Journal of Vestibular Research xx (2021) x–xx
DOI:10.3233/VES-201557
IOS Press



# Two conditions to fully recover dynamic canal function in unilateral peripheral vestibular hypofunction patients

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Received 21 August 2020
Accepted 10 February 2021



**Abstract**.
**BACKGROUND:** The crucial role of early vestibular rehabilitation (VR) to recover a dynamic semicircular canal function was recently highlighted in patients with unilateral vestibular hypofunction (UVH). However, wide inter-individual differences were observed, suggesting that parameters other than early rehabilitation are involved.
**OBJECTIVE:** The aim of the study was to determine to what extent the degree of vestibular loss assessed by the angular vestibulo-ocular reflex (aVOR) gain could be an additional parameter interfering with rehabilitation in the recovery process. And to examine whether different VR protocols have the same effectiveness with regard to the aVOR recovery.
**METHODS:** The aVOR gain and the percentage of compensatory saccades were recorded in 81 UVH patients with the passive head impulse test before and after early VR (first two weeks after vertigo onset: N = 43) or late VR (third to sixth week after onset: N = 38) performed twice a week for four weeks. VR was performed either with the unidirectional rotation paradigm or gaze stability exercises. Supplementary outcomes were the dizziness handicap inventory (DHI) score, and the static and dynamic subjective visual vertical.
**RESULTS:** The cluster analysis differentiated two distinct populations of UVH patients with pre-rehab aVOR gain values on the hypofunction side below 0.20 (N = 42) or above 0.20 (N = 39). The mean gain values were respectively $0.07 \pm 0.05$ and $0.34 \pm 0.12$ for the lateral canal ($p < 0.0001$), $0.09 \pm 0.06$ and $0.44 \pm 0.19$ for the anterior canal ($p < 0.0001$). Patients with aVOR gains above 0.20 and early rehab fully recovered dynamic horizontal canal function ($0.84 \pm 0.14$) and showed very few compensatory saccades ($18.7\% \pm 20.1\%$) while those with gains below 0.20 and late rehab did not improve their aVOR gain value ($0.16 \pm 0.09$) and showed compensatory saccades only ($82.9\% \pm 23.7\%$). Similar results were found for the anterior canal function. Recovery of the dynamic function of the lateral canal was found with both VR protocols while it was observed with the gaze stability exercises only for the anterior canal. All the patients reduced their DHI score, normalized their static SVV, and exhibited uncompensated dynamic SVV.
**CONCLUSIONS:** Early rehab is a necessary but not sufficient condition to fully recover dynamic canal function. The degree of vestibular loss plays a crucial role too, and to be effective rehabilitation protocols must be carried out in the plane of the semicircular canals.

Keywords: Unilateral vestibular hypofunction, degree of vestibular loss, early vs late vestibular rehabilitation, vestibulo-ocular reflex gain, compensatory saccades

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ISSN 0957-4271/$35.00 

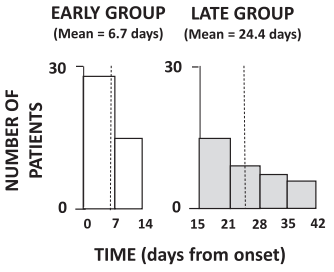
## 1. Introduction

Impairment of gaze stabilization is one of the most disabling deficits in the daily life of unilateral vestibular hypofunction (UVH) patients [15]. When the angular vestibulo-ocular reflex (aVOR) elicited during head rotation does not compensate perfectly the head velocity, that is, when eye movements generated in the opposite direction have not an equal magnitude and velocity due to the hypofunction side, the UVH patients complain of blurred vision and oscillopsia. This handicap impacts strongly their quality of life and, in the absence of specific vestibular rehabilitation (VR), it leads to avoidance behaviors (reduced head motion), difficulty reading and watching television, self-locomotor activity restriction, and social isolation as well in some cases.

Many clinical investigations have clearly shown that VR therapy is safe and effective in improving dizziness and function after unilateral vestibular loss [18, 47]. Based on gaze stability exercises [38] or using the unidirectional rotation paradigm [37], VR significantly decreased the aVOR directional preponderance observed after a vertigo attack. Two basic compensatory mechanisms have been identified as potential candidates for gaze stabilization during head motion in UVH patients. One refers to a saccadic substitution process first described in the frog model [8] and confirmed more recently in patients with the video Head Impulse Test [32, 38]. Internally generated signals trigger catch-up saccades in the direction of the deficient slow phase eye velocity, reduce the eye position error, and replace the deficient aVOR. This behavioral substitution process compensating the ocular motor disorders contributes to dynamic visual acuity recovery [16], recognized as a major functional impact of vestibular hypofunction [15]. A second mechanism is based on the high plasticity level of the aVOR as first illustrated in healthy subjects subjected to sensory conflicts [12] and, more recently, by the incremental adaptation technique which can generate an enhanced aVOR on the trained side [6, 33, 34, 38]. Little evidence of aVOR recovery was found in the literature on UVH patients. Most chronic UVH patients do not recover normal aVOR during passive, fast and unpredictable head thrusts [38]. However, the unidirectional rotation protocol consisting of high velocity passive rotations to the injured vestibular side was found to rebalance the two sides, and to reduce the directional preponderance by opposite effects on the lesioned (increase) and healthy (decrease) sides [37]. These data in humans confirmed those previously observed in the macaque model of unilateral vestibular lesion [44].

VR therapy with either gaze stability exercises or unidirectional rotations to the weaker side improve dynamic visual acuity by means of both compensatory saccades and enhancement of the active aVOR [38]. We have reported recently that early VR was better than late VR for UVH patients to recover normal dynamic visual acuity [27], a result that corroborated for the first time the early sensitive period we had already demonstrated in animal models [25, monkey; 48, cat]. The natural vestibular compensation [26] includes developmental plasticity mechanisms that are re-expressed after vestibular injury [22, 23] and tuned dynamically according to the post-lesion experience and training [24]. Using two different VR protocols based either on active gaze exercises with fast head rotations (to the hypofunction side only, HIT protocol) or passive whole body rotations (to the hypofunction side only, rotatory chair protocol), we demonstrated clearly that the recovery pattern exhibited by the UVH patients was in function of the time delay between onset of the symptoms and beginning of the VR therapy, whatever the VR protocol used [28, 29]. The UVH patients with early VR (the first two weeks after onset) were able to improve significantly their horizontal aVOR gain on the weaker side while those with later VR did not show significant changes. Another interesting finding was the high variability observed in the aVOR gain recovery of the UVH patients with early VR [see 28, Fig. 1B]. Could this variability depend on the degree of vestibular loss on the hypofunction side? We tested the hypothesis that patients with aVOR gains close to zero, thus exhibiting a complete loss of dynamic canal function, would not recover as much as the others with relatively higher aVOR gain values.

