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Original Research Article

Frequency-Amplitude Ratio of Cervical Vestibular Evoked Myogenic Potential for Identifying Meniere's Disease

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ABSTRACT

Objective: Frequency amplitude ratio (FAR) is one among several parameters of cervical vestibular evoked myogenic potential (cVEMP) found useful in diagnosis of Meniere's disease. This being the least explored of the parameters, there is not only a need for further investigation but also a need for identifying the best suited frequency amplitude ratio for diagnosing Meniere's disease.
Design: This prospective study aimed at investigating FAR of cVEMP in healthy individuals and individuals with Meniere's disease establishing the optimum frequency pair for assessment of Meniere's disease.
Study sample: Twenty two individuals with unilateral definite Meniere's disease were compared against 22 healthy individuals.
Results: Frequency amplitude ratios corresponding to 750/500, 1000/500, 1500/500 and tuned frequency/500 were all found useful in diagnosis of Meniere's disease by virtue of showing larger frequency amplitude ratio in Meniere's disease ears compared to the controls ($p < 0.05$). The frequency amplitude ratio of 750/500 frequency pair produced highest sensitivity (95.45%) and specificity (79.55%) when using a criterion point of ≥1.12 for diagnosis of Meniere's disease.
Conclusions: FAR is a reliable tool for diagnosis of Meniere's disease. The FAR of 750/500 is better suited to the identification of Meniere's disease than 1000/500.
Keywords: Frequency amplitude ratio, cervical vestibular evoked myogenic potential, Meniere's disease, sensitivity, specificity.

INTRODUCTION

The cervical vestibular evoked myogenic potential (cVEMP) is an inhibitory potential recorded from the tonically contracted sternocleidomastoid muscle. It has been gaining significance ever since its first reports in early 1990s. (1,2) cVEMP is highly useful in identification of several pathologies involving the peripheral vestibular organs, especially saccule and inferior vestibular nerve. (3-5) One of the pathologies which are prominently identified through the use of cVEMP is Meniere's disease. (6,7)

Described first in 1861 by Prosper Meniere, Meniere's disease (MD) is largely believed to be a progressive idiopathic disease of the inner ear which results in degeneration of the hair cells not only of cochlea but also of saccule and/or utricle. (8)

The case usually presents with a history featuring the tetrad of symptoms that include attacks of rotatory vertigo accompanied by nausea or vomiting, fluctuating sensorineural hearing loss triggered by attacks of vertigo but may become permanent later, tinnitus with broadband noise like quality and deep aural pressure that generally precedes the attack. [9,10] The prevalence of MD is reported to vary across the globe. It was reported to be 218.2, 513, 36.6, and 21.4 persons per 100,000 in the United States of America, [11] Finland, [12] Hida (Japan), [13] and Nishikubiki(Japan) [13] respectively. Although there are no published reports of its incidence in India, the worldwide incidence of MD is reported to be approximately 1.2%. [14] The difference amongst the studies could be attributed to the complex nature of the disease and inherent difficulties associated with its identification. Recognizing its prevalence and difficulties associated with its differential diagnosis, a number of tests have been developed to enable appropriate diagnosis and differential diagnosis of Meniere's disease from its symptomatic cousins. These tests range from one of the most ancient one in pure-tone audiometry to one of the most recent one in VEMP.

The effect of MD on different parameters of cVEMP has been investigated through several studies. The different parameters reported include amplitude, latency, threshold, asymmetry ratio, frequency tuning and frequency amplitude ratio (FAR).While latency and absolute amplitude are largely accepted as the least sensitive and specific of the parameters, threshold, asymmetry ratio and frequency tuning have met with a satisfactory degree of sensitivity but less than desired specificity. [15-17] The cVEMP parameter that has drawn the lowest amount of attention is FAR. Elsewhere in literature, this has also been called amplitude frequency ratio. [18,19]

