Significant difference.
thought to be toxic to the inner ear, a cervical vestibular evoked myogenic potential study showed that 54% of MD patients may have saccular dysfunction. In this study, we measured v-EH% by processing MRI semiquantitatively and analyzed whether vestibular EH effect VOR responses delivered by two different batteries of tests. The distribution of v-EH% widely ranged from 3.2% to 64.1%, and the median was 18.1% in this study group. The v-EH% of patients without vertiginous or cochlear symptoms was reported to be 16.2%. This number is only a reference for healthy subjects because the study group consisted of patients with chronic rhinosinusitis, but the median value in our study group was larger than this reference value. To examine the effect of EH volume, we separated the distribution of v-EH% from the presence of CP assessed using the two tests. The presence or absence of CP in MD patients was independent of v-EH% if assessed using vHIT (Fig. 4b) and was dependent on v-EH% if assessed using the caloric test (Fig. 4c). The EH volume in the vestibule may affect the caloric response and may not affect the vHIT response. These differing results of the vHIT and caloric test in MD patients has been hypothesized to relate to the EH volume effect. When the caloric test uses mechanics, the relationship between the VOR reaction and EH is relatively easy to understand. We applied the following simple formula: \( W = PAL \), where \( W \) (Work = caloric stimulation [Nm]) = \( P \) (Pressure = Force/unit area [N/area] \( \times A \) (cross-sectional area of the membranous labyrinth in SCs) \( \times L \) (migration length [m]). A large v-EH% means enlargement of the membranous labyrinth and is equivalent to a large A. When A is larger, L becomes smaller assuming that P is fixed (\( L = W/PA \) and W is a fixed energy). The value of a small L corresponds to a small cupula amplitude. The patient is assessed as having CP if the cupula amplitude is small. High-frequency angular acceleration stimuli to the cupula, which can be up to 10,000/1/s², such as for head impulses, will always generate a large cupula amplitude and is not affected by the EH volume. Another hypothesis of this difference is that predominant type II hair cell loss in MD would result in loss of low-frequency labyrinthine sensitivity, yielding poor caloric test results. However, a recent study demonstrated that both type I and II hair cells were equally affected in MD. A theory was proposed that the membranous duct enlarged by EH would disperse the hydrostatic force across the cupula by the local convective flow, and the caloric response would decrease.

Our study has some limitations. First, we estimated whole vestibule volume including all the SCs to examine the effect of EH volume for two different angular acceleration stimuli. It is reasonable to assess volume of the horizontal and posterior SC portions separately. However, a small volume will vary widely because of deviations in the image if the target moves slightly during the scanning procedure. We used whole vestibular volume, which is stable and reliable, for this research. Second, this clinical study was prospective, but it was also a cross-sectional observational study. MD is a chronic disease with a varying course of vestibular and cochlear symptoms. Although we examined patients in this study several times over 10 months, patients should also be observed longitudinally over a prolonged period of time.

CONCLUSION

In this study, we showed that abnormal vHIT findings in MD patients were observed most frequently in the posterior SC followed by the horizontal SC. A detailed examination of vHIT and caloric test results showed that the contradictory reaction of VOR in MD patients may result from high specificity but low sensitivity of CP as assessed using horizontal vHIT. Moreover, it is suggested that the EH volume in the vestibule will affect the caloric response and will not affect vHIT response.

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