Research Article

The Cervical Vestibular-Evoked Myogenic Potentials (cVEMPs) Recorded Along the Sternocleidomastoid Muscles During Head Rotation and Flexion in Normal Human Subjects

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ABSTRACT

Tone burst-evoked myogenic potentials recorded from tonically contracted sternocleidomastoid muscles (SCM) (cervical VEMP or cVEMP) are widely used to assess the vestibular function. Since the cVEMP response is mediated by the vestibulo-collic reflex (VCR) pathways, it is important to understand how the cVEMPs are determined by factors related to either the sensory components (vestibular end organs) or the motor components (SCM) of the VCR pathways. Compared to the numerous studies that have investigated effects of sound parameters on the cVEMPs, there are few studies that have examined effects of SCM-related factors on the cVEMPs. The goal of the present study is to fill this knowledge gap by testing three SCM-related hypotheses. The first hypothesis is that contrary to the current view, the cVEMP response is only present in the SCM ipsilateral to the stimulated ear. The

second hypothesis is that the cVEMP response is not only dependent on tonic level of the SCM, but also on how the tonic level is achieved, i.e., by head rotation or head flexion. The third hypothesis is that the SCM is compartmented and the polarity of the cVEMP response is dependent on the recording site. Seven surface electrodes were positioned along the left SCMs in 12 healthy adult subjects, and tone bursts were delivered to the ipsilateral or contralateral ear (8 ms plateau, 1 ms rise/fall, 130 dB SPL, 50–4000 Hz) while subjects activated their SCMs by head rotation (HR condition) or chin downward head flexion (CD condition). The first hypothesis was confirmed by the finding that the contralateral cVEMPs were minimal at all recording sites for all the tested tones during both HR and CD conditions. The second hypothesis was confirmed by the finding that the ipsilateral cVEMPs were larger in HR condition than in CD condition at recording sites above and below the SCM midpoint. Finally, the third hypothesis was confirmed by the finding that the cVEMPs exhibit reversed polarities at the sites near the mastoid and the sternal head. These results improve understanding of the cVEMP generation and suggest that the SCM-related factors should be taken into consideration when developing standardized clinical cVEMP testing protocols.

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INTRODUCTION

Vestibular-evoked myogenic potentials recorded from the tonically contracted sternocleidomastoid muscles (SCM) (cervical VEMP or cVEMP) are widely used in vestibular clinics to assess the peripheral balance function (Colebatch et al. 1994). Given limitations in objective assessment of the vestibular function, the cVEMPs offer a novel approach (Halmagyi et al. 2005; Rosengren et al. 2010). However, despite increasing clinical application, important issues remain to be addressed. For example, the origins of the cVEMP responses have yet to be elucidated. In contrast to the earlier reports that identified the saccule as the sole source of the cVEMPs (Murofushi et al. 1995; Todd et al. 2000), recent animal studies have demonstrated sound sensitivity in vestibular afferents from the semicircular canals and the utricle (Zhou et al. 2004, 2005, 2007; Xu et al. 2009; Zhu et al. 2011 and 2014). Our recent human study (Wei et al. 2013) also showed that cVEMP frequency tuning curves are better modeled as a summation of two mass spring systems with resonance frequencies of 300 and 1000 Hz. Furthermore, it is currently assumed that there is a single innervation zone in the SCM and that the cVEMPs exhibit the same positive-negative waveforms when recorded at different locations along the SCM. In a recent study, however, we showed that the cVEMPs recorded at the lower portion of the SCM exhibited reversed polarity compared with that recorded at upper portions of the SCM during head rotation (Wei et al. 2013), suggesting compartmentation of SCM neural innervation. These new results suggest that in order to develop standardized cVEMP testing protocols, continued efforts are needed to systematically identify the factors that affect the cVEMP responses in normal human subjects.

