Non-invasive Vagus Nerve Stimulation (nVNS) in Healthy Subjects: Is There Electrophysiological Evidence for Activation of Vagal Afferents?

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**BACKGROUND**

- Non-invasive vagus nerve stimulation (nVNS; gammaCore®) may improve migraine and cluster headache. Animal experiments suggest that nVNS acts via stimulation of vagal afferents, but proof in humans is lacking.
- Vagal somatosensory evoked potentials (vSEP) were identified after invasive VNS or transcutaneous stimulation of auricular vagal branches, but late components could be muscle artifacts.
- The objective of this study was to search for reliable vSEP during nVNS in healthy volunteers.

**METHODS**

- Evoked potentials were recorded in 12 healthy subjects (7 males).
- Active electrodes were placed at A1/A2 (ref Cz) or C3/C4 (ref F3/F4) during 2-minute stimulation over the left/right cervical vagus nerve (25 Hz, 6-24 V) and during stimulation over the inner tragus with a monopolar stimulator (2 Hz, mean intensity 8 mA, 50 stimuli).
- Control recordings were performed with electrodes over orbiculares oculi muscles (blink-relax montage) and during positioning of the nVNS device over the sternocleidomastoid (SCM) muscle to distinguish between myogenic responses and vagus nerve evoked potentials.
- Analyses with Signal Software and AutoSignal™.

**RESULTS**

- Identification of 3 reproducible peaks (P1, N1, P2) in 10 subjects on the side of stimulation at mean latencies of 2.95 ms, 5.20 ms, and 9.63 ms (Figs. 1 & 3).
- When voltage increased from 6 V to 18 V, P1-N1 amplitude increased significantly (p<0.01) from 0.04 µV to 0.52 µV (C3/C4) and from 0.13 µV to 2.04 µV (A1/A2) (Fig. 2).
- Inner tragus stimulation elicited P1, N1, and P2 peaks with shorter mean latencies (2.21 ms, 3.72 ms, 5.71 ms) and a mean P1-N1 amplitude (A1/A2) of 5.0 µV (Fig. 7).
- Placed over the SCM muscle, nVNS evoked no reproducible response (Fig. 1).

**CONCLUSIONS**

- nVNS elicits a short-latency far-field potential that increases in amplitude with increasing stimulus intensity and disappears when the stimulator is positioned over neck muscles. This potential is similar to the one obtained after electrical stimulation of vagal branches in the outer ear. Given its short latency, the vSEP is probably generated byafferent volleys downstream along the vagus nerve (e.g. at the level of the foramen jugulare).
- The therapeutic effects of nVNS in primary headaches might thus be mediated by generalized activation of vagus nerve afferents.