Neurostimulation of the Human Tongue for the Treatment of Obstructive Sleep Apnea – An Neuroanatomically Driven Approach

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Abstract

**Introduction:** Obstructive Sleep Apnea (OSA) is a devastating condition affecting millions. The gold standard of treatment is continuous positive airway pressure (CPAP) but close to half of the patients that are prescribed this therapy are non-compliant with dire consequences. Over the last few decades many alternatives have been tested with meager results. **Objective:** Hypoglossal nerve (HGN) stimulation based treatment may prove to be an effective treatment for Obstructive Sleep Apnea (OSA). Despite the fact that this treatment is being evaluated by multiple clinical studies, the mechanism of the treatment remains unclear. This study reviews the science behind the unique approach implemented in the Targeted Hypoglossal Nerve (THN) Sleep Therapy.

**Results:** We discuss the relevant anatomy of the tongue, targeted HGN stimulation, upper airway responses, the requirements of the novel approach and the method employed by THN Sleep Therapy to advance the treatment of this serious disease. A feasibility trial of 13 subjects over 12 months showed significant improvement in Apnea-Hypopnea Index (AHI) (45.3 to 21.0 53.6% mean improvement, 68.2% in responders), Oxygen Desaturation Index (ODI) (33.3 to 15.2 54.3% mean improvement), Epworth Sleepiness Scale (ESS) (11.2 to 7.9 29.5% mean improvement) and Fatigue Severity Scale (FSS) (4.6 to 3.6 21.7% mean improvement).

**Conclusion:** Scientific evidence demonstrates not only the uniqueness and the feasibility of the THN Sleep Therapy but also its therapeutic potential in the treatment of OSA. Results of a feasibility study of the system demonstrate the effectiveness of this approach.

**Keywords:** Obstructive sleep apnea, Electrical stimulation, Hypoglossal nerve, Tongue muscles

Introduction

Neurostimulation has been applied to many neural system dysfunctions often with great success but attempts to utilize it for Obstructive Sleep Apnea (OSA) have had mixed results. Conventional views on the application of stimulation to a medical condition can lead to the inefficient use of existing technology. The tongue and its neural supply are unique and quite different from other neuromuscular systems and require a unique approach to their treatment.

OSA was recognized over 40 years ago and the realization of its prevalence and consequences are becoming clearer. OSA is commonly characterized by repetitive episodes of obstructions of the retroglossal airway, blood oxygen desaturation, and subsequent arousal from sleep. Airway blockage is associated with a reduction of lingual muscle tone and is attributed to inadequate neural signals normally provided by the HGN. Continuous positive airway pressure (CPAP) therapy is usually prescribed as the first-line treatment, however, large numbers of patients (40%) are non-compliant and find it difficult to adhere to CPAP therapy, resulting in a surgical intervention as the only alternative treatment, if any.

The Human Tongue

The human tongue is made up of eight pairs of skeletal muscles – four extrinsic muscles (attached to bony support): the genioglossus, styloglossus, hyoglossus and palatoglossus, and four intrinsic muscles: the transversalis,
verticalis, inferior longitudinalis and superior longitudinalis.

Tonic activities are responsible for maintaining and holding the tongue’s posture such as preventing it from falling into the pharyngeal or retroglossal airway - primarily performed by the posterior one-third of the tongue [5]. Phasic motions (speaking, chewing, swallowing, suckling etc.) are mostly performed by the anterior two-thirds of the tongue [5]. The posterior third of the human tongue has an unusually high capillary density of fatigue resistant muscle fibers [6].

The Human Hypoglossal Nerve

All tongue muscles are innervated by the XIIth cranial nerve (hypoglossal), except for one of the extrinsic muscles, the palatoglossus, which is innervated by the Xth cranial nerve (vagus) of the pharyngeal plexus. At the level of the hyoid bone (proximal third and mid portions), the hypoglossal nerve is normally comprised of one single fascicle becoming polyfascicular only in its distal third [7][8]. Moreover, distribution of the lateral and medial nerve branches in humans is not well defined. The lateral branch includes multiple small branches supplying independently the styloglossus, hyoglossus and inferior longitudinalis muscles, whereas the medial branch innervates the genioglossus, superior longitudinal, transversalis, and verticalis muscles [5]. While the HGN in the submandibular region is afascicular, it is nonetheless organized, but not to the degree that a fasciculated nerve would exhibit. This means that at any point around the circumference of the HGN there is a group of nerve fibers that innervate a unique set of muscles within the tongue, but likely never all muscle groups, i.e., the nerve is probably not homogenous.