Since the cVEMP response is mediated by the vestibulo-collic reflex (VCR), its amplitude is dependent on factors related to both the sensory (vestibular end organs) and motor (SCM) components of the VCR pathways. However, compared to the numerous studies that focused on effects of sound parameters on the cVEMPs, there are few studies that examined effects of SCM-related factors on the cVEMPs. As one of the largest muscles in the neck, the human SCM runs from the sternum and clavicle to the mastoid and occipital bone and provides both rotator and flexor functions. When the two SCMs contract together, the neck is flexed and the chin is led downward. When the two SCMs are reciprocally activated, the head is rotated away from the side of contraction. It is well known that the cVEMP response is dependent on

tonic activation levels of the SCM, but it is unclear if the cVEMP response is dependent on how the tonic activation is achieved, i.e., by head rotation or head flexion. One goal of the study is to test this hypothesis by directly comparing the cVEMP responses during HR and CD conditions. In addition, the present study is to test whether the cVEMP responses have a contralateral component as suggested by the original study of Colebatch et al. (1994). Li et al. (1999) suggested that the observed contra-cVEMPs in the Colebatch et al. study is an artifact as a result of using a non-neutral reference. In this study, we systematically re-examined this issue with tones from 50 to 4000 Hz at recording sites along the whole length of the SCM during both HR and CD conditions. Finally, we further tested the hypothesis that the SCM is compartmented and the polarity of the cVEMP responses is dependent on the recording site. Taken together, these results provide important insights into understanding cVEMP generation and developing standardized cVEMP protocols.

METHODS

Twelve healthy subjects (six female and six male, age ranging from 22 to 33 years old) with written informed consent participated in this study. They had no history of otologic diseases and were not taking any medications. The experimental protocol was approved by the Institutional Review Board at the University of Mississippi Medical Center. During the test, subjects were instructed to sit upright in a standard ENT exam chair. Tone bursts were delivered alternatively to the two ears when the subjects' SCMs were activated by two different methods. In the first condition, subjects turned their heads to the right and exerted pressure against a weighted arm placed on the left temple. This is referred to as the head rotation (HR) condition. In the second condition, a commercial spring loaded system provided counter tension in the head extension direction, requiring bilateral tonic contraction of the SCMs to maintain the upright head position. This is referred to as the chin down (CD) condition. In both conditions, the head maintains the same orientation with respect to gravity.

Acoustic tone bursts (8 ms plateau, 1 ms rise/fall) were generated by a MA3 stereo microphone amplifier (TDT system, Tucker-Davis Technologies, Alachua, FL, USA) and were delivered via an insert ear phone (ER-3A). Tone bursts at 12 frequencies (50, 75, 100, 125, 250, 350, 500, 750, 1000, 1500, 2000, and 4000 Hz) were presented at 130 dB SPL. Tone bursts were randomly delivered to each ear at a rate of 5 Hz via the insert ear phone.

Surface electrodes were placed at seven locations along the left SCM (Fig. 1). A standardized method for electrode placement was used for all subjects. The SCM muscle was measured from the palpable tendon at the mastoid tip to the sternal/clavicular tendon of the muscle (ranging from 120 to 185 mm). Labeled surface electrodes were then placed overlying the muscle: five electrodes from the mastoid tip to the sternal tendon at equidistant intervals and two electrodes equally placed on the clavicular portion of the muscle (Fig. 1). All the active electrodes were referred to the right wrist. Electrode impedance was maintained below 5 k Ω . EMG signals were amplified (2500 gain), bandpass-filtered (5 to 1000 Hz), and sampled at 10 kHz (CED Power 1401, Cambridge Electronics Devices). Each tone was delivered 100 times to each ear. Data was stored on a hard disk for offline analysis.

For each tone, the cVEMP was averaged over 100 repetitions (Spike 2, Cambridge Electronics Devices) and displayed by SigmaPlot (Systat Software Inc, CA, USA). Positive potentials are shown as upward deflections. Amplitudes of the first and second peaks (Pk1, Pk2) were measured with respect to the pre-stimulus baseline. Standard deviation of the mean (SEM) is used to describe the dispersion of data. The rectified pre-stimulus SCM tonic levels were measured in the two conditions (HR and CD, Fig. 4) and used to scale the cVEMP responses in CD condition so that they were compared to the cVEMP responses in HR condition at the same tonic levels. The values of Pk1, Pk2, SEM, latencies, and rectified pre-stimulus (30 ms) tonic EMG levels are averaged and compared for the two conditions (HR and CD) with a three-way ANOVA (tone frequency/recording site/contraction mode).