The present retrospective study conducted on eighty one UVH patients was aimed at testing this hypothesis. The aVOR gains recorded before VR on the weaker side of the patients have been submitted to a cluster analysis to assess the distribution of the values, and to determine whether the whole population of the UVH patients was homogenous (Gaussian distribution) or composed of sub-populations with different levels of pre-rehab aVOR gains (bimodal distribution for instance). The data were analyzed independently for those patients submitted to early (first two weeks after vertigo attack onset: $N = 43$) versus late (third to sixth weeks after vertigo attack onset: $N = 38$) VR therapy, and for patients rehabilitated either with the unidirectional rotation paradigm




| | |
|---|---|
| EARLY Group | 4 weeks VR (twice a week) |
| LATE Group | 4 weeks VR (twice a week) |
| UNIDIRECTIONAL ROTATION PARADIGM (Horizontal plane) | GAZE STABILITY EXERCISES (Horizontal, LARP, RALP planes) |

Fig. 1. Experimental protocol. Upper part: Histograms showing the time delay distribution in days between onset of the symptoms and the inclusion visit during which the physiotherapist conducted the first rehabilitation session. The group subjected to early rehabilitation (N = 43) was rehabilitated 6.7 days after symptoms onset on average, while the group with late rehab (N = 38) was rehabilitated 24.4 days after symptoms onset on average. Lower part: The early and late groups were submitted to a rehabilitation program including a similar number of sessions distributed twice a week for 4 weeks at the physiotherapist's office (mean duration: 30 min each). The patients were rehabilitated using either the unidirectional rotation paradigm or gaze stability exercises (see text).

or gaze stability exercises. Recovery of the aVOR gain and the percentage of compensatory saccades were the major outcomes of the study. Supplementary outcomes were the objective measurement of the static and dynamic subjective visual vertical, and the subjective assessment of quality of life with the dizziness handicap inventory test.

## 2. Material and methods

### 2.1. Subjects

Unilateral vestibular hypofunction (UVH; vestibular neuritis) was diagnosed by the same ENT physician (Dr Laurent Tardivet) on the basis of clinical examination and patient's history. This retrospective study included 81 UVH patients who exhibited the big five inclusion criteria – acute onset of spinning vertigo, spontaneous horizontal rotatory nystagmus beating to the intact side, positive Head Impulse Test (HIT) on the weaker side, nausea, and postural imbalance – as defined by Strupp and Magnusson [39]. The weaker side was considered as pathological when the aVOR gain elicited during the HIT was below 0.70 and when overt/covert saccades were observed. Horizontal aVOR gains on the intact side above 0.80 were also required for patients' inclusion. Positional vertigo, central vestibular pathology, ocular motor dysfunctions, and drug treatment constituted exclusion criteria. The aVOR gain measurement was determined during passive HIT with the VHIT Ulmer recording device (Synapsis, Marseille, France). The three pairs of semicircular canals were tested in order to document the vestibular deficit, that is, to determine which part of the vestibular nerve was impaired (superior and inferior branches or superior branch only). Among the 81 UVH patients, 62 had pathological HIT responses to horizontal canal test, vertical anterior canal test and posterior canal test on the hypofunction side while 19 had pathological HIT responses to horizontal canal test and vertical anterior canal test only. It was verified that the proportion of UVH patients with complete impairment of the superior and inferior branches of the vestibular nerve or impairment of the superior branch only was similar in the different sub-groups defined below. Due to its unpleasant effects, particularly for acute UVH patients, the caloric test was not systematically performed. When done, the response was diminished on the hypofunction side. Testing of the otolith system (VEMPs) was not performed in the absence of the necessary equipment.

The present study focused on the deficit and recovery of the aVOR gain on the injured side. It covered patients included in our previous publications [28, 29] and new UVH patients. The mean age of the UVH patients was 62.7 years (± 15.1; range: 18–86 years) and the hypofunction side was the right for 41 patients and the left for the remaining 40 patients. The inclusion visit was in the range 2 days (for the earliest) – 42 days (for the latest) after symptoms onset. The day of patient inclusion was the day of the first rehabilitation session. All patients provided written informed consent to participate in the study and were asked not to take anti-vertigo drugs after inclusion.

### 2.2. Head impulse test and measurement of the aVOR gain

Patients were tested while seated with the head tilted down by 30° to put the horizontal semicircular canal in the horizontal plane. Head rotations to the healthy and weaker sides were done passively with 10° peak amplitude, 200°/s peak velocity and

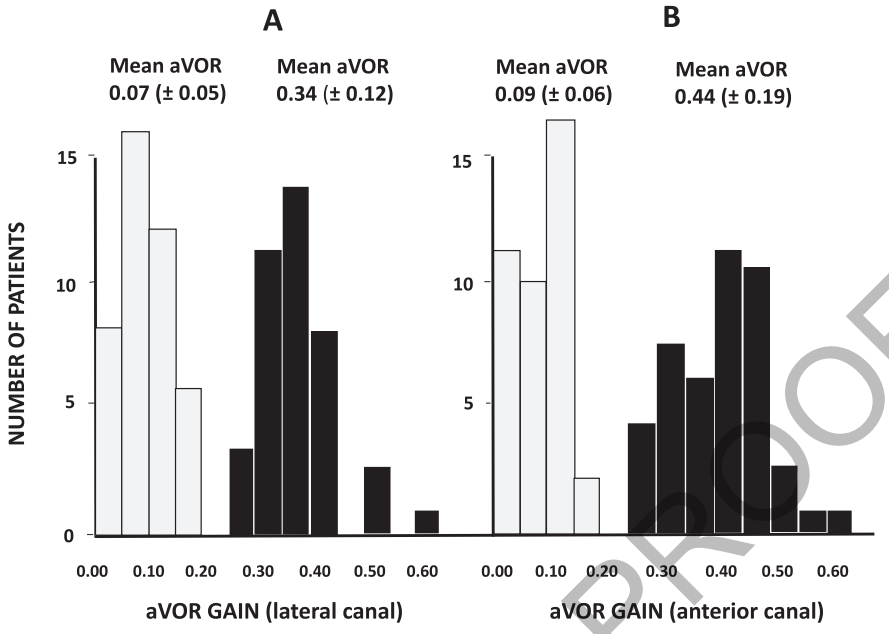



Fig. 2A-B. Cluster analysis and distribution of the aVOR gain values in the unilateral vestibular hypofunction patients. A) Histogram distribution and cluster analysis for the lateral semicircular canal on the lesioned side. The figure shows the number of patients (ordinates) per 0.05 class intervals of the aVOR gain values (abscissae) recorded on the lesioned side before vestibular rehabilitation. The histogram distribution of the whole population (N = 81) is split into two significantly distinct sub-populations with aVOR gains below 0.20 (open bars) or above 0.20 (filled bars) ($p < 0.0001$). Mean aVOR gains (± SD) calculated for each sub-population are shown. B) Histogram distribution and cluster analysis for the vertical anterior semicircular canal on the lesioned side. Same conventions as in A.

around 2000°/s peak acceleration. Recording of the aVOR of the vertical anterior and posterior canals was done by turning the patient's head 45° to the right (LARP) and then to the left (RALP). Head thrust tests were performed randomly to elicit unpredictable HITs with respect to timing and direction of head movement. Gain values of the aVOR were assessed by the ratio peak eye velocity/peak head velocity (Synapsis software). An average gain value was calculated before and after VR from 5 correctly performed tests on the intact and diseased sides for the horizontal and anterior semicircular canals mainly concerned in the present study. However, many more than 5 trials were generally done due to blinks or absence of perfect focus on the target by the patients. The posterior semicircular canal gain values were not included in the study due to low aVOR gains recorded on the intact side, outside the inclusion criteria in many patients. The latency and the total number of compensatory saccades occurring during and after the head movement was calculated by the software. The study focused on the covert saccades triggered during head motion in the direction of the slow phase component. These saccades were defined on the basis of their latency and, according to the VHIT Ulmer software, saccades occurring in the range 100 ms–180 ms after head rotation onset were defined as covert saccades. The percentage of covert saccades was assessed before and after VR.

