The Caloric Test and the Video Head-Impulse Test in Patients with Vertigo

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OBJECTIVE: The caloric test and the video head-impulse test are diagnostic tools that examine the function of the horizontal semicircular canal. There are major differences between the two tests. These are stimulus characteristics, methodology, and function examined.

MATERIALS and METHODS: This is a prospective work in 123 patients with different types of vestibular disease seen because of dizziness in which both procedures were performed the same day. First, the spontaneous nystagmus and head-shake nystagmus were measured. The video head-impulse test was carried out, and finally, the caloric test was performed with water at two different temperatures. Both ears were irrigated alternately. Main outcome measures were the canal paresis in the caloric test and gain of vestibulo-ocular reflex, gain asymmetry, and refixation saccades in the vHIT.

RESULTS: The caloric test and the vHIT results were fully coincident in 60 patients (48.7%), and the results for both were normal in 36 patients. Discrepancies were found in 3 patients regarding the deficient side, and in 14 patients, an added contralateral (according to the caloric test) abnormal result was obtained. In 46 patients, one of the tests was normal while the other was not, but both were in accordance with the diseased side. The correlation coefficient for canal paresis and gain asymmetry was 0.67, and the agreement was low: κ=0.252.

CONCLUSION: The assessment of horizontal semicircular canal function with the vHIT needs to take into consideration not only the gain in VOR but also the existence of refixation saccades. The information from both methods is redundant in some cases but complementary in most, and the existence of discrepancies is very low.

KEY WORDS: Vertigo, head-thrust test, dizziness, vestibulo-ocular reflex

INTRODUCTION

The caloric test is one of the main examinations of patients with dizziness, as it provides a measure of vestibular deficit. Nowadays, it is performed using water or air as the stimulus to create a temperature gradient in the temporal bone. In this way, the evoked nystagmus is registered with videonystagmography systems, although electronystagmography is still in use. The purpose of this paper is not to evaluate their advantages and disadvantages, but it should be stated that the caloric test has greater capacity to independently test each labyrinth, although it uses a non-physiological stimuli equivalent to a <0.002-Hz sinusoidal stimulation [1].

In patients with unilateral vestibulopathy, the relative value of canal paresis in the caloric test has high sensitivity and specificity, and for serial testing, the importance of using absolute slow-phase eye-speed scores from each ear (rather than canal paresis) has great relevance for the follow-up of patients [2].

New video-based equipment that enables registration of the eye response to sudden head impulses mimicking the performance of the scleral search coil (SSC) in a magnetic field installation has recently become available for clinical use [3, 4]. With this video head-impulse test (vHIT) system, it is possible to measure the gain of the vestibulo-ocular reflex (VOR) and to register eventual refixation saccades with stimulations (head impulses) that acquire high velocity (>150º/s) and acceleration (1-16 Hz). This system is good not only for initial evaluation of the patient but also for follow-up, as has been demonstrated in patients with MD with rapid fluctuations in vestibular function [5].

In terms of frequency analysis, the information provided by both systems is relevant. At high frequencies of stimulation, such as those provided in the vHIT, the VOR is the main physiological function that helps to stabilize gaze in the initial post-stimulus period of time (<100 ms). However, we also have to deal with low velocities and low frequencies of stimulation, for which velocity storage, smooth pursuit, and optokinetic nystagmus provide important help to the VOR and with which the caloric test is very informative [6].
The purpose of this work was to evaluate the results in the caloric test and the vHIT of patients seen because of vertigo. As both tests provide data about the functioning of the horizontal semicircular canal, we were interested in the degree of coincidence between both and, in case of contradiction, which was important.