RESULTS

Figure 1 shows the grand averages of the ipsi- and contra-cVEMP responses evoked by tone bursts of 350 Hz (A) and 1000 Hz (B), recorded at seven sites along the two branches of the left SCMs in HR (red solid lines) and CD (blue dotted lines) conditions. Since the pre-stimulus SCM tonic levels were slightly different in HR and CD conditions (Fig. 3), the cVEMP responses in the CD condition were corrected by their pre-stimulus tonic levels so that they can be compared to the HR condition cVEMP responses at the same tonic levels (Fig. 1, black solid lines). While the ipsi-cVEMP recordings exhibited well-defined positive and negative peaks that are dependent on tone frequency and recording site, the contra-cVEMP recordings did not exhibit identifiable peaks at any of the seven recording sites (Fig. 1).

Figure 1 shows that there was a clear polarity reversal in the ipsi-cVEMPs responses between the upper and lower sites in the sterno-mastoid branch of the SCM (CH3 vs. CH5), but not along the cleido-mastoid branch of the SCM (CH3 and CH6). This is consistent with results of our previous study (Wei et al. 2013). Figure 2 further quantitatively compares the amplitudes of Pk1 and Pk2 from the seven recording sites in the HR and CD conditions (A 350 Hz, B 1000 Hz). The SCM is divided into three branches (Fig. 2), the mastoid branch (CH1/CH2/CH3, blue symbols), the sternal branch (CH4/CH5, black symbols), and the cleido branch (CH6/CH7, red symbols). For the SCM mastoid branch, the ipsi-cVEMPs were nearly identical in the HR and CD conditions at CH3, but were larger in HR condition than in CD condition at the other two sites (CH1/CH2). Furthermore, the ipsi-cVEMPs near the sterno head (CH5) exhibited reversed polarity as compared to the responses near the mastoid head (CH2) and the cleido head (CH7).

The rectified pre-stimulus tonic levels of SCM EMG in HR and CD conditions (Fig. 3) were used to scale the frequency tuning curves in Figure 4 so that each of the measurements had the same tonic activation levels. Three-way ANOVA shows significant main effect for each of the three variables (tone frequency, recording site, and SCM activation method, $P < 0.001$). At CH1, 2, and 4, Pk1 and Pk2 exhibited larger amplitudes at several tone frequencies in the HR condition (red symbols) than in the CD condition (black symbols) (Fig. 4A, $P < 0.001$). At other sites (CH3, CH5, and CH7), the amplitudes were not significantly different in the two conditions ($P > 0.1$). In contrast to the ipsi-cVEMP responses, the contra-cVEMP responses were minimal in all conditions (Fig. 4B).

Latencies of Pk1 and Pk2 were compared for HR and CD conditions (Fig. 5). Unlike the amplitudes of the cVEMP peaks, the latencies were similar in the two conditions (three-way ANOVA, no significant main effect for SCM activation method, $P > 0.1$).

DISCUSSION

Although the cVEMP testing is widely used, there is a lack of consensus on a standardized testing protocol which limits its potential for assessing the vestibular function. To address this issue, we have been identifying the factors that may affect interpretation of the cVEMP testing. In particular, we have focused on factors related to the sensory components and the motor components of the VCR pathways. On the one hand, we have conducted neurophysiological studies

FIG. 1. Grand averaged responses of the ipsi- (left ear, *Lear*) and contra-cVEMPs (right ear, *Rear*) evoked by 350 Hz (**A** the left seven panels) and 1000 Hz tones (**B** the right seven panels), which were recorded from the seven sites of the SCM (CH1–7). Tonic SCM activation was achieved by head rotation (HR, red traces) or chin down flexion (CD, blue dash traces). Solid black traces are the

cVEMPs in the CD condition that are corrected by their pre-stimulus SCM tonic levels so that they can be compared to the cVEMPs in the HR condition at the same tonic levels. Time 0 ms is tone onset. Upward deflection is positive and downward deflection is negative.