### 2.3. *Distribution of the population of UVH patients*

#### 2.3.1. *Towards two distinct sub-populations of UVH patients*

The histogram showing the distribution of the aVOR gain values recorded before VR was constructed by pooling the individual mean aVOR gains per 0.05 class intervals. A Gaussian pattern of distribution was not found and, on the contrary, a bimodal distribution was observed with very low gain values for some patients and relatively higher gain values for others (see Fig. 2). To determine whether there was really a bimodal distribution attesting to two different sub-populations, or a skewed distribution, the data were subjected to a cluster analysis. This procedure was used to provide independent, statistical criteria and was performed with Systat software (version 5.0) and the K-means splitting method. It provides the best partitioned clusters on the basis of a

Table 1
Main characteristics of the two sub-populations of unilateral vestibular hypofunction patients

| | SUB-POPULATION 1 aVOR Gain < 0.2 | | SUB-POPULATION 2 aVOR Gain > 0.2 | |
|---|---|---|---|---|
| | *Early* $n = 20$ | *Late* $n = 22$ | *Early* $n = 23$ | *Late* $n = 16$ |
| AGE | $64.3 \pm 13.1$ | | $60.1 \pm 17.8$ | |
| | $63.2 \pm 13.2$ | $66.4 \pm 13.8$ | $58.1 \pm 17.2$ | $67.1 \pm 12.3$ |
| Mean aVOR Gain | $0.07 \pm 0.05$ | | $0.34 \pm 0.12$* | |
| | $0.05 \pm 0.05$ | $0.09 \pm 0.06$ | $0.32 \pm 0.13$ | $0.40 \pm 0.15$ |
| SPE Velocity (°/s) | $6.43 \pm 3.78$ | | $6.30 \pm 2.74$ | |
| | $8.92 \pm 5.56$ | $3.94 \pm 2.01$* | $8.88 \pm 4.05$ | $3.73 \pm 1.44$* |
| % Saccades | $70.5 \pm 26.3$ | | $63.7 \pm 27.5$ | |
| | $87.2 \pm 17.4$ | $62.4 \pm 38.2$ | $65.2 \pm 20.7$ | $56.9 \pm 32.9$ |
| DHI Score | $59.2 \pm 25.7$ | | $59.5 \pm 24.9$ | |
| | $66.5 \pm 15.8$ | $57.3 \pm 18.5$ | $62.4 \pm 22.2$ | $55.0 \pm 26.3$ |
| Vestibular Rehab Protocol | 42% UR; 58% HIT | | 38% UR; 62% HIT | |

The table shows the mean age (± SD) of the sub-populations with pre-rehab aVOR gains below 0.20 and above 0.20 (± SD), the mean slow phase eye velocity (± SD) recorded at their inclusion visit, the mean (±SD) percentage of compensatory saccades, their initial DHI score (± SD), and the percentage of patients rehabilitated with the gaze stabilization exercises (HIT) or the unidirectional rotation paradigm (UR). The mean data (± SD) are shown in the middle of the columns for each subpopulation, and separately for the patients submitted to early (left part of the columns) or late (right part of the columns) rehabilitation. SPE: slow phase eye velocity; UR: unidirectional rotation paradigm; HIT: head impulse test; DHI; dizziness handicap inventory. *indicates significant differences at $p < 0.001$.

statistical analysis in which the groups are not known in advance.

#### 2.3.2. *Towards four different sub-groups of UVH patients*

Each sub-population of UVH patients was subdivided into two distinct sub-groups on the basis of the time delay between onset of symptoms and beginning of the first VR session done at the end of the inclusion visit. According to our previous reports on early versus delayed VR therapy [27–29], the patients subjected to rehabilitation as early as the first two weeks after symptoms onset constituted the early subgroups whereas those rehabilitated between 16 to 42 days after onset formed the late sub-groups (Fig. 1). This method led to four distinct sub-groups composed of UVH patients with aVOR gains below 0.20 (N = 42) and early ($n = 20$) or late ($n = 22$) rehab, and patients with aVOR gains above 0.20 (N = 39) and early ($n = 23$) or late ($n = 16$) rehab. Table 1 shows that the main criteria differentiating these four sub-groups before rehab were the mean aVOR gain and the slow phase eye velocity of the spontaneous nystagmus in the dark. The age, the DHI score and the percentage of compensatory saccades were not significant criteria.

### 2.4. *Vestibular rehabilitation protocols*

This retrospective study included 81 UVH patients subjected to vestibular rehabilitation performed by the same physiotherapist (Alain Thiry). Two different VR protocols were used. Some patients have been rehabilitated with gaze stabilization exercises (around 60%) and others with the unidirectional rotation paradigm (around 40%) (cf Table 1). The proportion of UVH patients rehabilitated with the two protocols was similar in the four sub-groups of patients. Moreover, we recently reported similar improvement of the dynamic canal function with the two protocols [28], which is the reason why we initially pooled patients in each subgroup.

Briefly, gaze stability exercises were performed in standing patients using active repeated fast head movements to the weaker side only with small amplitude (10°), high velocity (200°/s) and high acceleration (around 1500–2000°/s$^2$). Gaze stability exercises were performed in the horizontal plane in order to stimulate the semicircular canals on the weaker side, and in the vertical planes (LARP and RALP) to stimulate the anterior and posterior semicircular canals on the weaker sides. Eye and head movements were recorded with a goggleless camera (VHIT Ulmer, Synapsys, Marseille, France). During the training session, the patients were in front of a screen on which optotypes (letters) of different size were randomly projected during 50 ms. Patients had to recognize five different optotypes of the same size which was progressively decreased by steps corresponding to 1/10 changes on the Snellen visual acuity

chart. Maximum duration of a training session was 30 minutes.

The unidirectional rotation paradigm consisted of whole body passive rotation of the patient to his/her weaker side only using the rotatory chair (Framiral, Grasse, France). Patients were seated, head tilted by 30° down to put the horizontal canal plane close to the horizontal, and suddenly rotated during three full 360° turns (or more, depending on patient's tolerance) at high velocity (200°/s, 1000°/s$^2$–2000°/s$^2$), eyes closed during the whole rotation. The chair was suddenly stopped at the end of the last lap and the patient was asked to open the eyes while fixating a stationary target located 2 meters ahead at eye level. Due to the post-rotatory nystagmus, the target was seen as illusory moving during a time period that progressively decreased as a result of habituation of the intact labyrinth. Five to ten trials were successively done during the same training session with maximal duration that did not exceed 30 minutes.

An equal number of training session was done for each sub-group. As a rule, all the UVH patients received training sessions twice a week for four weeks after inclusion. For all the patients, the first rehab session was done just after the inclusion visit.

### 2.5. Supplementary outcomes

Besides the recovery of the aVOR, the study investigated the Dizziness Handicap Inventory (DHI) [see 20] score of the UVH patients before and after VR. The global score incorporated the 25 physical, functional and emotional items scored on a three points scale with 4, 2 or 0 point for "yes", "sometimes" and "no", respectively. The maximum DHI score was 100 and, generally, patients with unilateral vestibular loss were in the range of moderate handicap with DHI scores ranging from 40 to 60 points. The French version of the DHI was used in the study [36].