**MATERIAL and METHODS**

**Patients**

In this study, we have included patients seen because of dizziness due to peripheral vestibular disease. In the assessment, several other tests were performed to provide a specific diagnosis, although we will review the caloric test and the vHIT. Our initial population was 137 patients, but we excluded 14 because of technical problems in the caloric test: thermal artifact (n=5), poor quality of the traces because of excessive blinking (n=4), poor cooperation (low alertness, n=3), and doubtful results according to the shape of the external ear canal that could prevent good irrigation (short diameter, n=2). The vHIT was performed on all 137 patients without difficulty except for those patients with excessive blinking, with whom the procedure took slightly longer; however, in a small subset of patients (n=25), we collected the time of testing: from placement of the goggles until printing, mean time was 8±3 min. In this study, we have included 123 patients: 69 (56.1%) women and 54 (43.9%) men. The caloric test and vHIT were performed on the same day, with a minimum time gap.

**Vestibular Examination**

Spontaneous nystagmus was assessed with a videonystagmography system (VN415 Interacoustics, Assens Denmark) and measured after calibration with the patient seated, without visual fixation and with the eyes in primary position; the eye used for registration was the left. If a nystagmus was detected, it was characterized by its intensity in % of the slow phase velocity (SPV) and by the beating direction according to its fast phase. Head-shaking nystagmus was assessed by moving the head of the patient (slightly inclined by 30º) vigorously 20 times with an amplitude of movement of 30º. The eye movements were registered in the horizontal and vertical planes for 2 minutes after the head shaking ended. A test was considered positive when nystagmus was present for at least 5 seconds after the head shaking terminated and if the maximum slow phase velocity of the nystagmus was also higher than 3º/s.

The bithermal caloric test was performed in line with Fitzgerald and Hallpike, and left eye movements were recorded by means of a videobased system (Ulmer VNG, v. 1.4, SYNAPSIS®, Marseille, France). Each ear was irrigated alternately with a constant flow of water at temperatures of 30ºC and 44ºC and for a constant period of time (40 seconds). The maximum SPV of nystagmus was calculated following each irrigation, and Jongkees’ formula was used to determine canal paresis (CP) and directional preponderance (DP); in CP, a positive result indicates left canal paresis, and a negative result indicates right canal paresis. If the asymmetry between the responses for the left and right ear was >20%, the result was considered indicative of unilateral vestibular weakness (UW). For directional preponderance, a difference between the right and left beating nystagmus of >30% was considered pathological. An ice-water caloric stimulation was carried out whenever there was >85% CP, and if there was no response, 100% canal paresis was then considered.

**VOR Evaluation**

It was performed with a video system (vHIT GN Otometrics, Assens, Denmark). This system was selected because in previous work, it had been found that the simultaneous recordings of the response to head impulses from the vHIT and the SSC yielded almost the same results, with an average concordance correlation coefficient r(c)=0.93 [6].

For this test, the patient wears a pair of lightweight, tightly fitting goggles on which a small video camera and a half-silvered mirror that reflects the image of the patient’s right eye into the camera are mounted. The eye is illuminated by a low-level infrared light-emitting diode. A small sensor on the goggles measures the head movement. The whole goggle system weighs about 60 g and is secured tightly to the head to minimize goggle slippage. Calibration is performed, and the procedure of vestibulo-ocular testing is initiated. The clinician asks the patient to keep staring at an earth-fixed target 90-100 cm in front and gives the patient brief, abrupt, horizontal head rotations through a small angle (about 10-20 degrees), unpredictably turning to the left or right on each trial. The head movement speed is measured by the sensor in the goggles, and the image of the eye is captured by the high-speed camera (250 Hz) and processed to yield eye velocity. At the end of each head turn, the head-velocity stimulus and eye-velocity response are displayed simultaneously on the screen, so the clinician can see how good the stimulus and response were, providing a quick way to maximize the quality of the head impulse. In a full test, 20 impulses are delivered randomly in each direction. At the end of the full test, all the head velocity stimuli and eye velocity responses are displayed on the computer screen, together with a graph of the calculated VOR gain (ratio of eye velocity to head velocity) for every head rotation; in this system, the evaluation of head velocity and eye velocity does not rely on one single measurement but on the area under the curve for both velocities. The parameters evaluated are the VOR mean gain and the appearance of saccades after head impulses to right and left. A relative parameter was created and defined as gain asymmetry (G) from the gain value obtained for rightward head-impulses (Gr) and leftward head-impulses (Gl) using the formula:

\[
G = \left| \frac{G_r - G_l}{G_r + G_l} \right| \times 100
\]

As such, a positive Gs result indicates that the gain for leftward impulses is lower than that for rightward head impulses, and a negative result indicates the contrary.

