

DEVELOPMENT OF ASYNCHRONOUS, INTRALINGUAL ELECTRICAL STIMULATION TO TREAT OBSTRUCTIVE SLEEP APNEA

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Abstract—We are evaluating the feasibility of using a single intralingual BIONTM microstimulator to prevent airway obstruction in patients with obstructive sleep apnea (OSA). Neuromuscular and hypoglossal nerve stimulation of the genioglossus have been reported to expand the oropharyngeal airway and reduced the severity of sleep disordered breathing, but currently available technology is invasive and cumbersome. BIONs are chronically implanted, single channel electrical stimulators powered and commanded by inductive coupling. One such microminiature device (16mm long x 2 mm diameter) can be injected submentally into the genioglossus muscle to stiffen and protrude the tongue. Preliminary results suggest that intermittent opening of airway at the same rate but not synchronized to the respiratory cycle may be effective. Research is underway to complete the preclinical studies required to identify the safety, efficacy and practicality of this technology and implantation approach.

Keywords— BIONs, obstructive sleep apnea, electrical stimulation, asynchronous

I. INTRODUCTION

A. Pathophysiology

OSA occurs when the soft tissues of the upper airway collapse and occlude airflow during inspiration. During sleep, the usual reflexive tone in the oropharyngeal muscles is markedly reduced [1]. Collapse of the tongue is the most common cause of OSA, particularly in the supine posture where gravity pulls the flaccid tongue into retraction [2-3].

When the airway obstructs, the sleeping patient typically produces a prolonged inspiratory effort, attempting to open the airway [4]. If this is not successful, the patient eventually is aroused by the resulting hypoxia and hypercapnea and uses active tongue movement to breathe. The repeated pattern results in loss of deep sleep and risks hypoxic damage to the brain and heart.

B. Prior FES Approaches

There have been several attempts to use electrical activation of the tongue muscle to maintain airway patency. Transcutaneous stimulation of the tongue is awkward technically [5]. Intralingual stimulation of the tongue via percutaneous wires inserted deep and inferior to the frenulum produced only modest reductions in OSA episodes [6]. Similar wires inserted into the anterolateral tongue via a submental approach produced inconsistent changes in airway diameter in normal, awake volunteers [7]. A surgically implanted system developed in collaboration with

Medtronic targeted selected branches of the hypoglossal nerve and triggered the stimulation from an implanted substernal pressure sensor [8]. Airway opening was successful but the complexity of the devices and the surgical approach led to problems with reliability and acceptability.

C. BION Technology

BIONs® (BIONic Neurons) are a new class of chronically implantable stimulators. They are single channel, wireless electronic microstimulators (16mm long x 2 mm in diameter) that can be injected in or near muscles and nerves. Each BION receives power and digital command data via an RF transmission coil to produce stimulation pulses with controlled current (0-30mA) and duration (4-512 μ s). They offer a low-risk, reliable and cost-effective technology for delivering therapeutic electrical stimulation.

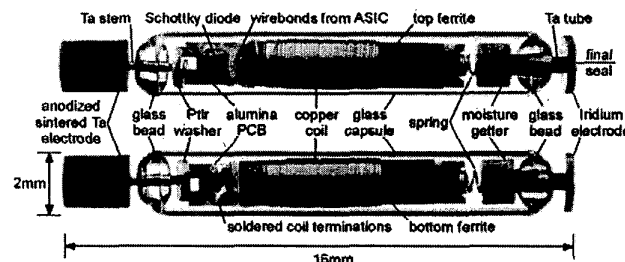


Fig. 1. The main components of BION implant.

BIONs have been demonstrated to produce stable thresholds at their deployment sites and have been shown to be safe and effective for stimulating muscles in animals [9,10]. Results from ongoing small cohort clinical trials have shown them to be effective in preventing and reversing shoulder subluxation and increasing knee function in patients with knee osteoarthritis [11].

BIONs are injected through an insertion tool that consists of a plastic sheath around a removable metal trochar. Trial electrical pulses can be applied through the trochar to identify the desired target. The trochar is then removed from the sheath and the BION is injected through sheath into the site.

We are determining the appropriate stimulation site, insertion approach, and control strategy required to treat OSA. We here describe preclinical studies to demonstrate the safety and likely efficacy of this approach.