FAR refers to the ratio of amplitude between two frequencies. To the best of our knowledge, the utility of FAR of cVEMP in the diagnosis of MD has been sparingly explored. [18,19] Using the presumption of shift in frequency dynamicity from peak at 500 Hz in healthy individuals to 1000 Hz in individuals with MD, they found a FAR between 500 Hz and 1000 Hz to be a clinically useful measure for identification of MD. However an elementary drawback that is likely to creep in with such an assumption is the possibility that tuning peak does not necessarily shift to 1000 Hz in all the individuals with MD. [7,15,20] The frequency corresponding to largest amplitude and lowest threshold was demonstrated to shift to750 Hz, 1500 Hz, or 2000 Hz, in addition to the presumed 1000 Hz. [7,15,20] Though highest peak prevalence is shown to be centred around 1000 Hz, a considerable number of participants with MD reflected the peak amplitude at 750 Hz and 1500 Hz in the above studies. Only a small minority of subjects showed 2000 Hz as the frequency with highest amplitude. Further, researchers have also found difficulty in associating a particular frequency to which the frequency tuning curve is tuned due to a minimal difference; usually well within the test-retest reliability value, between the amplitudes at two frequencies in the frequency tuning curve of an individual. So there is a need to investigate the frequency amplitude ratio between other frequency pairs in order to identify an optimal pair of frequencies for FAR of cVEMP which might facilitate better and easier identification of MD. This might also bring about better sensitivity and specificity values, which however need evaluation. Thus, the present study aimed at investigating FAR of cVEMP using most often encountered frequency tuning shifts among individuals with MD as well as healthy individuals. It also aimed to identify the optimum frequency pair for FAR of cVEMP that would enable identification of MD accurately.

MATERIALS AND METHODS

Participants

The study included 22 individuals with unilateral definite MD (13 females & 9 males) in the age range of 25-50 years (mean age = 41.23 years, standard deviation = 4.63 years) who fulfilled the criteria of unilateral 'definite Meniere's disease' based on the recommendations of the Committee on hearing and equilibrium of the American Academy of Otolaryngology- Head and Neck Surgery (AAO-HNS).[(9)] The prerequisite for the inclusion of individuals in this group included history of at least two definitive episodes of vertigo (true spinning sensation) lasting for no less than 20 minutes each, at least one instance of documented hearing loss along with episodes of tinnitus accompanied by aural fullness, with other causes of such precipitations ruled out. All the participants with MD in the present study also reported of aura, mostly in the form of sensation of tinnitus or deep aural pressure. The study also consisted of 22 healthy individuals with normal audio-vestibular system who were age and gender matched to the participants with MD. The study adhered to the guidelines existing at All India Institute of Speech and Hearing, Mysore, India (unpublished) which follows the general ethical standards existing world over for protection of human subjects in experiments. All the participants, irrespective of the group, signed the informed written consent and their participation to the study was on a non-payment basis.

The participants of the study underwent several evaluations for the fulfillment of the subject selection criteria. A detailed structured case history was followed by pure-tone audiometry, which was done to ascertain degree and type of hearing loss for individuals with MD and to ensure hearing thresholds within normal limits (<20 dB HL) for the group of healthy individuals. Immittance evaluation was done to rule out middle ear pathologies that could obscure cVEMP responses and auditory brainstem responses were acquired to rule out retro-cochlear pathology. In addition, the participants of MD group also fulfilled the AAO-HNS criteria for the diagnosis of 'definite MD'. The participants who presented with associated neurological deficits, diabetes and/or hypertension or other vestibular pathologies were excluded from the study. This was ensured through a screening by an experienced otolaryngologist and other detailed evaluations that were felt necessary for each participant (like laboratory investigations, neurological opinions, ophthalmological review etc.).