A normal result is defined by gain >0.6 without saccades; this value is taken from the most restricted obtained after evaluation of patients with vestibular neuritis and after neuroectomy. Abnormal results were of two types: normal gain with refixation saccades and low gain (<0.6) either with or without saccades (Figure 1). Refixation saccades were defined according to their appearance as covert (during the head impulse) and overt (once the head impulse ended) and were taken into consideration if the velocity of the saccade was above 50º/s.

**Statistical Analysis**

All data were stored and analyzed in a Statistical Package for the Social Sciences (SPSS) file version 19.0 (Inc.; Chicago, IL, USA). All tests were two-tailed, and p-values <0.05 were considered significant. The caloric test was classified as normal or abnormal; in the former case, both canal paresis and directional preponderance should have been
under the normal limits. For each side of lower CP, the patients were classified in 3 groups: 1) normal if canal paresis was in the range of 1%-20%, 2) mid if canal paresis was 21%-40%, and 3) severe if canal paresis was >41%. The vHIT was also classified as normal or abnormal.

The relationship between Gs and canal paresis was assessed by means of the intraclass correlation coefficient and Pearson’s correlation coefficient (R). Means of the gain of the VOR were compared with the Wilcoxon test. Proportions were compared by means of the Pearson chi-square or Fisher exact test when appropriate. The kappa statistics and the intraclass correlation coefficient with their 95% confidence intervals (95% CI) were used to assess agreement between different diagnostic methods. An assessment of sensitivity, specificity, and positive and negative predictive values was made, taking into consideration the caloric test result as the reference test.

**RESULTS**

In Table 1, we present relevant clinical data of the final population of this study (n=123).

The mean value of canal paresis was 31±30%, and the mean value of directional preponderance 23±18%; the caloric test was normal in 61 (49.6%) patients and abnormal in 62. Group classification gave the following results: left canal paresis in 56 patients (15 in the severe range, 15 in the mid-range and, 26 in the normal range) and right canal paresis in 67 (13 in the severe range, 19 in the mid, and 35 in the normal). With regard to gain of the VOR as measured in the vHIT, mean Gs was 8.7±9%. In Table 2, we present the findings in the vHIT for rightward and leftward head impulses; it is interesting to note that normal findings for both side impulses were obtained in 51 patients.

In Figure 2, we present the analysis of canal paresis and Gs for each patient. Pearson’s correlation coefficient was 0.677 (p=0.001) and R² was 0.45. Patients were classified according to the existence of spontaneous nystagmus or head-shake nystagmus: 1) in patients with spontaneous nystagmus, the intraclass correlation coefficient was 0.61 (95% CI 0.34-0.77; p<0.0001), and 2) in patients with head-shake nystagmus, the intraclass correlation coefficient was 0.64 (95% CI 0.31-0.81; p=0.001).

Gain of the VOR is analyzed in more detail in Figure 3, in which its mean value ±95% CI is shown for rightward and leftward head impulses according to the side and amount of canal paresis; a similar analysis is shown for the finding of refixation saccades in Figure 4. Gain of the VOR after rightward and leftward head impulses was significantly different only in patients that were in the corresponding severe group: paired Wilcoxon test, p=0.02. When the side with severe deficit was the right, gain after rightward impulses was 0.76±0.23 and 1±0.13 after leftward impulses; when the deficit was on the left side and severe, gain after rightward impulses was 1±0.15 and 0.74±0.25 after leftward impulses.

In Table 3, we show the distribution of normal and abnormal results for the caloric test and the vHIT according to the criteria mentioned.

