**Introduction**

We investigated noninvasive vagal nerve stimulation vs sham far lateral neck stimulation to determine if there are measurable effects on the autonomic nervous system, based on 1) the subjective experience of pain as measured by the verbal numeric rating score, and 2) the sympathetic response to pain as measured by galvanic skin response.

**Methods**

Seven healthy male subjects were enrolled in a crossover pilot study comparing noninvasive vagal nerve stimulation versus sham stimulation. All subjects underwent initial neurosensor testing with a MEDOC TSA II unit to determine heat pain thresholds and tolerances using the method of limits.

Noninvasive vagal nerve stimulation was administered via the gammaCore™ device from ElectroCore. The device delivers a 50 Hz waveform for a 1 ms pulse duration. These 1 ms pulses are delivered at 25 Hz for 120 seconds (Fig 1). The device is held in position on the neck superficial to the right vagus nerve (Fig 2).

Heart rate variability and galvanic skin response were measured using a BIOPAC system and analyzed with AcqKnowledge software (Fig 3). Subjects first underwent SSG followed by five successive heat pain trials with the MEDOC TSA II unit, then returned a week later to undergo nVNS followed again by five heat pain trials (Fig 4). Related-samples statistical analyses were performed using Wilcoxon signed rank test (WRSRT) with the statistical program SPSS. The Institutional Review Board at the University of California, San Diego Health Systems approved the protocol. Informed consent was obtained for all study procedures.

**Results**

Galvanic Skin Response (GSR)

Noninvasive vagal nerve stimulation demonstrated a significant decrease in pain-mediated GSR means for trial 1 (p=0.028), and trended down for trials 2 and 3 (Fig 6). Peak-to-peak GSR following heat pain trended to decrease for heat pain trial 3 (p=0.063) (Fig 7). See Fig. 3 for contrast between GSR means and peak-to-peak.

Mean Galvanic Skin Response For 5 Heat Pain Stimuli

Table 1: BAI, Beck Anxiety Index; BDI, Beck Depression Inventory; 2: PCL-C, PTSD Checklist-Civilian Version

<table>
<thead>
<tr>
<th>Group</th>
<th>HP1</th>
<th>HP2</th>
<th>HP3</th>
<th>HP4</th>
<th>HP5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>9.5 (4.3)</td>
<td>9.1 (3.7)</td>
<td>8.8 (3.8)</td>
<td>9.0 (4.6)</td>
<td>8.9 (4.0)</td>
</tr>
<tr>
<td>VNS</td>
<td>7.4 (4.5)</td>
<td>7.4 (4.6)</td>
<td>6.9 (4.1)</td>
<td>6.9 (3.9)</td>
<td>7.2 (4.3)</td>
</tr>
</tbody>
</table>

**Discussion**

These pilot data show that noninvasive vagal nerve stimulation blunted the autonomic response to and decreased the subjective experience of heat pain. The mechanism of vagal nerve stimulation autonomic neuromodulation likely involves afferent vagal fiber encoding.

Transcutaneous vagal nerve stimulation with the gammaCore™ device involves A-alpha, A-beta, A-delta, and B fiber activation, while sparing C fibers that can be associated bronchoconstriction and bradycardia (Fig 8).

Verbal Numeric Rating Scale (VNRS) for Pain

Mean VNRS pain scores for noninvasive vagal nerve stimulation vs sham demonstrated 1) a significantly larger decrease from heat pain 1 to heat pain 5 (p=0.042), and 2) significantly lower score vs pain heat pain 5 (p=0.038). Similarly, noninvasive vagal nerve stimulation trended to show a significantly lower score within heat pain 1 and 3 (Fig 5).

**Verbal Numeric Rating Scale For 5 Heat Pain Stimuli**

Peak to Peak Galvanic Skin Response For 5 Heat Pain Stimuli

The majority of afferent fibers in the vagus nerve, of which 80% are sensory and 20% are parasympathetic, project to the nucleus of the tractus solitarius (NTS). The NTS, in turn, has extensive projections to the thalamus, amygdala, and neocortex. Activated vagal afferent fibers modulate networks that overlap nodes important in affective pain processing. These nodes can be pathologically upregulated (amygdala, insular cortex, hippocampus, lateral orbitofrontal cortex) or downregulated (ventromedial prefrontal cortex) in disease states like post-traumatic stress disorder.

Future studies will focus on 1) neuroimaging pilot data, including functional magnetic resonance imaging and magnetoencephalography, and 2) changes in autonomic response during heat pain, including heart rate variability and cardiac vagal tone. Positive results in these domains may suggest a role for noninvasive vagal nerve stimulation in treatment of disorders like chronic pain and PTSD.