USE OF OTOACOUSTIC EMISSION PHASE CHANGE TO EVALUATE COUNTERMEASURES FOR SPACEFLIGHT-ASSOCIATED NEURO-OCULAR SYNDROME

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INTRODUCTION

Spaceflight-associated neuro-ocular syndrome (SANS) is a human spaceflight risk recognized by NASA. Elevated intracranial pressure (ICP) has been implicated as a root cause of many SANS signs and symptoms, yet there is no reliable noninvasive means of monitoring ICP. We have developed a noninvasive method of monitoring ICP change that exploits ear canal acoustic and otoacoustic emission (OAE) measurements. Changed ICP alters pressure in the inner ear, leading to changes in the tension and position of middle ear (ME) components; tension of these components determines the phase of the stimulus in the ear canal and the OAE response sound transmission back through the ME **(Figure 1)**.

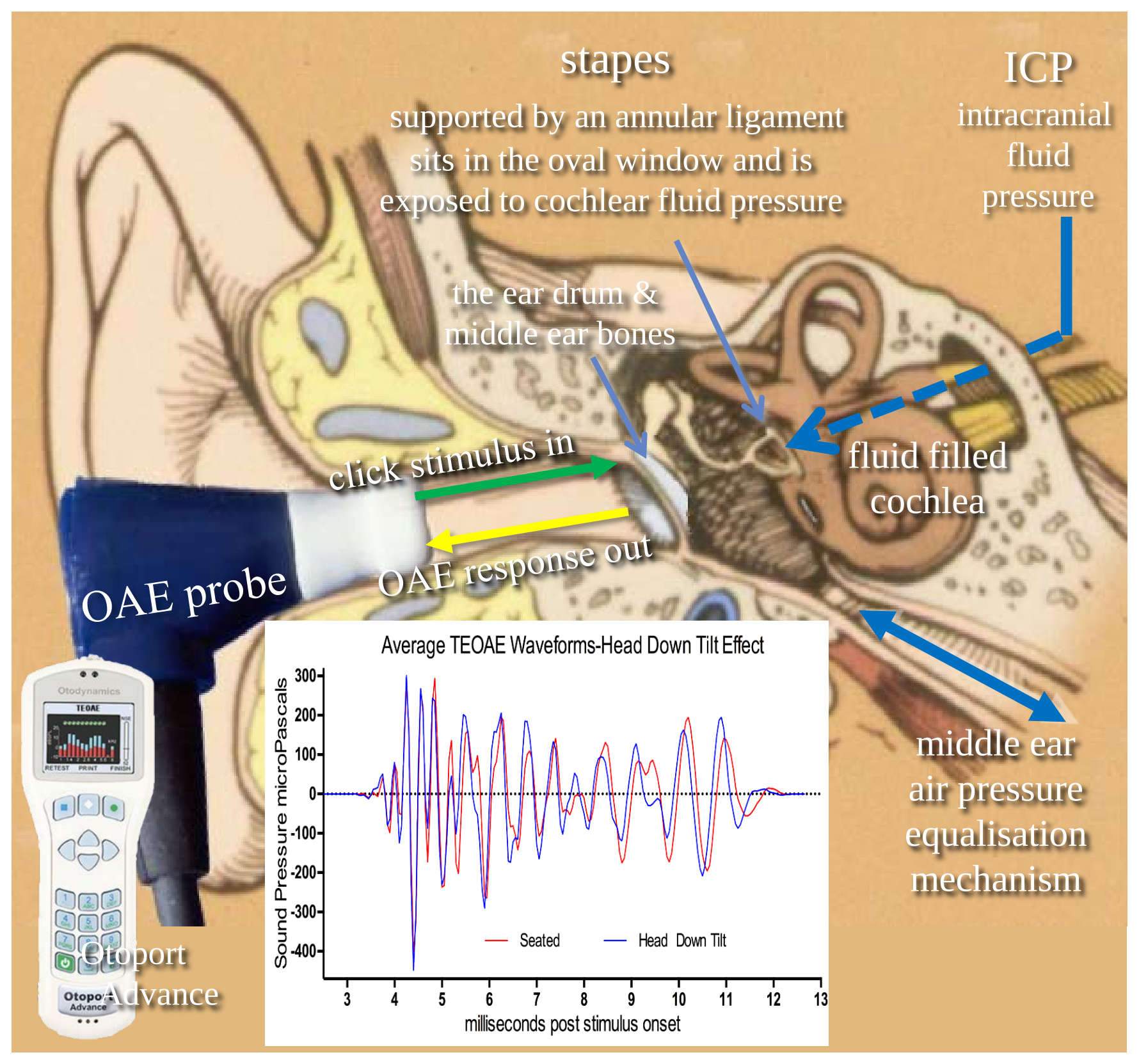

Figure 1: **A**natomical components, with the OAE probe fitted into the ear canal. The probe contains a loudspeaker and a microphone. The middle ear (ME) mechanism physically couples the ear canal to the cochlea via the stapes. Fluid in the cochlea is normally in pressure equilibrium with ICP. Raised ICP pushes on the stapes, displacing it and the ME bones, pushing the ear drum outwards. This increases elastic tension in the stapes annular ligament AND the tympanic membrane (drum). Tension increase in turn leads to a shortening of transmission time through the ME, seen as a phase change in the OAE. **Inset** is an example of a click evoked OAE response, showing how the later, lower frequency waves arrive earlier under head down tilt (ICP is higher and annular ligament more tense).

The OAE method has been validated in several studies, including our own experiments as part of the NASA Fluid Shifts study. Systematic OAE phase changes demonstrating increased ME tension (an ICP indicator) are observed as posture is changed from seated to supine to head-down tilt (HDT). This effect can be substantially mitigated by lower body negative pressure (LBNP). The OAE technique has also been used on International Space Station (ISS) crewmembers, providing evidence that ICP in microgravity is similar to that seen on the ground in the supine position.