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**Table 1. Diagnosis of patients in this study**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>Age ±3</th>
<th>SpNyst ±4</th>
<th>HSN ±3</th>
<th>Diagnosis</th>
<th>Activity</th>
<th>F/up ±7</th>
<th>IT ±5</th>
<th>N (T) ±1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menière’s disease</td>
<td>41</td>
<td>55±3</td>
<td>19 (4±2)</td>
<td>18</td>
<td>24</td>
<td>32 (12-89)</td>
<td>17</td>
<td>9</td>
<td>(28)</td>
</tr>
<tr>
<td>Vestibular migraine</td>
<td>23</td>
<td>48±3</td>
<td>14 (3±1)</td>
<td>9</td>
<td>18</td>
<td>21 (9-33)</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPPV</td>
<td>20</td>
<td>62±2</td>
<td>9 (3±2)</td>
<td>1</td>
<td>11</td>
<td>2 (1-19)</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic subjective diziness</td>
<td>11</td>
<td>57±5</td>
<td>2 (2±1)</td>
<td>0</td>
<td>11</td>
<td>Chronic undelayed</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vestibular neuritis</td>
<td>9</td>
<td>60±6</td>
<td>6 (3±1)</td>
<td>6</td>
<td>0</td>
<td>Chronic undelayed</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vestibular schwannoma</td>
<td>6</td>
<td>58±4</td>
<td>3 (3±1)</td>
<td>3</td>
<td>4</td>
<td>Chronic undelayed</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posttraumatic 5</td>
<td>5</td>
<td>61±1</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>Chronic undelayed</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otosclerosis</td>
<td>4</td>
<td>34±5</td>
<td>1 (3)</td>
<td>0</td>
<td>4</td>
<td>Chronic undelayed</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic serous otitis media</td>
<td>2</td>
<td>57±4</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>20 &amp; 23</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labyrinthitis</td>
<td>2</td>
<td>52±5</td>
<td>3 (3±2)</td>
<td>1</td>
<td>0</td>
<td>Chronic undelayed</td>
<td>2</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>123</td>
<td>55±15</td>
<td>57 (2.7±1.5)</td>
<td>38</td>
<td>78</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data as mean and 95% confidence interval (CI 95%). SpNyst: number of patients with spontaneous nystagmus (mean slow phase velocity of nystagmus); HSN: number of patients with head-shake nystagmus. Diagnosis: number of patients that are not following any treatment when seen. Activity: days since last vertigo spell or nature of the main symptom. F/up: patients that are seen in regular follow-up with or without medical treatment; IT N, number of patients treated with intratympanic medication, T, time (months) since treatment. BPPV: benign paroxysmal positional vertigo.
Results were coincident in 62% of the patients, while in the remainder, they differed. From this analysis, Pearson’s chi-square was 7.819 (p=0.005), and in the Fisher exact test, p=0.004. Overall, the agreement between them was low: \( \kappa = 0.252 \) (95% CI 0.082–0.423).

Taking the caloric test as the reference, sensitivity of the vHIT was 59% (95% CI 43.7%–71.5%), specificity was 66.1% (CI 95% 53%–77%), positive predictive value was 62.1% (95% CI 49.3%–73.8%), and negative predictive value was 62% (95% CI 49.3%–75.6%).

When the side of the canal paresis and vHIT were taken into account (Table 4), both were coincident in 60 patients (48.7%): caloric test and vHIT normal (36 patients), right and left canal paresis coincident with abnormal result after rightward and leftward head impulses, respectively (11 and 13 patients). Side discrepancies (abnormal right or left in the caloric test, while normal on the contrary in the vHIT) were found only in 3 patients, which was due to: 1) one patient seen now because of a benign paroxysmal positional vertigo (BPPV) who was treated years before for another (horizontal canal BPPV) on the other side and 2) a patient seen for bilateral otosclerosis that on one side behaved like Ménière’s disease. In 14 patients, there was surprising bilateral involvement according to the vHIT, as it was unexpected by the caloric test, which showed unilateral canal paresis. An explanation was found in 6 cases, of which in 4 cases, the contralesional abnormal finding was in patients with very severe unilateral vestibular deficit according to the caloric test and the vHIT (with gains lower than 0.4); the remainder needed further evaluation on follow-up. The caloric test and vHIT were interestingly complementary in 46 patients: in 21, the caloric test was abnormal and the vHIT was normal, and vice versa in 25.