The static and dynamic subjective visual vertical (SVV) was also assessed at the beginning of VR and immediately at the end of the last VR session. The patients were standing and facing a screen 1m in front of them, at eye level. They wore goggles narrowing the visual field to the intended visual scene on which a red laser bar was projected (Framiral, Grasse, France). The line was positioned randomly ± 15° relative to the true gravitational vertical and the patients were asked to rotate the bar clockwise or counterclockwise by means of two pushbuttons located in their hands until they align the laser line with their perception of verticality. The static SVV assessment was performed binocularly in darkness. Five trials were carried out for each initial positioning of the bar and the mean was calculated. The dynamic SVV was measured with the same device, but with a random visual pattern made of white dots of different sizes rotating clockwise or counterclockwise at 20°/s. The patients were asked to keep the laser bar vertical during the visual scene rotation. The visual rotation induced in healthy subjects a symmetrical tilt of the vertical up to 10°–15° in the direction of the visual field rotation [31] and, therefore, no directional preponderance was present in control subjects. We assessed the directional preponderance of the dynamic SVV in the UVH patients by subtracting the values recorded during each trial to the hypofunction side from the intact side. An average was calculated over three trials performed randomly on each side.

### 2.6. Statistical analysis

Repeated-measures analyses of variance (ANOVAs) were performed with sub-groups (aHVOR gain below and above 0.20, early and late rehab) and parameters (aHVOR gain, compensatory saccades, DHI score, static and dynamic SVV) as between-patients factors, and pre-rehab versus post-rehab data as the within patients factors.

Given the small size of each sub-group of UVH patients, and the values that did not follow a normal Gaussian pattern, the statistical analysis was performed with non-parametric tests. The sub-groups were compared with the Mann-Whitney U test while the pre-rehab and post-rehab data were compared with the Wilcoxon signed rank test. The level probability to consider the results as significantly different was fixed at $p < 0.05$.

## 3. Results

### 3.1. Two sub-populations of UVH patients with different pre-rehab aVOR gain

Figure 2 shows the histogram distribution of the horizontal (Fig. 2A) and anterior (Fig. 2B) canal aVOR gain values recorded in the 81 UVH patients on their weaker side. The histograms have been constructed by pooling the individual values per 0.05 class intervals. A bimodal distribution pattern was observed, suggesting strongly that the UVH patients did not constitute a homogeneous population. This observation was confirmed by the cluster analysis

that clearly split the group of UVH patients into two well-identified and significantly different clusters ($P < 0.0001$). This statistical method defined two different sub-populations of UVH patients with horizontal and anterior aVOR gains either below 0.20 or above 0.20.

The first sub-population was composed of 42 UVH patients (51.8%) exhibiting a mean aVOR gain of $0.07 \pm 0.05$ (range 0.00 to 0.19) for the lateral canal, and of $0.09 \pm 0.06$ (range: 0.00 to 0.18) for the anterior canal. The second sub-population was made of the 39 remaining UVH patients (48.2%) who showed a significantly higher mean aVOR gain of $0.34 \pm 0.12$ (range 0.23–0.62) and $0.44 \pm 0.19$ (range 0.21–0.64) for the lateral and anterior canals, respectively ($P < 0.0001$ compared to the first two groups). These two sub-populations with low and higher mean aVOR gains did not differ significantly regarding the age (64.3 years $\pm$ 13.1 *vs* 60.1 years $\pm$ 17.8), the percentage of patients rehabilitated with gaze stabilization exercises (58% *vs* 62%) or the unidirectional rotation protocol (42% *vs* 38 %), the maximum slow phase eye velocity ($6.43 \pm 3.78$ *vs* $6.30 \pm 2.74$), the DHI score ($59.2 \pm 25.7$ *vs* $59.5 \pm 24.9$), and the percentage of compensatory saccades ($70.5\% \pm 26.3$ *vs* $63.7 \pm 27.5$) as assessed at the inclusion visit. The slow phase eye velocity of the spontaneous nystagmus was the only pre-rehab parameter showing significant differences between the early and late sub-groups, the latter displaying significantly lower values compared to the former as a result of spontaneous compensation occurring over time (see Table 1). The whole set of data clearly show that the two sub-populations defined by the cluster analysis differed only by their initial aVOR gain, either below 0.20 or above 0.20.

### 3.2. *aVOR gain recovery and compensatory saccades in the sub-groups of UVH patients*

To determine whether the two different pre-rehab aVOR gain levels determined by the cluster analysis would influence the development of the recovery mechanisms (aVOR recovery or compensatory saccades), and to analyze the effectiveness of early *versus* delayed vestibular rehabilitation therapy for the recovery process, the four sub-groups of patients were analyzed separately.

Figure 3 shows the distribution of the aVOR gain values recorded from the lateral canal on the hypofunction side before and after rehabilitation across patients of the two sub-populations with gains below 0.20 (grey boxplots) and gains above 0.20 (black boxplots). The boxplots are formed by the 1st and 3rd quartiles, show the median (2nd quartile, solid horizontal line), while whiskers indicate the minimum and maximum aVOR gain values. The aVOR gain values after rehab were significantly improved in the sub-population with pre-rehab aVOR gain above 0.20 and in the sub-groups with early rehab. The lowest improvement was seen in the sub-group with low pre-rehab aVOR gain and late rehab ($0.09 \pm 0.06$ to $0.16 \pm 0.09$; $p = 0.08$), while the strongest improvement was observed in the sub-group with higher pre-rehab aVOR gain and early rehab, the only one to fully recover a normal aVOR gain (from $0.32 \pm 0.13$ to $0.84 \pm 0.14$; $p < 0.0001$). In this sub-group fully recovering a dynamic canal function, no impact of delay in starting VR was found: the patients beginning the therapy 2–7 days after symptoms onset and those beginning rehab in the later time period 8–14 days after onset recovered in the same way. The other two sub-groups (aVOR gain < 0.20 and early rehab; aHVOR gain > 0.20 and late rehab) showed intermediate recovery patterns but did not recover a normal aVOR gain. The data indicate therefore that early VR is a necessary but not sufficient condition to fully restore a dynamic aVOR function on the hypofunction side. The degree of vestibular loss on the weaker side constitutes another crucial factor.

Figure 4 summarizes these mean results for the lateral canal and shows an opposite pattern for the compensatory saccades, the second mechanism involved in gaze stabilization recovery. The percentage of compensatory saccades before rehab was not significantly different between the sub-populations with aVOR gain values below 0.20 ($70.5\% \pm 26.3\%$) and above 0.20 ($63.7\% \pm 27.5\%$). After rehab, the percentage drastically dropped down in the group of UVH patients fully recovering a dynamic canal function ($p < 0.0001$) whereas it increased in the UVH patients who showed the weakest improvement of their pre-rehab gain values ($p < 0.03$). The patients with a full aVOR gain recovery therefore showed the lowest percentage of compensatory saccades ($18.7 \pm 20.1\%$), and *vice versa* for the sub-group with little aVOR gain recovery which exhibited the highest percentage of compensatory saccades ($82.9 \pm 23.7\%$).