The OAE method is also a rapid and noninvasive means of assessing the effectiveness of SANS countermeasures. Here we report results from two studies which used OAEs. In the most recent study (Venous Congestion Countermeasures - VCCM), three promising countermeasures [LBNP, an impedance threshold device (ITD), and veno-occlusive thigh cuffs (VTC)] were applied individually and in combination. In our previous ITD-only study, ITD was investigated for its ability to reduce ICP and cephalic venous congestion in supine and various HDT postures. Internal jugular vein (IJV) ultrasound showed a clear decongestive effect at all postures, however OAE data showed that ITD only caused a phase decrease (tension decrease) in HDT postures. In supine, ITD appeared to INCREASE tension. This paradox leads us to hypothesize that the OAE method is not accurately representing ICP changes with countermeasures (CM), which can alter ME tension through other means, such as ME pressure (MEP) changes. More generally, the exact mechanism for observed OAE response and stimulus phase shifts are not clearly understood, specifically with regard to the effects of MEP. The VCCM study examined the effects of externally-applied MEP on OAE recordings to document the relationship between these parameters. Analysis of these data provide new insights to these OAE mechanisms, in addition to results on CM effectiveness.

METHODS

In this analysis we use OAE data from two sources: the ITD and VCCM studies. In the VCCM study (N=10), baseline OAE phase and MEP were measured in seated and supine positions. Then, in supine position only, LBNP, ITD, and VTC were applied individually and in combination to investigate the effects on OAE and MEP. Two subjects' data were entirely excluded in each study due to too weak OAE responses and a further 10% of individual readings (of 670) were excluded due to poor signal to noise ratios, and two readings which were >2 standard deviations from the mean were excluded. The ITD-only study (N=15) examined the effect of ITD breathing on OAE phase and MEP in seated, supine and 3 levels of HDT. Four subjects' data where excluded from the ITD due to noise related response delay instability. Transient evoked otoacoustic emissions (TEOAEs) and ear canal acoustic stimulus responses were recorded from 600 Hz to 6 kHz, using the Otoport Advance clinical OAE instrument (Otodynamics Ltd., Hatfield, UK). For each subject we analysed 2 or 3 frequency bands with highest signal to noise in the range 0.8-1.8kHz, where most procedure-related changes are seen. OAE response phases are not corrected for concomitant stimulation phase changes. MEP measurements were made with a Tympstar middle ear analyser (Grason-Stadler, Eden Prairie, MN, USA)