in monkeys and rats and showed that acoustic stimulation similar to that used in clinics activates multiple vestibular end organs (Zhou et al. 2004, 2005, 2007; Xu et al. 2009; Zhu et al. 2011, 2014). Consistent with the animal studies, our recent human study showed that frequency tuning of the cVEMPs is better described as a summation of at least two mass-spring-damper systems, rather than a single mass spring model (Wei et al. 2013). These results argue against the prevailing hypothesis that the saccule is the sole generator of the cVEMPs and suggest that sound-activation of other vestibular end organs contributes to the cVEMPs. On the other hand, we have examined whether the SCM is compartmented and has multiple innervation zones (McLoon 1998). We found that the cVEMPs recorded at the sites close to the sterno head exhibit reversed polarity compared to that recorded at the upper sites (Wei et al. 2013), which is consistent with the idea of SCM compart-

mentation. In the current study, we extended our investigation of the SCM-related factors by further testing three specific hypotheses, i.e., the cVEMP response is ipsilateral and dependent on how the SCM tonic level is achieved (e.g., by head rotation or head flexion), and the polarity of the cVEMP response is dependent on the recording site.

The Contra-cVEMPs During Head Rotation and Flexion

While it is the ipsi-cVEMP response that is used in clinical vestibular testing, it is believed that there is a contra-cVEMP response that exhibits negative-positive waveform, opposite of the ipsi-cVEMP response (Colebatch et al. 1994). Consistent with this observation, it has been reported that acoustic clicks evoke short-latency excitatory responses in motor units of the contra-SCMs (Colebatch and Rothwell 2004).

FIG. 2. Effects of SCM activation mode (HR or CD) on cVEMP peaks (Pk1 and Pk2) at recording sites along the SCM. **A** The cVEMPs were evoked by 350 Hz tone. **B** The cVEMPs were evoked by

1000 Hz tone. *Triangles* are for the HR condition, and *circles* are for the CD condition.

FIG. 3. Pre-stimulus SCM tonic levels during the left ear (**A**) and right ear tone stimulation (**B**). *Black symbols* are for the CD condition, and *red symbols* are for the HR condition.

FIG. 4. Frequency tuning of the cVEMPs that were recorded along the SCM in HR and CD conditions for tone stimulation in the ipsilateral (left) ear (A) or the contralateral (right) ear (B). Circles are for Pk1 amplitudes, and triangles are for Pk2 amplitudes. Black

symbols are for the CD condition (corrected by pre-stimulus SCM tonic level), and red symbols are for the HR condition. Dashed blue lines are for the CD condition without correction.

However, Li et al. (1999) pointed out that these studies measured the contra-cVEMPs with a reference electrode placed on the sternum, which is not an electrically neutral site. When the reference electrode was placed on the right wrist, they did not observe any contra-cVEMPs. Nevertheless, because limited conditions were tested, their conclusion has not been widely accepted. The present study re-examined the contra-cVEMP response by using a neutral reference electrode on the right wrist, using multiple frequency stimulation, and recording from multiple sites along the full length of the SCM in both head rotation and head flexion conditions. As shown in Figures 1 and 4, the contra-cVEMPs were minimal in all conditions tested.

These results not only confirm and expand on the earlier study of Li et al. (1999), but also point out a serious gap in the current understanding of the contra-cVEMPs. Based on the synaptic organizations of the VCR shown in Figure 6, the SCM motoneurons

receive excitatory inputs from all the three contralateral canals and the utricle, which are comparable in strength to the inhibitory inputs from all the three ipsilateral canals and the two otoliths (for review, Uchino et al. 2005). Based on this model, the contra-cVEMPs are expected to exhibit similar amplitudes to the ipsi-cVEMPs with reversed polarity. However, this prediction is not validated by data of the present study and the study of Li et al. (1999). It is worth noting that the VCR synaptic connectivity patterns shown in Figure 6 are derived from studies in cats (for review, Uchino et al. 2005). Since it has been well documented that non-primate quadrupeds such as cats have very different neck-muscle organization than human bipeds (Graf et al. 1994; Richmond et al. 2001; Corneil et al. 2001), it is possible that the VCR connectivity patterns in humans are different from that in cats. In other words, Figure 6 may not reflect the synaptic organization of the human VCR pathways. More studies are needed to establish the VCR