To what extent the nature of the VR protocol may influence the recovery of the dynamic canal function is another interesting question for the physiotherapist. Figure 5 plots the distribution of the aVOR gain values for the patients with pre-rehab gains below or

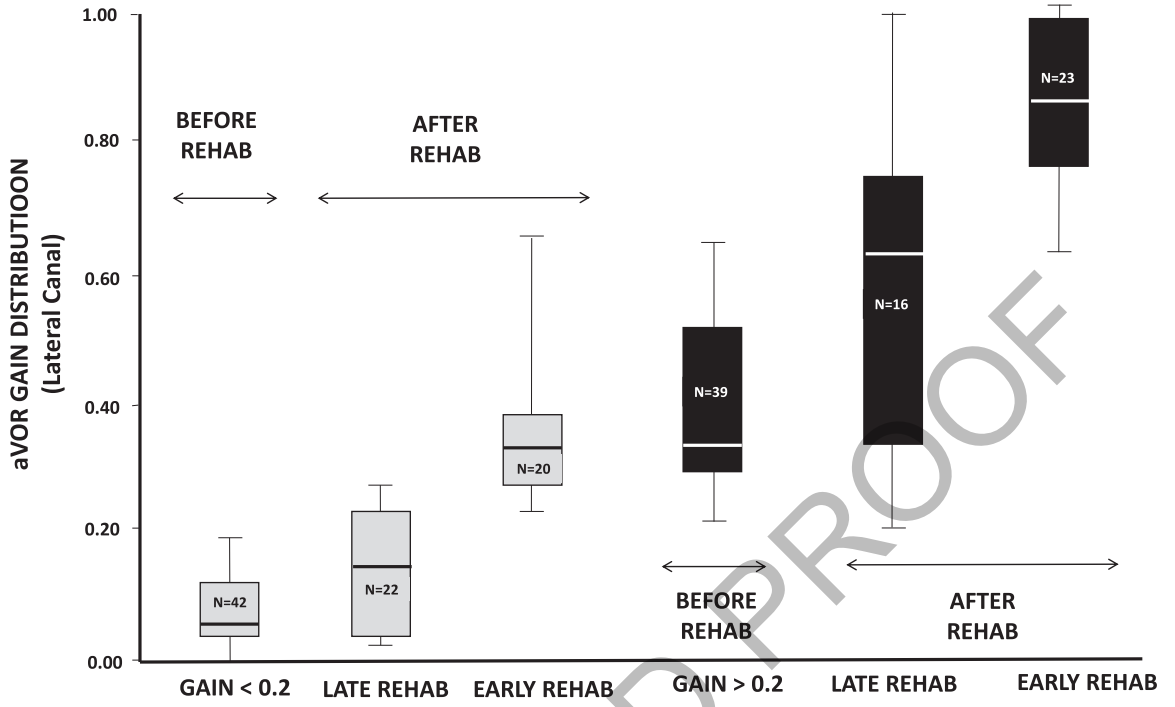



Fig. 3. Vestibular rehabilitation-induced changes of the angular vestibulo-ocular reflex in the two sub-populations of unilateral vestibular hypofunction patients. Lateral canal aVOR gain distribution for each sub-population with gain values below 0.20 (grey boxplots) or above 0.20 (filled boxplots) is shown before and after rehabilitation as boxplots with the 1st and 3rd quartiles, the median (horizontal heavy line), and whiskers indicating the minimum and maximum gain values. The effects of early versus late rehab are shown in each sub-population. The number of patients in each condition is plotted inside the boxplots.



above 0.20, subjected to early or late therapy either with the unidirectional rotation paradigm or the gaze stability exercises. The boxplots formed by the 1st and 3rd quartiles, the median (2nd quartile, solid horizontal line), and whiskers as the minimum and maximum aVOR gain values showed no significant differences between the two protocols. Gaze stability exercises in the plane of the lateral canal as well as unidirectional whole body rotation in the horizontal plane lead to similar aVOR improvements, whatever the time delay from onset of symptoms to starting therapy, and whatever the aVOR baseline (gain < 0.20 or > 0.20).

Different results were observed for the anterior canal. Figure 6 clearly shows that gaze stability exercises in the plane of the vertical anterior canal is the only effective VR protocol to improve significantly the aVOR recovery. This was observed in both sub-groups with baseline aVOR gains below 0.20 ($p < 0.0001$) and above 0.20 ($p < 0.001$), and the greatest improvements were found again when the therapy was done early compared to late ($p < 0.0001$ and $p < 0.01$ for the two sub-groups, respectively). The unidirectional rotation paradigm performed in the plane of the horizontal canal has no effect on the aVOR recovery of the anterior canal.

A remaining question was whether there is a linear relationship between the pre-rehab and post-rehab aVOR gain values. This has been explored for the lateral canal by means of a simple regression analysis in the sub-group of patients with pre-rehab gain above 0.20. The data for this sub-group indicated that the baseline gain values differed significantly between the patients ($F_{1,21} = 18.6$; $p < 0.0001$), but patients with low baseline gain experienced the same recovery as patients with higher baseline after rehab. The analysis performed on the slopes computing each individual baseline gain value to each post-rehab individual gain value did not point to significant differences ($F_{1,21} = 1.2$; $p = 0.28$).

### *3.3. DHI score in the different sub-groups of UVH patients*

The DHI scores established before rehab showed similar global values for the two sub-populations