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RESULTS

In supine position, using only OAE phase as an indicator (Figure 2):

- **LBNP and VTC appear to be effective CMs, with VTC approximately half as effective as LBNP. Retained effectiveness during recovery for both CMs is minimal.**
- **ITD appears to be negatively effective, but exhibited a small positive effectiveness during recovery, about twice that of LBNP and VTC.**
- **During combined CMs, VTC do not enhance LBNP effects and ITD tends to decrease effectiveness as compared to single CM. Following multiple CM treatment trials, ITD recovery tends to enhance effectiveness (i.e. when ITD was used but discontinued).**

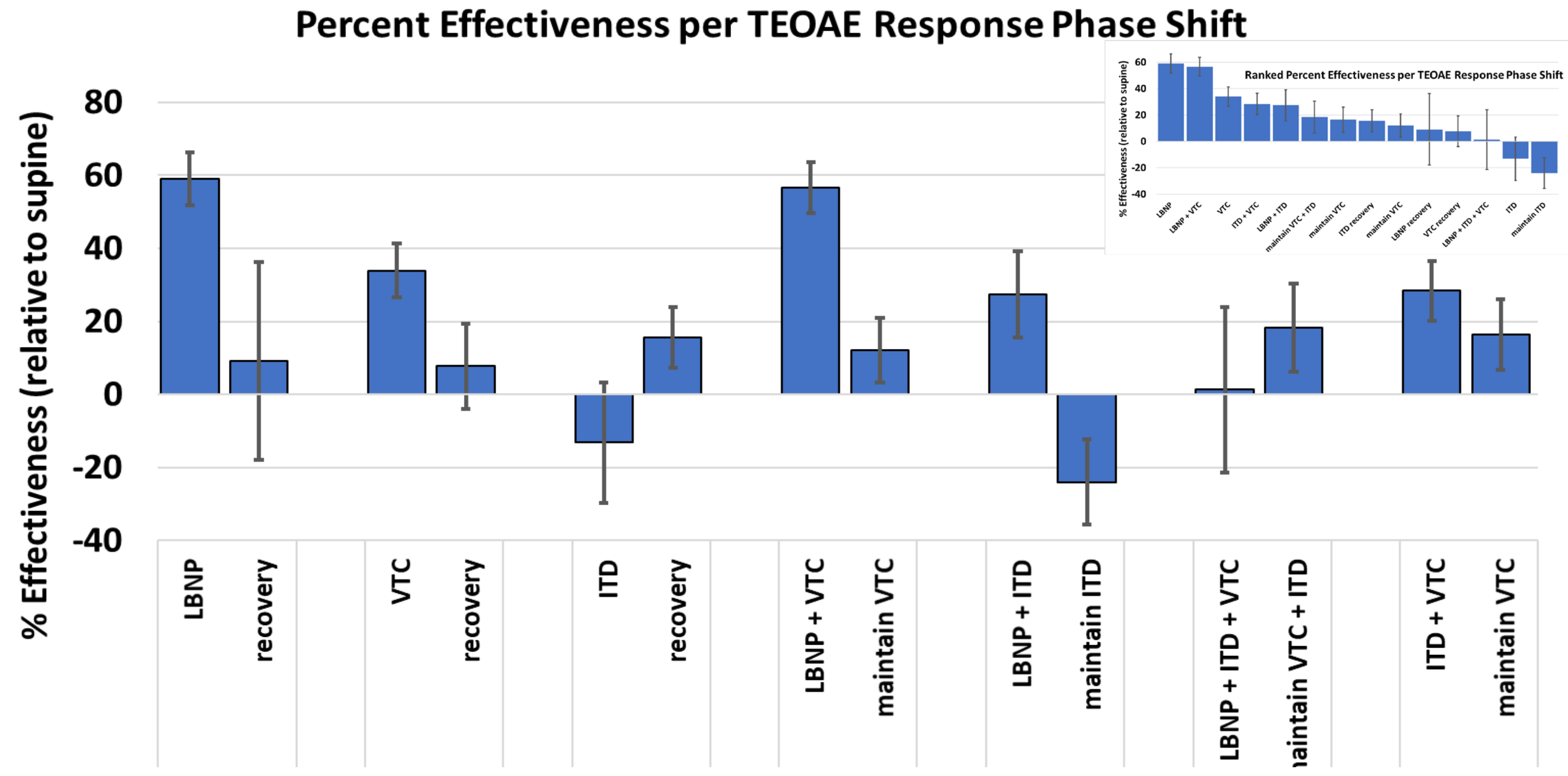


Figure 2: OAE phase shift was used to determine percent effectiveness ratings of individual and combined countermeasures (VCCM experiment, N=8). Due to differences in OAE phase on the three test days, OAE phase shift was normalized to the seated position for each testing day (day 1 for individual CMs; mean of days 2 & 3 for combined CMs). Percent effectiveness was calculated based on the ability of the treatment to counteract the shift induced by supine position as compared to seated (100*(1-(treatment phase shift)/(supine phase shift))). **Inset:** same data plotted in ranked order of effectiveness.

ITD breathing results in posture-dependent effectiveness (Figure 3). Effectiveness is negative in seated and supine, but becomes positive in 15° HDT.