Procedure

Upon fulfillment of the subject selection criteria, the participants of both the groups underwent cVEMP recording. For this, the participants were seated in an upright position on a straight back chair. The electrode montage involved placement of non-inverting electrode at two-thirds the way up the SCM muscle, inverting at the sterno-clavicular junction and ground on the forehead, similar to the one used previously.[(7,21,22)] In order to achieve a constant level of muscle activity, the participants were instructed to their head in a direction opposite to the stimulated ear and reach a constant point (usually at about 60-70^{o} from the midline) on the shoulder with the lateral part of their chin. This method (unrectified method) was shown to be equally effective in controlling variability to other methods such as electromyographic normalization and visual feedback of electromyographic activities. [(23)] Additionally, this method of recording cVEMP was shown to yield better test-retest reliability than that recorded using the visual feedback method. [24,25] All the cVEMP parameters as well as the reference point on the shoulder (degree of head rotation) were kept constant across the individuals, ears and recordings. A series of four different octave and mid-octave frequencies (500 Hz, 750 Hz, 1000 Hz, & 1500 Hz), which have been shown to result in maximum amplitude and lowest thresholds in persons with MD, [5,15,20] were used to record the cVEMP responses. The stimuli of 250 Hz and 2000 Hz were not considered due to lower response rates and lack of tuning to these frequencies. The stimuli were ramped using 2 ms rise/fall time and 1ms plateau time as this combination of the rise/fall and plateau times was reported to be most effective in producing cVEMP. [22] The stimuli were presented at the rate of 5.1 Hz with an intensity level of 125 dB SPL. The responses were band pass filtered from 10 to 1500 Hz and amplified by a factor of 5000. The artefact rejection mode was switched off throughout the recording in order to avoid rejection of cVEMP responses owing to its considerably larger amplitude compared to some of the other auditory evoked potentials. The response window was set to 70 ms with a pre-stimulus recording of 15 ms. A total of 200 responses were averaged per recording and two recordings were acquired per frequency per ear. An inter-recording rest period of 2 minutes was given to avoid the responses getting contaminated by fatigue. The order of stimuli presentation was counter-balanced to avoid order effect.

Measures

The parameter considered and noted was peak-to-peak amplitude of P13-N23 at different frequencies for both the groups. This was used for the calculation of frequency-amplitude ratio for different frequency pairs. For calculation of FAR, the amplitudes at 750 Hz, 1000 Hz, 1500 Hz and tuned frequency were each divided by the amplitude at 500 Hz. This resulted in FARs corresponding to four frequency pairs namely 750/500, 1000/500, 1500/500 and tuned frequency/500 (TF/500).

RESULTS

The cervical vestibular evoked myogenic potentials were recorded from 22 healthy individuals and 22 individuals with unilateral Meniere's disease. Figure 1 shows representative cVEMP waveforms of different frequencies obtained from one ear of a healthy individual and also from the Meniere's affected ear of an individual with Meniere's disease.

Table 1: Frequency-amplitude ratio for different frequency pairs for both the groups

Population	Frequency-amplitude ratio			
	750/500	1000/500	1500/500	TF/500
Affected ears of MD	1.35 (0.24)	1.33 (0.57)	1.05 (0.65)	1.72 (0.49)
Unaffected ears of MD	1.10 (0.36)	1.01 (0.47)	0.76 (0.37)	1.25 (0.49)
Healthy individual's ears	1.00 (0.60)	0.79 (0.33)	0.68 (0.31)	1.23 (0.52)

Note: 'MD'- Meniere's disease; please note that both the ears of healthy individuals were put together for the descriptive statistics.

The frequency amplitude ratio (FAR) was defined as the ratio of peak-to-peak amplitude of cVEMP between two frequencies. For this, the amplitudes at 750 Hz, 1000 Hz and1500 Hz along with the amplitude at tuned frequency were compared with the amplitude obtained at 500 Hz. Tuned frequency was the frequency at which maximum amplitude was obtained. The amplitude at 500 Hz was kept as constant denominator owing to it being the frequency of tuning for cVEMP among the healthy individuals. The largest FARs were obtained in the affected ears of individuals with Meniere's disease irrespective of the frequency pair. Table 1 shows the FAR for 750/500, 1000/500, 1500/500 and tuned frequency/500 across different groups.