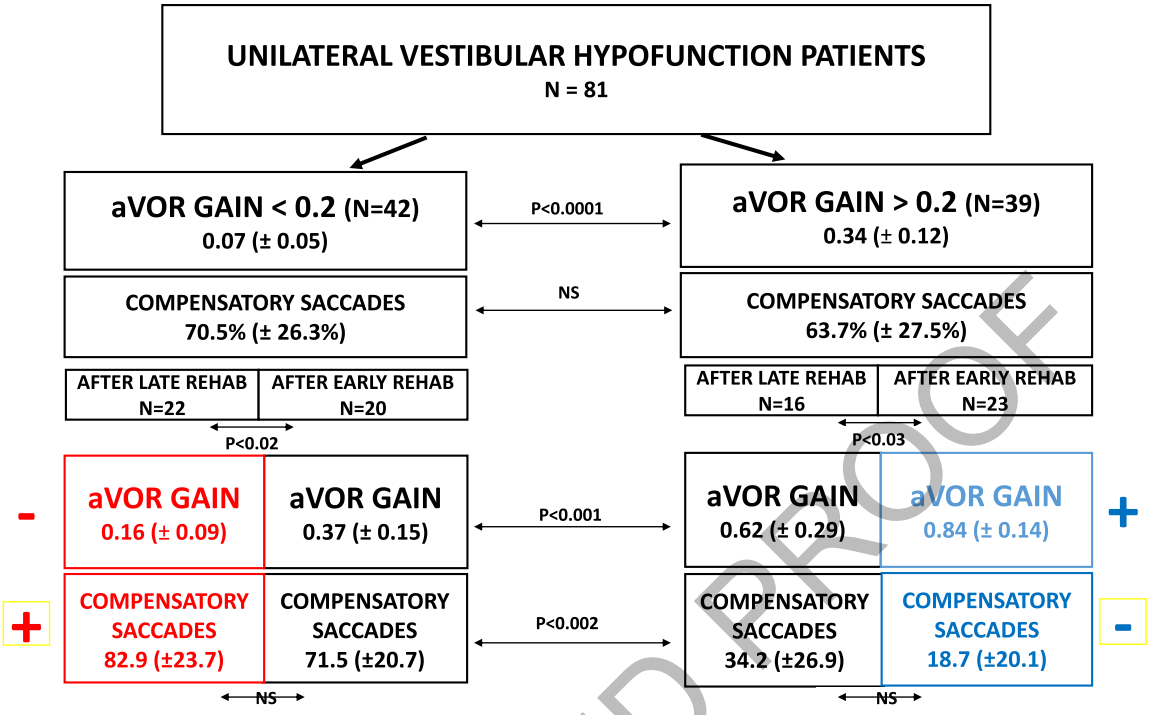



Fig. 4. Schematic drawing illustrating the effects of early versus late rehabilitation in the two sub-populations of unilateral vestibular hypofunction patients. Changes in the lateral canal aVOR gain and percentage of compensatory saccades recorded on the lesioned side are illustrated for the four sub-groups with pre-rehab gain values below 0.20 (left part) or above 0.20 (right part), with early or late rehabilitation. The mean (±SD) is shown for each sub-group, and the significant differences are indicated with the probability level. Patients with early rehab and initial gain values above 0.20 are the only ones to recover a normal aVOR function (see +, right part) and to show the lowest percentage of compensatory saccades (see –, right part). By contrast, patients with initial gain below 0.20 and late rehab display the highest percentage of compensatory saccades (see +, left part) and unchanged aVOR gain values (see –, left part). The results indicate that aVOR gain recovery is better with early rehab compared to late rehab, and that early rehab is a necessary but not sufficient condition to fully recover dynamic canal function on the lesioned side.



of UVH patients with aVOR gain below or above 0.20. All patients were in the same range of moderate handicap ($59.2 \pm 25.7$ and $59.5 \pm 24.9$ for the two groups, respectively: see Table 1). As a rule, the DHI scores decreased significantly after rehab without significant differences between the sub-groups, whatever the time period between symptoms onset and beginning of VR, whatever the VR protocol, and patients shifted from moderate to slight handicaps (Table 2). For instance, both sub-groups either recovering a normal aVOR gain after early rehab or using the compensatory saccades strategy after late rehab showed similar DHI score reduction ($21.3 \pm 25.8$ *vs* $20.1 \pm 17.3$, respectively). The results suggest that the subjective perception of dizziness handicap does not depend on the behavioral strategy used by the patients (the covert saccades), and is probably not related to their quality of life. However, 10 patients among the 38 patients subjected to late rehab did not achieve the 18 points DHI score reduction (26.3%), which is the minimal clinically important difference in a treatment outcome, while only 2 were found among the 43 patients subjected to early rehab (5.6%).

### 3.4. *Subjective visual vertical in the different sub-groups of UVH patients*

Is gaze stabilization strategy (aVOR recovery or compensatory saccades) correlated with perception of the subjective visual vertical? Table 2 shows that whatever the strategy used by the UVH patients, the static subjective visual vertical was recovered similarly and returned toward normal values in the four sub-groups. On the other hand, the directional preponderance observed with the dynamic subjective visual vertical test remained uncompensated in all the sub-groups after rehab. Directional preponderance was assessed by measuring the asymmetry between vertical perception with visual scene rotations to the

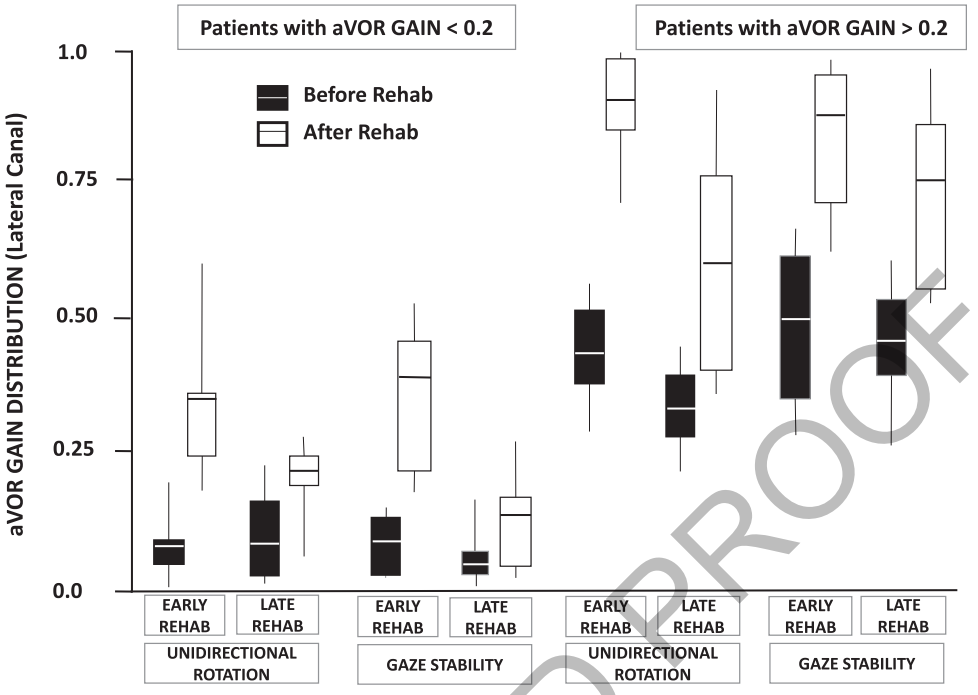



Fig. 5. Comparison of the effectiveness of the two rehabilitation protocols for the lateral canal aVOR gain recovery. The figure shows the distribution of the aVOR gain values recorded before (filled boxplots) and after (open boxplots) vestibular rehabilitation with gaze stability exercises or the unidirectional rotation paradigm. Results are shown for the four sub-groups with early or late rehab and pre-rehab gain values below 0.20, and for the four sub-groups with early or late rehab and pre-rehab gain values above 0.20. Boxplots are shown with the 1st and 3rd quartiles, the median (horizontal heavy line), and whiskers indicating the minimum and maximum gain values in each sub-group. Similar changes are observed with the two rehabilitation protocols.

intact and diseased sides. The UVH patients showed mean values above the normal range of healthy controls (more than 2 degrees) [see 31] before and after rehab. Rotation of the visual environment to the intact side elicited much less deviation of the dynamic subjective visual vertical than when rotation was made to the hypofunction side.

## 4. Discussion

Taken together, the data from this retrospective clinical study on patients with acute unilateral vestibular hypofunction confirmed two previous findings and showed three new findings. The confirmed findings are 1) training with the gaze stabilization exercises protocol or the unidirectional rotation paradigm induces a better recovery of the angular vestibulo-ocular reflex when rehabilitation is performed early, and 2) two different strategies are used by the patients to improve their gaze stabilization function: dynamic recovery of the aVOR with early rehab and behavioral substitution based on compensatory saccades with late rehab. The new findings are 1) early rehab is a necessary but not sufficient condition to fully recover a dynamic canal function. The degree of hypofunction on the lesioned side plays a crucial role too, 2) the aVOR recovery is function of which semicircular canal has been stimulated during rehab, and 3) subjective outcomes such as the DHI score, and objective measurements such as static and dynamic SVV are not correlated with gaze stability recovery.