DISCUSSION

The subjects in this study were heterogeneous in terms of the cause of their dizziness (a limitation of the study) but are representative of a typical specialized otoneurological clinic. Most of them were new patients, but others were seen in follow-up, and a caloric test was scheduled depending on the period of time since their previous visit, as occurs with all patients diagnosed of vestibular neuritis and labryrinthitis. In this work, and because of the heterogeneous nature of the disorder, we were interested in the analysis of the results from both tests, particularly as performed on the same day with a minimum time lag in between; in this way, we were able to rule out discrepancies due to the fluctuating nature of some of the diseases.

One of the first issues of interest has to do with the inclusion of patients. From the initial population of 137 subjects, 14 (10%) were discarded, because when analyzing the caloric test result, different artifacts were detected; this number is very representative of our practice in the vestibular laboratory throughout the years. Until now, our procedure in these cases was to repeat irrigations or the complete test or to perform a complete rotatory chair test whenever this was not initially scheduled (the impulsive test and the sinusoi-
The assessment of the vHIT result relies on the analysis of both the gain of the VOR and refixation saccades. We were able to characterize the response, consistent with these variables in 4 groups: 1) normal gain without refixation saccades, 2) normal gain with overt refixation saccades, 3) low gain without refixation saccades, and 4) low gain with refixation saccades. We have chosen 0.6 as the cut-off value for normal gain from the work with patients with vestibular neuritis (6), which provides a more sensitive assessment for our work, although the specificity becomes low; as such, 0.8 should be chosen also according to manufacturer recommendations and independent research. In the normal gain with refixation saccades, these occur immediately after the eye has stopped its movement in response to the head impulse, and their velocity is 40%-60% lower than the former. They sometimes go unnoticed in bedside evaluation of VOR with the head-thrust or head-impulse test, and we think that this is the main reason for the lack of correlation between the two examination methodologies: clinical or bedside and video-assisted. These are visually evoked rapid eye movements, as they disappear when the test is performed in darkness. We think that this partially explains the low sensitivity of the bedside vestibular test compared to the scleral harmonic acceleration test), in line with recommendations from other studies [7]. With the vHIT, we are now able to gather valuable vestibular information from those patients and others, such as those in which, due to abnormalities or diseases in the external or middle ear, water irrigation is contraindicated, with minimum discomfort and without taking a long time.

Table 2. Results in the video head-impulse test (vHIT) according to the direction of the impulse

<table>
<thead>
<tr>
<th>vHIT</th>
<th>Head</th>
<th>IMPLUSE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rightward</td>
<td>Leftward</td>
</tr>
<tr>
<td>Normal gain without saccades</td>
<td>70</td>
<td>75</td>
</tr>
<tr>
<td>Normal gain and saccades</td>
<td>50</td>
<td>42</td>
</tr>
<tr>
<td>Low gain with/without saccades</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

vHIT: video head-impulse test

Table 3. Distribution of patients according to results in the caloric test and video head-impulse test (vHIT)