Tongue Hydrostat – A Unique Muscle Structure

Previous studies have used the muscular-hydrostat theory to explain the mechanism by which co-activation of the various muscle groups effect lingual movements [9]. This theory proposes that the mammalian tongue is a cylindrical structure with a constant volume that adjusts its shape and size by co-activating many of its muscular components. Thus, protrusion of the tongue results not simply by the action of the genioglossus alone but reflects the combined activities of the intrinsic verticalis and transversalis muscles and the extrinsic genioglossus muscle. Similarly, retrusive movements involve the styloglossus and hyoglossus muscles along with superior and inferior longitudinalis muscles. Coactivation of antagonistic muscle groups prevents the occlusive effect of the retractor, stiffens the soft tissue of the pharyngeal wall, thereby improving pharyngeal patency.

Electrical Stimulation for OSA Treatment

Previous neurostimulation efforts have activated the entire nerve (all fibers of HGN), or its distal branch, necessitating a triggered open-loop system to avoid the problems associated with electrical stimulation induced muscle fatigue, wherein the HGN activation is timed to the respiratory cycle [10][11][12]. Such efforts required respiration sensing and control methods to deliver well-timed delivery of stimulation in order to achieve a minimally useful clinical result. Since all portions of the HGN or its branches were activated by the single channel cuff electrode design, both desirable and undesirable tongue movements (e.g., retraction) were generated and without any fine control, particularly of the retractor muscles.

A better approach to utilize electrical stimulation would activate all muscle groups that result in restoration of tone and beneficial tongue position and would enable
simultaneous activation of all appropriate muscle groups, which could also cause fatigue but for the fortunate organization of the HGN at the proximal site of the sub-mandibular gland – afascicular, loose organization with many fibers of different muscle groups running in close proximity – which allows sub-populations of the whole nerve to be activated by regional nerve cuff contacts and still activate several motor units belonging to multiple muscle groups. Then by switching from contact to contact, different motor units belonging again to multiple muscle groups are activated in turn, which mitigates fatigue, and which mimics the natural motor activity of the tongue at wakeful rest. This is the method by which the aura6000™ Targeted Hypoglossal Neurostimulation (THN) System implements its therapy. In this system stimulation is supplied by a six contact cuff electrode secured around the hypoglossal nerve at the sub-mandibular gland, which proximal to all distal branches, is afascicular and which has mixtures of multiple muscle groups driven by nerve fibers across the entire nerve. By activating each of the six contacts in turn a broad mix of muscle fibers, a subset of the entire muscle population, is activated in turn as well, but only a subset of the entire muscle population by each contact.

Figure 1 - aura6000™ THN System – IPG, Lead with Cuff Electrode, and Remote Control and Charger.

The aura6000™ does not need nor have a sensor lead. It has six independent current sources each connected to a single one of the six contacts in the cuff electrode. With the contacts spaced circumferentially around the cuff, this effectively divides the hypoglossal nerve into six regions that are activated independently. Having two contacts to work with means that at worst, there would be 50% duty cycle as the system stimulates first one contact, while the muscles activated by the second rest before it is their turn to be activated. With two or more contacts utilized fatigue is always mitigated and the synchronization of stimulation to respiration is not required.

Clinical Study Results

In a clinical feasibility study conducted at the Cliniques Universitaires Saint Luc, Belgium [13], 14 patients with moderate to severe OSA and who were unable or unwilling to tolerate CPAP were implanted with the aura6000™ THN system. The cuff electrode was placed around the HGN in the sub-mandibular region, the lead tunneled to a pectoral pocket where the IPG was placed. Titration of the system took place 3 to 4 weeks post-surgery. Thirteen of fourteen subjects completed 12 month PSGs. Three patients were non-responders (one had central sleep apnea, one has an unusually large uvula causing significant obstruction of the airway and a third had significant complications due to cancer and a BMI of 39). In all thirteen subjects AHI decreased from 45.3 ± 17.6 (screening) to 21.7 ± 19.9 (52.1% mean improvement) at 12 weeks and 21.0 ± 16.5 (53.6% mean improvement) at 12 months respectively. Oxygen desaturation index (ODI) ( # excursions > 3% per hour) was reduced from 33.3 ± 21.6 at screening to 14.2 ± 16.7 (57.4% mean improvement) at 12 weeks and 15.2 ± 16.1 (54.4% mean improvement) at 12 months respectively. The number of respiratory related arousal events was decreased significantly from 276.6 ± 94.0 at screening to 177.8 ± 106.6 (35.7% mean improvement) at 12 weeks and
168.5 ± 95.8 (39.1% mean improvement) at 12 months.

In a subset analysis completed for 10 responders, the mean AHI improved by 61.5% at 12 weeks and 68.2% at 12 months. ODI, ESS and FSS scores and arousals showed similar significant improvements for the responder group.

Summary

A literature review and original cadaver and animal research guided the development of a unique system to treat OSA. Reduced oropharyngeal muscle tone is the major cause of the pharyngeal collapse in subjects with obstructive sleep apnea. The aura6000™ system has demonstrated the safety and efficacy of THN Sleep Therapy in the moderate to severe OSA patient. Three month and twelve month post-implant data from the pilot study suggest that the use of the aura6000™ system resulted in a substantial improvement in the severity of the OSA symptoms, sleep architecture, and quality of life.

References


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