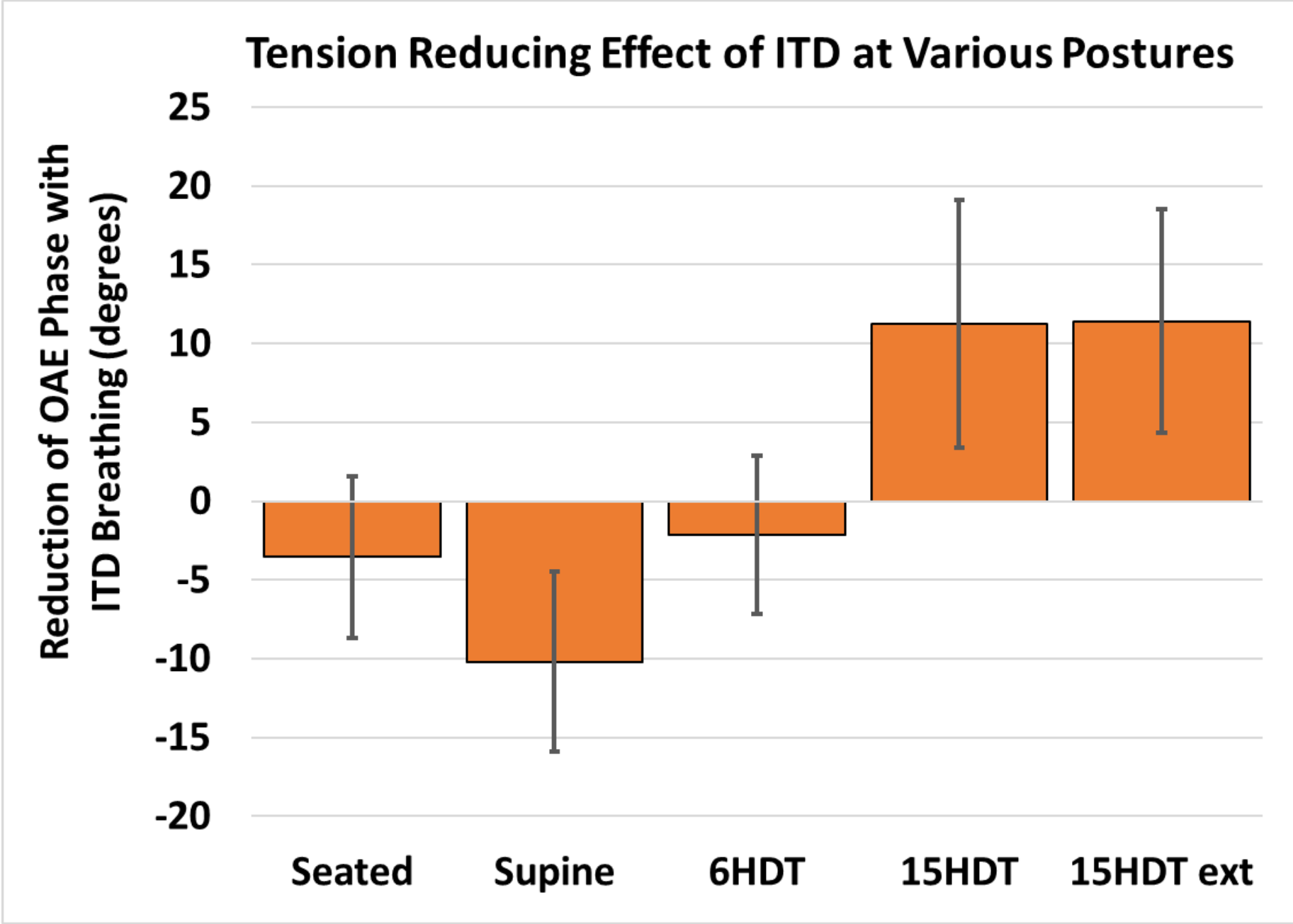