<table>
<thead>
<tr>
<th>Caloric test</th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>vHIT Normal</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>Abnormal</td>
<td>25</td>
<td>41</td>
</tr>
</tbody>
</table>

vHIT: video head-impulse test

Table 4. Detailed distribution of findings depending on side of findings

<table>
<thead>
<tr>
<th>Caloric test</th>
<th>Normal</th>
<th>Abnormal right</th>
<th>Abnormal left</th>
</tr>
</thead>
<tbody>
<tr>
<td>vHIT Normal</td>
<td>36</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Abnormal right</td>
<td>6</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal left</td>
<td>9</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Abnormal r&amp;l</td>
<td>10</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

vHIT: video head-impulse test

The correlation obtained between the amount of canal paresis and Gs in the vHIT is slightly higher than that reported in Ménétrier’s disease [8]. It can be argued that it is because of the inclusion of patients with a permanent, stable, and more severe deficit, as is the case of those suffering from vestibular neuritis or labyrinthitis [10]; however, there are also patients with less damaging disorders, such as those with BPPV or vestibular migraine, who are usually normal in the caloric test and in the head-impulse test evaluated at the bedside [11, 12]. This is reflected by the low level of mean canal paresis. It is interesting to acknowledge that the amount of this correlation changes depending on the existence of other signs, such as spontaneous nystagmus or head-shake nystagmus. This may be because these signs indicate an active or ongoing process or because they are present while the head-impulse perturbs its precision. The second element in the study, the refixation saccades, appeared mainly for impulses to the ipsilesional side and, in particular, when the amount of vestibular damage was severe. However, they were also registered for impulses on both sides when the amount of vestibular deficiency was in the middle or normal range. This needs better characterization (in terms of velocity of the saccade and time of appearance), which is currently on-going due to its relevance, as has been shown for the assessment of vestibular compensation [13].

When gain and saccades are taken into account, we can bring a normal or abnormal test to a close and provide side information. The existence or absence of coincidence between the caloric test and the vHIT results is an issue that must be addressed in each particular disease, as patients with similar diseases were spread out over the different categories of concordance between both tests. However, some insight can be given now.

In 36 patients, we can conclude that the horizontal canal function is normal along the wide range of frequency analysis obtained with both methods: lower for the caloric test and higher with the vHIT. This may be because the disease is in another part of the inner ear (as in the case of patients with BPPV) or because it does not strike in the inner ear (as in some cases of chronic subjective dizziness). As such, including patients with the same disease only will change the amount of correlation and give better answers to the indication of each test; this issue was not the purpose of our work.

In 41 patients, both tests were abnormal, and when analyzed in detail, this is the most heterogeneous group made of different classes. In one grouping, made up of 24 patients, there was good coincidence, as the side of the caloric hypofunction correlated with the side with a vHIT abnormality; in these patients, the conclusion is that the amount of vestibular dysfunction is very relevant, as it appears after any kind of vestibular stimulation. In these patients, the use of the vHIT in follow-up and to disclose abnormalities on the normal side is of great importance, as the caloric test data are always given on both sides when the amount of vestibular deficiency was in the middle or normal range. This needs better characterization (in terms of velocity of the saccade and time of appearance), which is currently on-going due to its relevance, as has been shown for the assessment of vestibular compensation [13].

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acceleration vestibular loss [15], in which the main clinical symptom defined as a new entity under the characteristic of high frequency/normality is reliable, we can conclude the existence of what has been vHIT), we recommend retesting the vHIT, and in case where the ab -

caloric one [14]. In 4 patients of this class, we think that this means search coil method of assessment) to detect more abnormalities than in most; the level of discrepancies in results is very low.

In conclusion, the assessment of horizontal semicircular canal function with the vHIT needs to take into consideration not only the gain in VOR but also the existence of refixation saccades. The information from both methods is redundant in some cases but complementary in most; the level of discrepancies in results is very low.

In 21 patients, there was a contradiction, as the caloric test was abnormal but the vHIT was normal, and vice versa in 25, as the caloric test was normal but the vHIT was abnormal (in 15, there was a bilateral finding). Our data are lower than those shown by others [15], probably because they analyzed the caloric response from each ear independently and we used the conventional Jongkees’ formula to decide on a normal or abnormal caloric response. In these 46 pa-

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tion with the vHIT needs to take into consideration not only the gain in VOR but also the existence of refixation saccades. The information from both methods is redundant in some cases but complementary in most; the level of discrepancies in results is very low.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Navarra (2012).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.


Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has re-

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