A two-way repeated measure ANOVA was done for ear and frequency pair with group as between subject factor. The results revealed a significant main effect of ear [F (1, 42) = 7.88, p<0.05], frequency pair [F (3, 126) =48.32, p<0.001] and group [F (1, 42) = 14.75, p<0.001] on FAR. There was no interaction between ear and group [F (1, 42) = 1.16, p>0.05], frequency pair and group [F (3, 126) = 1.23, p>0.05], ear and frequency pair [F (3, 126) = 2.44, p>0.67] as well as ear, frequency pair and group [F (3,126) = 1.23, p>0.05]. The Bonferroni adjusted multiple comparisons for FAR showed significant difference between all the four frequency pairs (p<0.05). The largest mean was observed for FAR of tuned frequency/500 and smallest for 1500/500. Figure 2 shows the comparison between ears with MD, unaffected ears of individuals with MD and ears of healthy individuals across the four FARs.

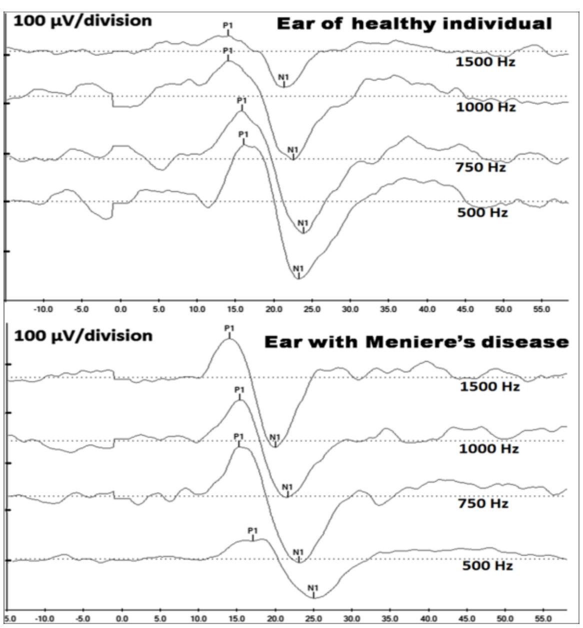

Figure 1: Representative waveforms from an affected ear of individual with Meniere's disease and an age and gender matched healthy individual's ear.

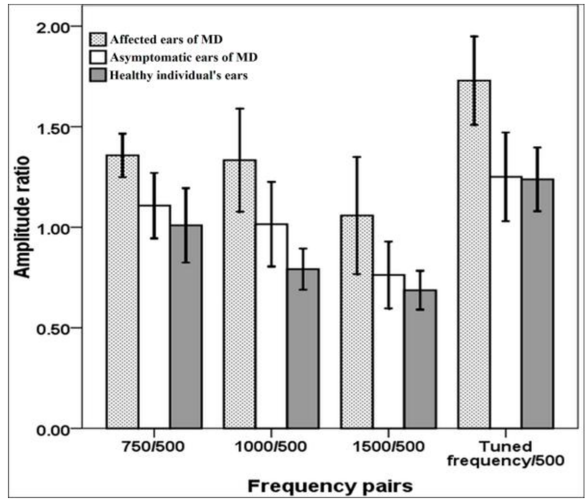

Figure 2: Mean and 95% confidence intervals of frequency-amplitude ratio of healthy individual's ears and affected as well as unaffected ears of individuals with Meniere's disease.

The ROC curves were drawn for obtaining the best criterion point for a particular FAR that would produce largest sensitivity and specificity combination. This was also done to obtain the sensitivity and specificity of the FAR criterion point for each of the frequency pairs in the diagnosis of MD. Figure 3 shows the ROC curves for different FARs. For the FAR of 750/500, the area under the curve was found to be 0.84 and it declined to 0.83, 0.80 and 0.67 for tuned frequency/500, 1000/500 and 1500/500 respectively. The optimum criterion point was established to be >1.128, >0.780, >0.617 and>1.13 for the diagnosis of MD when evaluating using FAR of 750/500, 1000/500, 1500/500 and tuned frequency/500 respectively. For these criterion points, the sensitivity at each of the above FARs in the same order was 95.45%, 90.91%, 86.36% and 95.45% whereas the specificity was 79.55%, 56.82% and 50% and 59.09% respectively. Thus highest sensitivity and specificity values were attained for FAR of 750/500.