### *4.1. Early vestibular rehabilitation: a necessary condition*

Several investigations in unilateral vestibular loss patients had already described the two primary mechanisms responsible for dynamic visual acuity improvement, that is, enhancement of the aVOR gain and increase of the compensatory saccades [38]. Whereas passive head thrust rotations did not cause much improvement of the aVOR gain and of dynamic visual acuity in chronic patients [16, 41], recovery of a near normal aVOR has been observed when rehabilitation was done within 1 month after onset of the

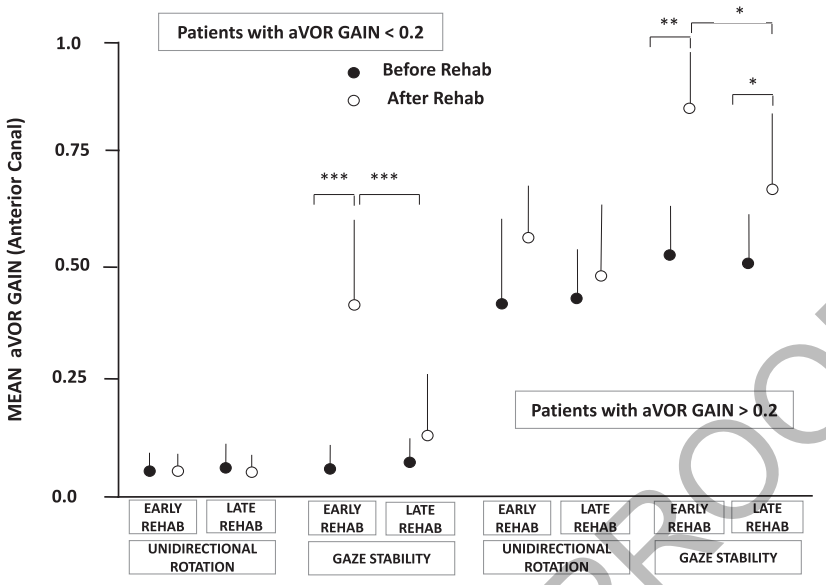



Fig. 6. Comparison of the effectiveness of the two rehabilitation protocols for the anterior canal aVOR gain recovery. The figure shows the mean aVOR gain values (±SD) recorded before (black symbols) and after (open symbols) vestibular rehabilitation with gaze stability exercises or the unidirectional rotation paradigm. Results are shown for the four sub-groups with early or late rehab and pre-rehab gain values below 0.20, and for the four sub-groups with early or late rehab and pre-rehab gain values above 0.20. The rehabilitation protocol consisting of carrying out gaze stability exercises in the plane of the anterior canals (LARP or RALP) significantly improves the anterior canal recovery, particularly in the sub-group of patients with pre-rehab gain above 0.20 and early rehab which returns to normal aVOR gain values. In contrast, no change was observed with the unidirectional rotation protocol that stimulates the semicircular lateral canal only. $^{*}p<0.01$; $^{**}p<0.001$; $^{***}p<0.0001$.

Table 2
Supplementary outcomes recorded after rehabilitation of the unilateral vestibular hypofunction patients

| | SUB-POPULATION 1 aVOR Gain < 0.2 | | SUB-POPULATION 2 aVOR Gain > 0.2 | |
|---|---|---|---|---|
| VESTIBULAR REHAB | *Early* $n=20$ | *Late* $n=22$ | *Early* $n=23$ | *Late* $n=16$ |
| STATIC SVV | $1.22 \pm 0.94$ | $1.01 \pm 0.88$ | $1.12 \pm 0.95$ | $1.29 \pm 1.06$ |
| DYNAMIC SVV | $2.92 \pm 2.02$ | $3.38 \pm 2.90$ | $2.21 \pm 2.14$ | $2.79 \pm 2.42$ |
| DHI SCORE | $20.1 \pm 17.3$ | $26.7 \pm 20.3$ | $23.3 \pm 25.7$ | $37.2 \pm 27.5$ |

The table shows the effects of early *versus* late rehabilitation on the static and dynamic subjective visual vertical (SVV), and on the dizziness handicap inventory (DHI) score. Dynamic SVV is the judgment of verticality with a moving visual environment (see text). Data are shown for each of the two sub-populations of unilateral vestibular hypofunction patients with aVOR gain values below 0.20 (N = 42; $n=20$ and $n=22$ for early and late rehab, respectively) or above 0.20 (N = 39; $n=23$ and $n=16$ for early and late rehab, respectively). No significant differences were found between the different sub-groups.



symptoms [21]. We have more recently stated that the first two weeks was the most relevant time window for optimal recovery of dynamic visual acuity [27], aVOR gain [28] and balance control as well [29]. The present study confirms that whatever the level of the pre-rehab aVOR gain, below 0.20 or above 0.20, the post-rehab aVOR gain is significantly much more strongly improved when rehabilitation was performed very early after onset of the symptoms (first two weeks). Such a critical or sensitive period has long ago been reported in animal models of acute unilateral vestibular lesion [see 25, 48], confirming the general statement that brain remodelings and neural plasticity are both time and neural activity dependent [see 11, 1, for reviews]. The early time window for vestibular lesion-induced neural plasticity covers the first few weeks after vestibular lesion [22]. Training and sensorimotor activity during this window of opportunity reinforce and optimize the expression of the plastic events [26]. Until our recent papers on UVH patients, this concept was still under debate in the vestibular pathology literature, some

studies underlying the benefits of early rehabilitation [9, 40] while others showed benefits at all stages of the recovery process [17, 42]. This is the reason why the American Physical Therapy Association ranked as number one the clinical research recommendation to examine the concept of critical period for optimal vestibular compensation [14]. There is no doubt now that it is better to do vestibular rehabilitation early, if it can be arranged. This study also confirms that VR therapy based either on gaze stability exercises or whole body unidirectional rotation in the horizontal plane lead to similar improvement of the dynamic recovery of the lateral canal.

### 4.2. *Early vestibular rehabilitation: a necessary but not sufficient condition*

Among the UVH patients with early VR, and independently of the rehabilitation protocol used, some patients seemed to recover much better than others. We had already highlighted this point [see 28; Fig. 1B] by stressing the wide dispersion of the individual aVOR gain values observed in patients subjected to early rehabilitation with the gaze stability exercises and the unidirectional rotation paradigm. The hypothesis tested here was therefore whether the degree of vestibular loss on the weaker side was the source of variability. If recovery of the aVOR depends on the degree of vestibular loss, the synaptic reorganization and neural repair induced peripherally (sensory epithelium) or centrally (vestibular nuclei) should depend on the number of remaining vestibular afferent synapses and fibers. In other words, UVH patients with very low pre-rehab aVOR gains should have less chance of recovering a dynamic canal function than patients with relatively higher aVOR gains.

