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Waiting for the evidence: VEMP testing and the ability to differentiate utricular vs. saccular function

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Abstract

The advent of Cervical Vestibular Evoked Myogenic Potentials ("CVEMPs") marked a milestone in clinical vestibular testing because they provided a simple means of assessing human otolith function. The availability of air-conducted (AC) sound and bone-conducted vibration (BCV), to evoke CVEMPs and development of a new technique of recording ocular vestibular-evoked myogenic potentials (OVEMPs) has increased the complexity of this simple test, yet extended its diagnostic capabilities. Here we highlight the evidence-based assumptions that guide interpretation of AC sound- and BCV-evoked VEMPs and the gaps in VEMP research thus far.

In this issue, Manzari et al present evidence to suggest that ocular vestibular evoked myogenic potentials (OVEMPS) probe utricular function when responses are elicited by bone conduction vibration (BCV) at the midline of the forehead (at F_z). This is in contrast to the more widely-used cervical VEMP (CVEMP) test, in which air-conducted (AC) sounds are believed to activate saccular afferents, resulting in inhibition of the ipsilateral sternocleidomastoid muscle (SCM).[1] In a large series of individuals (133) with acute unilateral vestibular hypofunction and evidence of preserved inferior vestibular nerve function, Manzari et al. demonstrate that forehead BCV elicits a normal CVEMP but a consistently diminished OVEMP from the affected ear. The results indeed suggest that, as used here, the forehead BCV OVEMP is a test of unilateral utricular function and is an important accompaniment to the traditional CVEMP. It is worth examining in greater detail the evidence behind their interpretations.

The evidence that AC sound activates *otolith organs* rather than the semicircular canals comes from single unit studies of Murofushi and Curthoys[2] who found that air-conducted (AC) clicks activated primary vestibular afferents in anaesthetized guinea pigs. They localized the afferents to the inferior vestibular nerve and the posterior division of the superior nerve, which match the path of saccular afferents. Most of the click sensitive afferents were irregularly-discharging and responsive to both pitch and roll tilts but unresponsive to yaw plane angular acceleration. Retrograde tracing of nerve endings from the region of the recording sites in the inferior nerve led to the sacculus and the superior nerve to both the sacculus and utricle. McCue and Guinan[3] sampled only inferior vestibular nerve afferents and demonstrated activation of irregularly discharging afferents by AC clicks and tones; the peripheral processes of 2 cell bodies were traced to the saccular macula. These two studies led to acceptance of AC click-sensitive afferents being predominantly saccular, although some degree of utricular stimulation had been demonstrated. The

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evidence that bone conduction vibration (BCV) activates primarily utricular afferents comes from Curthoys et al,[4] who reported low thresholds for stimulation of irregular utricular afferents with BCV. However, their study was limited to the superior vestibular nerve; therefore, saccular sensitivity to vibration was not completely examined. Although it is assumed that saccular afferents must also be sensitive to BCV, this assumption remains untested. Finally, it should also be noted that their findings in guinea pigs may not generalize to other species.

What pathways from the endorgans are then activated? For a background to CVEMPs, Kushiro et al[5] demonstrated in decerebrate cats an ipsilateral SCM inhibitory potential upon saccular stimulation and ipsilateral inhibitory/contralateral excitatory potential upon utricular stimulation. Thus, in response to AC clicks, the ipsilateral SCM p13-n23 (initially inhibitory) response was thought to be saccular, while the less commonly occurring contralateral SCM n1p1(initially excitatory) crossed response[1] was interpreted as being of utricular origin. The infrequent occurrence of crossed n1p1 responses in healthy controls and its high prevalence in third window syndromes where acoustic vestibular stimulation occurs at low threshold[6] can be interpreted as an indication of a higher threshold for utricular stimulation by AC sound in the healthy control. The utricular contribution to the ipsilateral p13n23 response to AC sound has been assumed to be negligible in the normal ear. Finally, the selective loss of AC CVEMP and preservation of the forehead tap-evoked CVEMP after resection of an inferior vestibular schwannoma provided further confirmation of a saccular origin for AC CVEMP and an “extra saccular” contribution to the tap-CVEMP.[7] Preservation of AC CVEMP after superior vestibular neurectomy has also been demonstrated in the macaque monkey.[8] For a background to OVEMPs, Suzuki et al., upon stimulation of the utricular nerve, demonstrated strong activation of the ipsilateral superior oblique (SO) and contralateral inferior oblique (IO) muscles and lesser activation of the ipsilateral superior rectus (SR) and contralateral inferior rectus (IR).[9] Saccular nerve stimulation, in contrast produced no activation in a majority of extraocular motor neurons. Thus, saccular connections with the extraocular muscles seem to be weak.[10] OVEMPs – whether evoked by AC sound or BCV – would therefore seem to primarily represent utricular activation. However, this assumption has not been validated by selective lesion studies.

