**Introduction**

The autonomic nervous system has two broadly antithetic branches known as the sympathetic (SNS) and parasympathetic nervous systems (PNS). The main neural substrate of the PNS is the vagus nerve, which has been observed to modulate inflammation through the cholinergic anti-inflammatory pathway (CAP), and is currently being studied as a potential anti-inflammatory therapy.

A non-invasive vagus nerve stimulator (nVNS) (electroCore, Basking Ridge, NJ, USA), has been developed. Two studies were performed to demonstrate this technology’s effect of the vagus nerve. Study 1 investigated the effects of nVNS on cardiac vagal tone (CVT). Study 2 investigated changes in cytokine expression to determine if nVNS activated the CAP.

**Methods - Study 1: Autonomic Measures**

40 healthy subjects (median age 32 years, range 23-56) were randomized to treatment with the gammaCore device either placed on the vagus nerve (active) or lateral to the vagus nerve, over the sternocleidomastoid muscle (sham).

| Heart rate, blood pressure and the validated autonomic nervous system parameters of CVT and cardiac sympathetic index (derived from the R-R intervals of the EKG signal) | were measured at baseline prior to stimulation, during stimulation and at 90 minutes and 24 hours post stimulation. |

**Results – Elevation of CVT**

All subjects tolerated the stimulus well, apart from one subject who felt light-headed during active nVNS and one subject who felt discomfort during sham stimulation. nVNS resulted in a small reduction in heart rate during stimulation of 5.5 beats per minute, standard deviation (SD) +/- 5.6. There was no effect on blood pressure.

![Cardiac Vagal Tone and Cardiac Sympathetic Index changes for Active and Sham](image)

**Methods - Study 2: Measuring Inflammatory Cytokine Levels**

Twenty “apparently” healthy normal subjects (median age 32 years, range 19-53) were recruited and screened to participate in a 2-Phase, randomized, blinded, crossover-designed trial. During Phase 1, subjects were randomized to receive either active gammaCore stimulation or sham (both on the right side of the neck) TID for 1 day. One week later, during Phase 2, the subjects initially randomized to active gammaCore stimulation were crossed over to receive active gammaCore stimulation on the left side of the neck TID for 1 day (Phase 2). The subjects randomized to sham in Phase 1 were crossed over to active stimulation, TID for 1 day, on the right side of the neck during Phase 2. Blood samples were drawn prior to initial stimulation and at 90 minutes following the first treatment. Whole blood culture was carried out with and without LPS (LPS(+)) (24 hours) in all samples. The samples were then analyzed for a variety of cytokines, including IL-1β, IL-6, and TNF-α (presented in pg/ml).

**Overall Conclusion:** nVNS has the potential to effectively stimulate the vagus nerve and thus may have a role as an anti-inflammatory intervention.

**Results – Reduction of Inflammatory Cytokines**

For all three cytokines reported, the Active cohort exhibited substantial reductions in cytokine expression as compared with baseline by 90 minutes, and these reductions were sustained through 24 hours.

To better understand baseline levels differences between Active and Sham, a post hoc analysis was conducted. This analysis revealed that, surprisingly, 8 of the 30 samples from the Active group exhibited elevated levels of TNF-α at baseline. These 8 subjects were separated into a subgroup (Active-High) and compared with the 22 subjects (Active-Low) and the Sham group.

**Study 2 - Conclusion**

nVNS activates the CAP, resulting in substantial and prolonged reductions in cytokines in LPS(+) samples, especially among those with elevated baseline levels, however, the effect was obscured in the LPS(-) samples.