The present study confirms this hypothesis. The cluster analysis pointed to bimodal distribution patterns of the individual gain values for both the lateral and anterior canals, and it statistically differentiated two distinct sub-populations with gain values below 0.20 and above 0.20 ($p < 0.0001$). The only sub-group to fully recover a normal aVOR function was the group of patients with pre-rehab gain above 0.20 and early rehabilitation (mean post-rehab gain: $0.84 \pm 0.14$ for the lateral canal; $0.83 \pm 0.17$ for the anterior canal). This sub-group was also the only one to show the greatest reduction of the percentage of compensatory saccades after rehab (mean: $18.7\% \pm 20.1\%$ for the lateral canal; $20.2\% \pm 15.7\%$ for the anterior canal). By contrast, the sub-group exhibiting the poorest horizontal aVOR gain recovery ($0.16 \pm 0.09$) and the highest increased percentage of compensatory saccades ($82.9\% \pm 23.7\%$) was the group of patients with pre-rehab gain values below 0.20 and late rehab. The data indicate clearly that the strategy to stabilize gaze is determined both by the time delay between onset of the symptoms and beginning of vestibular rehab, and by the degree of vestibular loss. The aVOR gain can be fully restored if remaining vestibular afferents are in sufficient number to induce synaptic reorganizations, centrally or peripherally, and if learning and training processes are performed early after vestibular injury. This Hebbian neural plasticity can be expressed in the group of patients with aVOR gain above 0.20 and early rehab. The time constant of the involved plastic mechanisms (sprouting of new terminals, increased number of postsynaptic receptors, peripheral repair) is compatible with the early time window described in this study [8, 10, 11]. The activity dependent neural mechanisms can reweight the vestibular input on the hypofunction side. By contrast, when the vestibular loss is much more severe (aVOR gain below 0.20) and when the rehabilitation is started outside this early opportunity time window, Hebbian plasticity is reduced or lost, and the reduction of neural reorganization is all the greater the later the rehabilitation is undertaken. The brain therefore elaborates a new strategy as an adaptive way to compensate the lack of hardware plasticity: the compensatory saccades triggered in the direction of the normal slow phase eye velocity, working as a behavioral substitution process. These covert saccades assist gaze stability during fast head motion. They are triggered by visual signals [45] in response to retinal position errors [3, 38, 43].

### 4.3. *Is there a better strategy to compensate for a unilateral vestibular deficit?*

In daily life conditions, when the patients have to turn suddenly the head to the diseased side under unpredictable conditions (somebody touching his/her shoulder, a sudden noise on the diseased side, ... ) it is clear that the full recovery of the aVOR gain is the best way to avoid blurred vision and balance disturbance. Restoring normal aVOR gain is also a prerequisite to regain normal dynamic visual acuity, and this strategy works well in both passive and active situations, in predictable and unpredictable conditions. On the other hand, the compensatory saccades play a functional role in predictable conditions only. This is the major limitation for patients using this behavioral strategy.

The two VR protocols used in the study are not equivalent. It is clear that the stimulation must be carried out in the plane of the semicircular canal to restore the canal dynamics. Gaze stability exercises have the advantage of acting on all three pairs of semicircular canals while the unidirectional rotation protocol only acts on the lateral canals. This explains why the dynamic recovery of the lateral canal function was observed with both protocols and the recovery of the anterior canal function with gaze stability exercises only. To be effective on all semicircular canals, the unidirectional rotation paradigm in the yaw plane should place the patient's head in a position such that the anterior (or posterior) canal is stimulated. Moreover, it is not certain that the two protocols involve the same plasticity mechanisms. Long-lasting stimulation at constant velocity performed with the unidirectional rotation paradigm activates habituation mechanisms and modifications of the time constant of the VOR on the healthy side [5]. The dynamics of gaze stability exercises performed with faster and short duration head rotation is totally different, and the adaptive mechanisms should also differ. Current experiments are investigating this interesting point.

Assessing the patient's quality of life seems however relatively independent of the strategy used to improve gaze stabilization. This has already been reported in patients with vestibular neuritis [30] and highlighted by the lack of correlation between the subjective perception of dizziness handicap and the vestibular tests [46]. Decrease in the global DHI score was observed in all the patients who shifted from moderate to slight handicaps after rehab. No significant differences were found between the four sub-groups of patients tested at the end of the rehabilitation session. On the other hand, all the patients included in this study showed a rapid normalization of their static SVV, with mean values ranging after rehab from $1.1^\circ \pm 0.06^\circ$ to $1.29^\circ \pm 0.14^\circ$, depending on the sub-groups. This rapid normalization is an argument suggesting that our UVH patients had very likely a near normal otolith function. The predominant role of the static gravitational/otolith input on the perceived verticality has been evidenced with different protocols [2, 35]. In addition, it has been shown that the static SVV required a longer time period to recover after a unilateral vestibular loss [4, 31]. By contrast, moving visual scenes influence the apparent direction of gravity in a symmetrical way in healthy subjects [7, 13]. The dynamic SVV remained asymmetrically modulated in our UVH patients, with significantly greater tilts of the perceived vertical for visual scene rotation to the lesioned side (due to crossed visual pathways onto the vestibular nuclei on the intact side) compared to rotation to the intact side (visual inputs projecting on the deafferented vestibular nuclei). Uncompensated preponderance values were therefore observed, ranging from $3.38^\circ \pm 2.90^\circ$ to $2.21^\circ \pm 2.14$ depending on the sub-groups. This observation confirms that compensation of the dynamic SVV is a long term process and constitutes a more or less permanent deficit in UVH patients [31]. The two VR protocols used in this study (gaze stability exercises, unidirectional rotation paradigm) are not effective for dynamic SVV recovery.

## 5. Conclusions

The study definitively concludes that there is a critical period for rehabilitation of unilateral vestibular hypofunction patients. The VR therapy, safe and effective for improving gaze stabilization, balance and quality of life [18, 19, 47], must be performed very early after onset of the symptoms to accelerate and to optimize the recovery process. Early rehab is however a necessary but not sufficient condition to get the best dynamic canal recovery. The degree of vestibular loss constitutes a second crucial parameter interfering with early training. When the weaker vestibular side is severely impacted (aVOR gain values below 0.20), the horizontal (lateral canal) and the vertical (anterior canal) VOR functions cannot be fully restored. Patients use compensatory saccades as a behavioral strategy to stabilize gaze. By contrast, when the weaker side is less severely impacted (aVOR gain above 0.20) and when rehabilitation is performed very early after onset of the symptoms, the dynamic horizontal and anterior canal functions can be fully restored, and the patients no longer use the compensatory saccades. The main message for patients is therefore to refer to a specialist as soon as possible after the vertigo attack in order to quickly obtain the right diagnosis, and for specialist in otorhinolaryngology to send the patient as soon as possible to a physiotherapist with a proper expertise in vestibular rehabilitation. The VR protocol matters, and this is another important point for the physiotherapist.

## Limits of the study

Neurovegetative symptoms may be experienced by some patients during whole body rotation. The

percentage of patients who showed pallor and sweating was around 20% while stopping peoples exercise program for the day was found only in 5% of the patients. This is a limitation for rehabilitation with the unidirectional rotation paradigm. When necessary to stop the training session, the physiotherapist started the next session with a reduced rotation speed. On the other hand, gaze stability exercises may be difficult to perform for patients with neck rigidity and, when coupled with optotype recognition (dynamic visual acuity training), they require high concentration which may induce fatigability.

Data regarding the recovery of the posterior canal dynamic function has not been reported in the present study due to low aVOR gain values also recorded on the intact side in many patients (gain below 0.7). The total number of UVH patients who fulfilled the inclusion criteria was not sufficient for proper statistical analysis of this semicircular canal. Further investigation on a wider sample of patients remains to be done.

## Authors contribution

LT diagnosed and selected the vestibular neuritis patients included in the study. AT carried out the vestibular rehabilitation of the patients. ML wrote the paper. LT, AT and ML together corrected the manuscript.

## Conflict of interest

The authors declare having no conflict of interest

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