FIG. 5. Latencies of the cVEMP peaks (Pk1 and Pk2) in the HR and CD conditions. Circles are for Pk1, and triangles are for Pk2. Red symbols are for the HR condition, and black symbols are for the CD condition.

synaptic connectivity in primates (humans and monkeys).

The Ipsi-cVEMPs During Head Rotation and Flexion

In the present study, we identified a new factor that affects the cVEMP responses. In addition to depend-

ing on sound stimulation parameters, location of recording site along the SCM, and the pre-stimulus SCM tonic level, we found that the cVEMPs are also dependent on how the SCM is activated, i.e., by head rotation or flexion. At upper and lower sites along the SCM, the cVEMPs are larger in head rotation condition than in head flexion condition (Figs. 1, 2, and 4). While the underlying mechanisms remain to

FIG. 6. Schematic illustration of the synaptic connectivity between vestibular end organs and the SCM motoneurons. *Open symbols* are for excitatory innervation, and the *filled symbol* is for inhibitory innervation. Based on Uchino et al. (2005).

be elucidated, a parsimonious interpretation is that head rotation and head flexion recruit different subgroups of SCM motoneurons, which have different sensitivities to sound stimulation. For example, head rotation involves push-pull innervations of the two SCM motoneuron pools and head flexion involves co-activations of the two SCM motoneuron pools. The results suggest that the subgroups of SCM motoneurons recruited during head rotation have larger sensitivities to acoustic stimulation than the subgroups of SCM motoneurons that are recruited during chin down flexion. It is important to note that previous cVEMP studies have not differentiated the two conditions. In fact, when a patient is asked to raise his/her head from the supine position and rotate to one side, both head rotation and head flexion are involved. Future standardized cVEMP testing protocols should take head action mode into consideration.

Polarity of cVEMPs at Different Recording Sites

We have provided new evidence to support the hypothesis that polarity reversal in the cVEMPs recorded at the site close to the sternal head is the result of SCM compartmentation and separate innervation zones, rather than volume conduction from the cVEMPs produced at the middle of the SCM (Fig. 1, CH3). In the current study, in addition to recording

from sites near the head of the sternum (CH5), we also recorded the cVEMPs from sites close to the clavicular head (CH7) (Fig. 2). If polarity reversal is the result of volume conduction, the cVEMPs near the clavicular head should exhibit a similar reversal in polarity. However, the cVEMPs recorded at CH7 exhibit the same polarity as that in the middle of the SCM (CH3), indicating that polarity reversal is specific to the site near the sternal head.

Summary and Future Studies

The results confirmed three hypotheses regarding the effects of SCM-related factors on the cVEMPs. First, the contra-cVEMPs are minimal at all the seven recording sites for all the 12 tones during both head rotation and flexion. Second, head rotation and flexion exhibit different effects on the cVEMPs. Third, the cVEMP responses recorded from the sternal branch of the SCM exhibit reversed polarity compared with the response recorded from the mastoid and clavicular branches of the SCM. Taken together, these results provide a new basis for the development of standardized clinical cVEMP testing protocols. They should serve as motivation for additional studies designed to develop a better understanding of the cVEMPs. These studies should include a detailed anatomic description of innervation zones of the SCM, determination of the optimal combination of sound stimuli and recording sites, as well as studies to provide a better understanding of synaptic organization of the contralateral VCR in primates (humans and monkeys).

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COMPLIANCE WITH ETHICAL STANDARDS

The experimental protocol was approved by the Institutional Review Board at the University of Mississippi Medical Center.

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