II. REQUIREMENTS

Development of functional electrical stimulation (FES) system to treat OSA require consideration of these aspects

1. *Selective protrusion of the tongue* – The complex neuromuscular architecture of the tongue permits it to generate movements in all directions; selective protrusion requires selective activation of the appropriate motor units.
2. *No arousal during sleep* – This will probably require small, smooth movements with no cutaneous stimulation.
3. *Preserve normal tongue function* – The electrodes must not interfere with tongue movement or damage the nerve.
4. *Minimally invasive, aseptic implantation*
5. *No body-worn components*
6. *High long-term reliability*

III. STIMULATION SITE

The hypoglossal nerve branches to the GG muscle enter the tongue inferolaterally to innervate muscle fibers that are oriented transversely, longitudinally and radially in parasagittal fans. The posteriorly directed portion of the parasagittal fan originates from the mandible and produces protrusion. Endplate bands innervate the midpoints of these fibers and extend to the midline [12]. Sanders et al using Sihler's stain have shown motor endplates near the tongue base are innervated by a separate hypoglossal nerve branch (human genioglossus illustrated in Fig. 2). This suggests that a single site of stimulation located in the midline (near these endplates as illustrated in Fig. 3) would recruit selectively those motor units that will produce symmetrical protrusion of the tongue, thereby opening the airway. This site is also distant from the mucosal surface and cutaneous nerves.

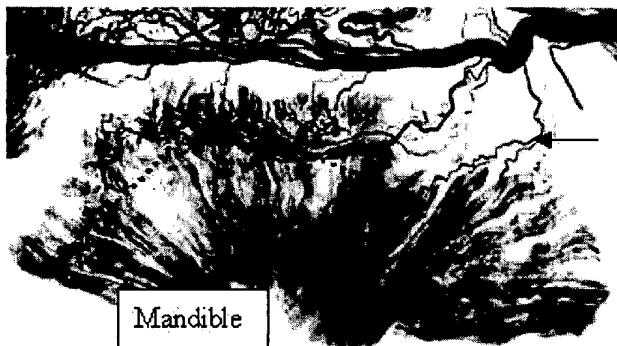


Fig. 2. The human genioglossus (GG), as shown in sagittal view. The single motor endplate band (red dotted line). A separate nerve branch innervates the motor endplates near the tongue base (arrow). Photo courtesy of Dr. Ira Sanders.



Fig. 3. Implantation site of a single BION in posterior midline of the genioglossus muscle with tantalum electrode (effective cathode) near the endplates (toward the tongue base).

IV. IMPLANTATION APPROACH

The BION can be injected into the target from under the chin along the midline. This minimizes the risk of damage to blood vessels and nerves as well as reducing the risk of oral infection. As the insertion tool is advanced along the line illustrated in Figure 4, trial stimulation pulses can be used to confirm the location of the motor endplates by palpating the muscle twitches. As expected from the anatomy, the first low threshold region corresponds to the geniohyoid muscle; the second corresponds to the targeted radial muscle fibers of the GG.

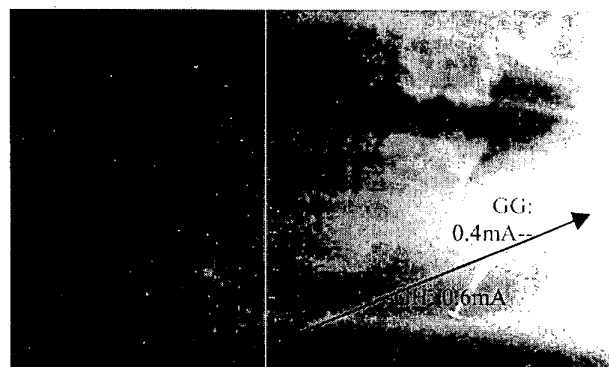


Fig. 4. Implantation of BION in pig tongue, measuring thresholds (in mA for 0.2ms pulsewidth) for contraction of geniohyoid (GH) and genioglossus (GG) as insertion tool was advanced on indicated line (final orientation of device appears rotated because of palpation of tongue during implantation).

V. BIOCOMPATIBILITY

The tongue has somewhat unusual neuromuscular architecture and hydraulic mechanics. In order to demonstrate that BIONs were tolerated and stable in this site, the ten pigs used for the implantation experiment (Fig. 4) were maintained for two or four weeks post-implantation before being sacrificed for histology. The implants had been coated with Procion Yellow fluorescent stain in a molten sugar solution [10] to assess the degree of BION movement from the injection site. The stain dissolves at the time of injection, binding permanently to adjacent collagen. Post mortem, the tissue is dissected under a microscope to determine the final location of the device in relation to the Procion Yellow marked deployment site. The five devices removed to date showed grossly unreactive sites with Procion stain. The remaining animals and histological evaluations are underway.

VI. STIMULUS CONTROL

Continuous stimulation of the GG to maintain airway patency might be expected to result in muscle fatigue. Stimulation could be administered only when the patient is in the inspiratory phase of respiration, but this would require the addition of a sensor. We hypothesized that if brief trains of stimulation pulses were applied to the GG at intervals close to the respiratory cycle of the patient, the patient would tend to synchronize spontaneously with the resulting intermittent periods of patency in the airway. That is because an inspiratory phase that happens not to coincide with GG stimulation will tend to be prolonged until the next train of GG stimulation opens the airway.