Based on the above defined criteria, the unaffected ears of individuals with MD were found to show positive results in 4 (18.18%) ears for FAR of 750/500. In case of the FAR of 1000/500 and 1500/500, the percentage of ears with positive results was considerably higher than that for FAR of 750/500. While 17 (77.27%) unaffected ears of individuals with MD were observed to demonstrate positive results for MD using the criteria for FAR at 1000/500, 14 (63.63%) ears revealed positive results for FAR at 1500/500 and 7 (31.81%) ears for FAR of tuned frequency/500.

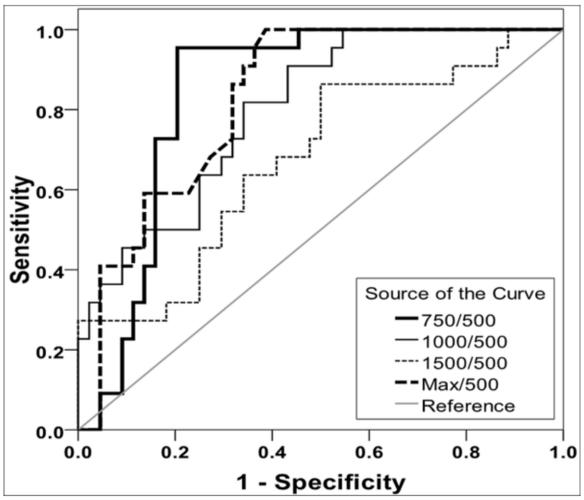

Figure 3: Receiver operating characteristic curves for frequency-amplitude ratios for various frequency pairs.

DISCUSSION

The present study aimed to compare FAR of cVEMP responses between healthy individuals and both the ears (affected and unaffected ears) of individuals with MD. It also aimed at identifying the best pair of frequencies for obtaining FAR of cVEMP response to enable the diagnosis of MD. To achieve this, cVEMPs were recorded corresponding to 500 Hz, 750 Hz, 1000 Hz and 1500 Hz for both ears of individuals belonging to both the groups. The amplitude corresponding to the frequency of 500 Hz was compared with the other remaining frequencies to obtain three different FARs and was also compared with the tuned frequency (frequency with maximum amplitude irrespective of frequency). The comparison between the groups revealed lowest value of FAR for healthy individuals and highest for affected ears of individuals with MD for all frequency pairs. This is in agreement with those reported previously in this context. [18,19] These studies, using the frequency amplitude ratio between 500 Hz and 1000 Hz, reported higher value of FAR in individuals with MD compared to healthy individuals. The higher FAR in individuals with MD might be associated with the changes in frequency corresponding to maximum amplitude in individuals with MD. Several studies have revealed the frequency corresponding to maximum amplitude to shift from 500 Hz in majority of healthy ears to 1000 Hz in ears affected with MD. [5,15,20] Such changes have been attributed to expansion of the saccular membrane due to fluid accumulation which causes a change in the resonance properties of the saccule. [26] While others have attributed electrical resonance of the hair cell to such a shift in frequency tuning, [27] the mass spring damping property of the saccule appears to be more acceptable explanation as it changes the mechanical property of the saccule and thus increases the resonance frequency. Thus, the ratio between amplitude at 1000 Hz to amplitude at 500 Hz would be likely to demonstrate a ratio of less than 1 in a healthy ear where as it is likely to be more than 1 for ears with MD. Since the above mentioned studies reported the shift in frequency producing maximum amplitude not only to 1000 Hz but also to 750 Hz and 1500 Hz in a high percentage of ears affected by MD, the same logic would apply for increased value of FAR for the remaining three frequency pairs in ears with MD. Hence, FAR appears to be a sensitive test for identification of MD.