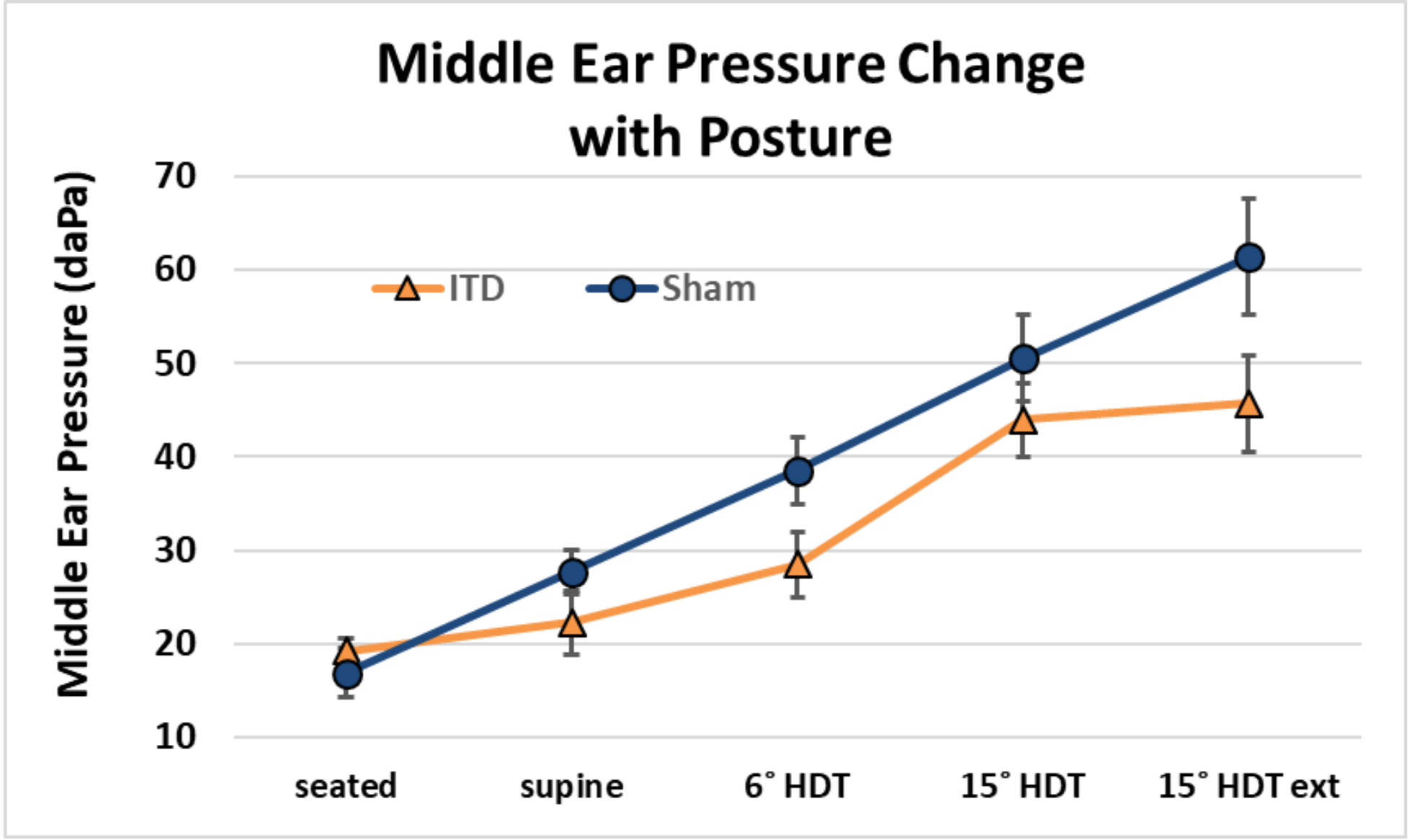