Currently, the most effective treatment for OSA is non-invasive, though cumbersome, continuous positive airway pressure (CPAP) therapy. By gating the application of CPAP with a pattern similar to the proposed intermittent GG stimulation, we can simulate at least some of the effects of

the proposed treatment. A computer controlled gating valve was used to intermittently interrupt CPAP therapy during sleep (Fig. 5). In addition, a check valve prevented rebreathing of expired air and a PEEP (positive end expiratory pressure) valves mechanically regulated the CPAP. When the CPAP was gated off, the patient could breathe through a demand valve, but this unaided breathing would be expected to result in many episodes of OSA in CPAP-dependent patients.

Two patients with documented severe OSA (>40 episodes/hr) were studied overnight. Baseline information such as respiratory rate and level of oxygen saturation was acquired during the first hour of sleep. Various duty cycles of gating of CPAP (30-50%) were studied at random during the night. For example, a 40% duty cycle in a 5 second respiration period means CPAP is applied for 3 sec and gated off for 2 sec. Preliminary results from a single subject indicate that the inspiratory cycle tended to remain synchronized to CPAP gating (Figure 6). However, we are uncertain whether the positive pressure itself might

INTERMITTENT CPAP APPLICATION TO PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

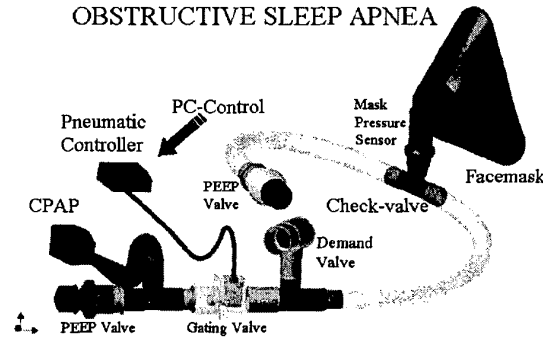


Fig. 5. Model to study rhythmically entrained breathing. Computer gating of CPAP machine in breathing circuit with pressure regulating valves to deliver intermittent positive pressure to open patient's airway.

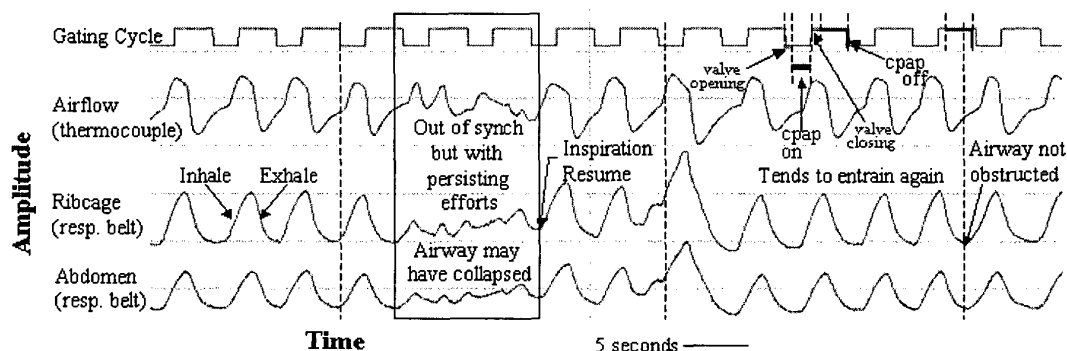


Fig. 6. Screen capture of polysomnogram, indicating patient's respiratory efforts responding to intermittent positive airway pressure. Respiratory efforts persist until the patient inhale during an open airway at which point the patient tend to synchronize to gated CPAP again (GREEN=CPAP ON splinting airway, RED=CPAP OFF no assist, ORANGE=pressure change).

have generated inspiratory airflow without the patient's effort. The second subject tended to be aroused by the CPAP fluctuations themselves.

We are developing analytical methods to quantify the degree of one-to-one entrainment between gating and respiratory efforts. In addition, we are developing analytical tools to assess how much the patient anticipates the gated on CPAP cycle, which would suggest entrainment by the nervous system as desired.

VII. FURTHER WORK UNDERWAY

We will use percutaneous wire electrodes to simulate BION activation of GG during sleep in OSA patients. Bipolar wires will be inserted through a 27-g needle along the midline of the tongue as illustrated in Fig. 3. The needle is then retrieved leaving the wires at the site for stimulation. Different patterns of electrical stimulation will be tested to evaluate how well the patient entrains breathing to intermittent airway opening. Full polysomnogram will be recorded to compare the efficacy of tongue stimulation to conventional CPAP or the untreated state.

Patients who respond well to the percutaneous stimulation will be offered a BION implant. After allowing the device to settle in situ for a few days, the clinician will determine the threshold for tongue protrusion and design a treatment program. The treatment program will be downloaded into a portable device that transmits power and commands. After evaluation of the device in the sleep laboratory, patients can be sent home to self-administer treatment.

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