The data presented by Manzari et al. would appear to further solidify the notion that midline forehead BCV elicits responses primarily from utricular afferents that result in the excitatory potential recorded from the contralateral inferior oblique muscle as the OVEMP response. However, in order to support this conclusion, the authors needed to be highly selective in choosing patients from amongst all those with acute vestibular syndromes. Their criteria for superior vestibular neuritis were: 1) absent or reduced caloric responses on one side and the presence of a head impulse sign for horizontal head rotations towards the affected ear, 2) CVEMPs were still present in response to AC sound stimulation of the affected ear (which rules out inferior vestibular nerve involvement), and 3) absence of auditory signs. These criteria are entirely appropriate to accomplish the goal of demonstrating that the substrate of the BCV OVEMP (probably utricular projections to the contralateral inferior oblique muscle) is separate from that of the BCV CVEMP (probably saccular projections to the ipsilateral sternocleidomastoid muscle). However, the apparent preservation of the BCV CVEMP that they demonstrated in neuritis and the conclusion that the BCV CVEMP represents saccular afferents should viewed with caution, since this study did not make corrections for background EMG activity, thus BCV CVEMP reflex symmetry was incompletely examined. Moreover, clinicians must also be cautious and realize that, while vestibular neuritis may, more often than not, be “superior” vestibular neuritis, there will be cases with inferior nerve involvement, either exclusively or in addition to superior nerve involvement. Furthermore, if one considers a broader spectrum of acute inner ear

hypofunction, including vestibular symptoms with acute sensorineural hearing loss, then the clean separation of utricular and saccular function tests may not be so readily found. Therefore, the diagnostic accuracy of BCV OVEMP, which in this series looks to be a good proxy for the caloric response, may fall when applied across a less idealized group of patients with acute vestibulopathies.

When interpreting any VEMPs, the interaction of the following factors needs to be considered: the afferents activated by the stimulus (AC sound is likely to activate predominantly saccular and BCV both saccular and utricular afferents), the stimulus intensity with respect to vestibular threshold (BCV using forehead tap stimuli are well above threshold but standard AC stimuli are “near threshold,” especially for OVEMP) and the effector muscles (extraocular muscles receive dominant utricular projections, the SCM has saccular and utricular projections). Technical details demand constant attention in VEMP testing: Poor maintenance of SCM tension can hamper measurement of the CVEMP response, and middle ear problems can affect any AC sound-evoked VEMP. Yet even when these details are addressed, a certain percentage of individuals, typically in older age-groups, without vestibular pathology may not have measurable OVEMP or CVEMP responses, and caution should be exercised when attributing the lack of response to vestibular pathology. VEMP results must always be interpreted in light of the complete case presentation.

To optimally utilize the available otolith function tests, clinicians could limit themselves to the best characterized responses to date: ie: AC CVEMPs and BCV OVEMPs to test saccular and utricular function respectively. For the future, to enable accurate interpretation of *AC OVEMPS and BCV CVEMPS*, the results of these two techniques need to be explored in studies on selective superior and inferior nerve lesions. Manzari et al provide one of the first large studies of what is likely to be a selective superior vestibular nerve lesion, but the fact remains that we do not know the nature of that lesion in detail, and it is not as clean cut (so to speak!) as a rare selective surgical vestibular neurectomy. The important question of the relative sensitivity of saccular and utricular afferents to sound and vibration should be addressed with single unit studies that compare the thresholds of each group of afferents to each stimulus. These studies may not be easy to conduct, but until this information is available, it is best to work within the limits of available evidence.

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