Figure 3: Change in otoacoustic emission (OAE) phase shift as a result of ITD breathing in multiple postures (ITD experiment, N=9). 6° and 15° head down tilt (HDT) and 15° HDT extended (ext; additional 30 minutes at 15° HDT) were tested in addition to seated and supine positions. In this figure the positive direction indicates a decrease in ME tension as compared to the same posture without an active ITD (sham). Note that for the supine posture, ITD *increased* ME tension, whereas ultrasound measures indicated a decrease in IJV pressure and cross-sectional area..

MEP increases with increasing head down tilt (HDT), which is partially mitigated by ITD (Figure 4)

Figure 4: Changes in posture systematically change measured MEP. Data from the ITD study (N=29 ears) show that ITD partially mitigates this effect. Note that MEP measurements are based on the externally applied air pressure that results in maximum ear drum compliance. Balancing out existing drum tension does not differentiate between pneumatic and mechanical forces, therefore measured MEP might not indicate actual MEP.



MEP increased in supine and was further increased by LBNP and VTC; ITD did not appear to have an effect on MEP in the VCCM cohort, but mitigated LBNP- and VTC-induced increases (Figure 5).

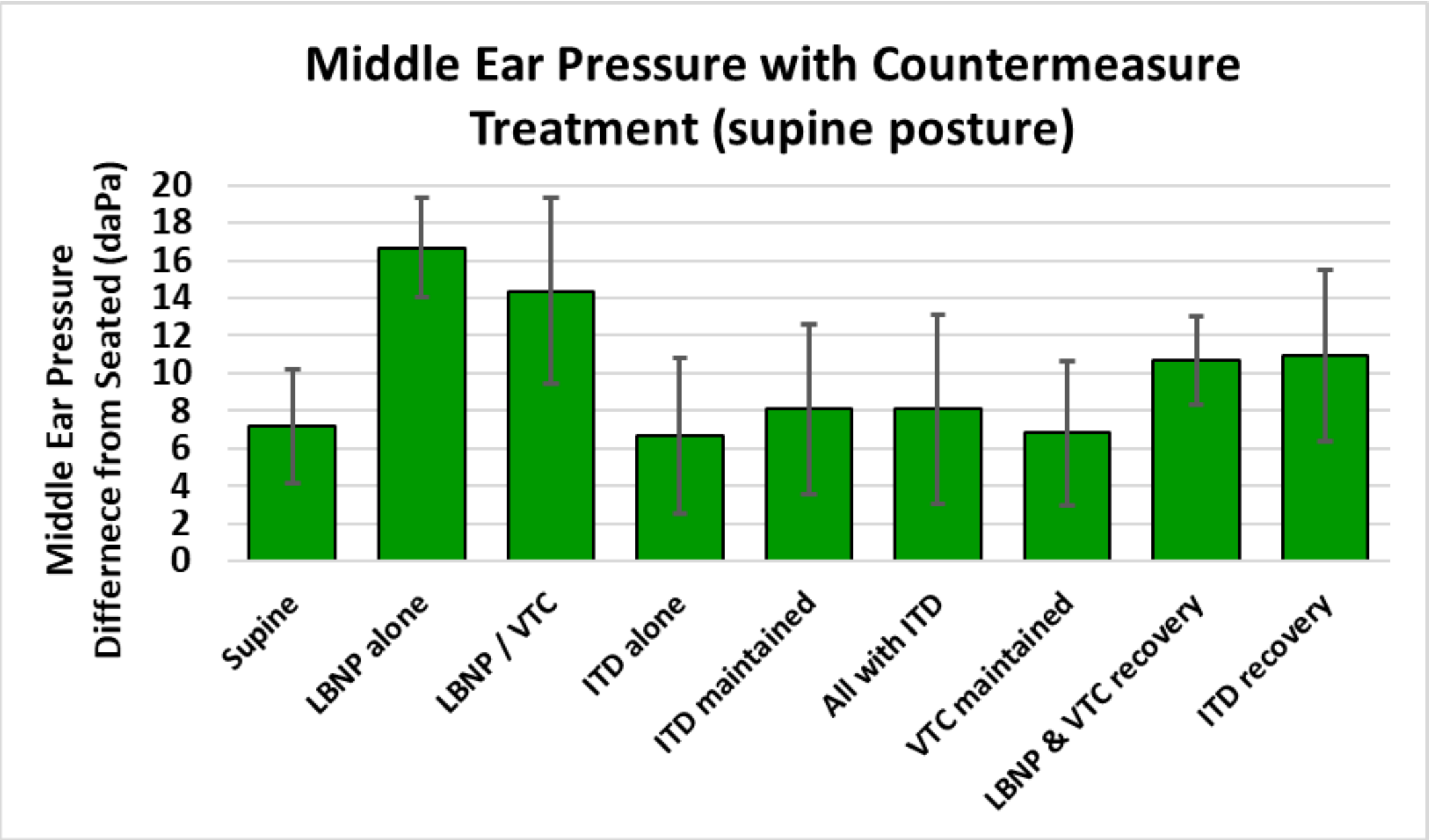


Figure 5: Middle ear pressure (MEP) during experimental procedures (VCCM experiment, N=20 ears). MEP affects ear system tension which in turn affects OAE phase shift, and potentially other ear-based non-invasive ICP measures such as cochlear and cerebral pressure (CCFP) analysis.

Phase changes in ear canal stimulus responses from seated to supine were clearly positive (as for OAE phase), but were not reduced by LBNP, VTC or ITD. (data not shown)

DISCUSSION AND INTERPRETATION

LBNP is an active, externally powered countermeasure affecting the entire lower body from the abdomen downward, inducing large fluid redistribution. Not surprisingly, this countermeasure also induces large shifts in OAE response phase (59% relief of supine effect, Figure 2).

VTCs operate on a similar principle of fluid redistribution but are based on passive, occlusion-mediated sequestration of fluid in the legs below the level of cuff application. This passive nature and less affected body area could explain why VTC was only about half as effective as LBNP (34% relief of supine effect, Figure 2). During combined CM application, VTC did not appear to enhance the effect of LBNP, perhaps because LBNP had already maximized fluid redistribution.