The four FARs were compared for their sensitivity and specificity in order to identify which one was better suited to clinical utility. For this, ROC curves were obtained for all the FARs. The results revealed largest area under the curve as well as highest sensitivity and specificity values for the FAR of 750/500 followed by tuned frequency/500. The lowest values corresponding to each of the above parameters were obtained for the FAR of 1500/500.Though previous studies reported increased FAR in individuals with MD, [18,19] they did not investigate the other three ratios investigated in the present study. As, stated earlier, the reason for the finding of higher FAR in individuals with MD could be the shift in frequency tuning from 500 Hz to other higher frequencies in individuals with MD. [18,19]

In a high percentage of cases, as our data showed, even though the frequency corresponding to largest amplitude was 1000 Hz, the amplitude at 750 Hz was equivalent or larger than that of 500 Hz. However, when the frequency corresponding to largest amplitude was 750 Hz, the amplitude at 1000 Hz was not necessarily larger than that at 500 Hz. This is likely to result in higher FAR for 750/500 in more number of individuals with MD compared to 1000/500, thus explaining the higher sensitivity for FAR of 750/500 compared to 1000/500.Thus, an increased FAR for 750/500 was better suited to clinical evaluation of MD compared to other frequency amplitude ratios. Considering the logic of shift in frequency tuning being the reason behind obtaining high FAR, the measure of tuned frequency/500 should yield highest sensitivity values, which was the case in the present study. However, the specificity was considerably lower than that of 750/500. This projects 750/500 as better frequency pair for identification of MD.

Although there was an increase in the resonance frequency causing greater FAR for all the four pairs of frequencies in individuals with MD, the FAR for 750/500 is a better measure which could be further strengthened by the findings of the unaffected ears of individuals with MD. Bilateral involvement or involvement of unaffected ear of individuals with MD has been reported to be present in 14-40% of individuals with MD. [28-31] When area under curve and optimum criterion point for 750/500 and tuned frequency/500 of cVEMP were considered, the unaffected ears of individuals with MD showed positive result for 18.18% and 31.81% of the individuals with unilateral definite MD respectively. This, however, shot to 77.27% and 63.63% for FAR of 1000/500, and 1500/500 respectively. The results of FAR for 750/500 and tuned frequency/500 of cVEMP appeared to be in agreement with the previous studies on bilateral involvement which reported involvement of unaffected ears in 14-40% of individuals. [29-31] The percentage of involvement of the unaffected ears of individuals with MD shown by other two frequency amplitude ratios was way above the findings of the previous studies. These results of unaffected ears, thus, provide further support for 750/500 FAR of cVEMP to be a better measure compared to the other three FARs used in the present study.

Comparing the sensitivity and specificity of two frequency pairs, 750/500 and tuned frequency/500, showed almost equal sensitivity but differed in specificity. The specificity of tuned frequency/500 was way below that of 750/500.Taking specificity into consideration, 750/500 was found to be a better parameter in diagnosing individuals with MD. One more limitation of using tuned frequency/500 as a tool for the detection of MD is that it needs cVEMP to be recorded for all the four frequencies, 500 Hz, 750 Hz, 1000 Hz and 1500 Hz, in order to obtain the frequency of tuning. So, it would be likely to consume a lot more time than just doing at 750 Hz and 500 Hz.

CONCLUSIONS

The present study supports FAR parameter of cVEMP responses as a powerful objective tool for the detection of individuals with MD. FAR measure was found to show high degree of sensitivity for identifying MD. However, the frequency pair of 750/500 revealed highest degree of sensitivity and specificity. This, coupled with considerably lowered testing duration that would result from recording at only two frequencies instead of 4 or more frequencies for frequency tuning, makes this the pair of choice for evaluating MD. The optimum criterion point for identification of MD using frequency amplitude ratio of 750/500 frequency pair is ≥1.12 and it purports to have sensitivity of nearly 95% and specificity of nearly 80% for identification of MD.

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Declaration of Interest: The authors report no conflict of interest.

Abbreviations

cVEMP- Cervical vestibular evoked myogenic potentials
MD- Meniere's disease
FAR- Frequency amplitude ratio
AAO-HNS- American Academy of Otolaryngology- Head and Neck Surgery
dB HL – Decibel hearing level
TF- Tuned frequency (frequency with largest amplitude of response)
ROC- Receiver operating characteristics

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