ITD uses negative thoracic pressure induced by resistive breathing in an effort to reduce cephalic venous congestion, and lower ICP. In both experiments, OAE phase during ITD breathing was advanced in relation to supine position with no treatment, indicating a more tense ME, or NEGATIVE effectiveness (VCCM study -13%, ITD study -51%). Further, during combined CM trials, ITD breathing reduced the positive effectiveness of other CMs. There are three possible explanations for the observation of ITD breathing apparently increasing ME tension in supine:

1. ITD breathing actually elevates ICP: This is not likely given that several studies have reported reduced ICP with negative thoracic pressure breathing (Convertino 2005, Kiehna 2013). Additionally, the ITD-only study demonstrated that IJV congestion was reduced with ITD breathing (~18% reduction in IJV cross sectional area in supine, 6° HDT, and 15° HDT, as well as reduction in IJV pressure as measured by VeinPress noninvasive methods [18% in supine]).
2. ITD breathing lowers ICP to the point that the oval window (OW) and ME is being tensioned inward: This is a plausible explanation but unlikely given that ITD induces 5 mmHg negative thoracic pressure, and average supine ICP is ~15 mmHg.
3. ITD breathing affects the ear by an unknown mechanism, which causes tension on the OW or tympanum: By process of elimination, this explanation is the most likely. Additionally, ITD recovery trials (during which ITD was used but discontinued) are among the most effective recovery periods at reducing ME tension. This implies that ITD was having intended effects during active ITD breathing, but the OAE method was not able to capture this due to interference.

OAE phase shift data from the ITD-only experiment (Figure 3) demonstrated an unexpected pattern of increased ME tension in the supine posture, almost no effect in 6° HDT, but with a trend toward ME relaxation in 15° HDT. These data suggest a local tensioning effect of ITD breathing which is overcome at higher angles of HDT. VCCM data corroborate the tensioning effect in supine. Given that ITD induces large pressure excursions in the airway, a plausible hypothesis is that these pressures affect MEP, altering ME tension and OAE phase shift. However, MEP data do not indicate dramatic alterations during ITD breathing, rather a reduction in posture-induce pressure (Figures 4 & 5). It is still plausible that the supine position alters the Eustachian tube and surrounding tissues to make the ME more susceptible to airway pressure changes, and we do not exclude the possibility of soft-tissue induced ME tension changes that do not alter MEP.

Interestingly, although LBNP and VTC reduce supine-induced ME tension as indicated by OAEs (Figure 2), they increase MEP as compared to the supine posture with no treatment (Figure 5). We have previously argued that the MEP increase in supine or HDT is a another manifestation of increased ICP, in which case we would have expected a decrease in MEP due to the application of effective CMs - consistent with the premise of relieving the supine effect. In this experiment we observe the opposite effect, which is perplexing. We continue to analyze these data, including ear canal acoustics (stimulation signals) to understand this phenomenon.

CONCLUSIONS

OAE data from the VCCM experiment support the use of LBNP and VTC as countermeasures. VTC as applied was found to be about half as effective as LBNP.

As anticipated, OAE data in the VCCM experiment failed to show ITD as countering supine-induced pressure. The ITD-only experiment demonstrated a counter effect for HDT tension but there are challenges in interpreting OAE data with ITD; in combination with reports in the literature, data from both studies suggest that OAE data are affected by active ITD breathing through an unknown mechanism.

Based on OAE data alone, LBNP is the most effective countermeasure, but ITD maintains the most effect once the CM is removed (recovery period).

We had anticipated that measurements of MEP in both experiments would help understand the mechanisms involved in OAE phase changes. LBNP and VTC cause an unexpected increase in MEP with a paradoxical decrease in OAE phase shift; ITD does not substantially affect MEP in the VCCM cohort. These observations add to interpretation difficulty.

Other data from the VCCM study (IJV ultrasound, etc.) are needed to determine overall CM effectiveness rankings.

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