UPPER AIRWAY STIMULATION FOR OSA: A REVIEW

Upper Airway Stimulation for Obstructive Sleep Apnea: Past, Present, and Future

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Obstructive sleep apnea (OSA) is an increasingly prevalent clinical problem with significant effects on both personal and public health. Continuous positive airway pressure (CPAP) has demonstrated excellent efficacy and low morbidity; long-term adherence rates approach 50%. Although traditional upper airway surgical procedures target the anatomic component of obstruction, upper airway stimulation tackles the twin goals of improving anatomic and neuromuscular pathology. After decades of trials demonstrating proof of concept of hypoglossal nerve stimulation in animal and human subjects, the results of a large multicenter, prospective trial were recently published. The trial demonstrated that hypoglossal nerve stimulation led to significant improvements in objective and subjective measurements of the severity of OSA. This novel approach is the first to combine sleep surgery techniques with a titratable medical device for the treatment of OSA. Further research is required to define optimal patient selection and device performance and to demonstrate long-term effectiveness.

Keywords: obstructive sleep apnea, upper airway stimulation, sleep disordered breathing

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CLINICAL SIGNIFICANCE

Obstructive sleep apnea (OSA) is characterized by repetitive collapse of the upper airway during sleep resulting in nocturnal hypoxemia and recurrent arousals.[1] The prevalence of OSA is significant and increasing with the obesity epidemic and aging population.[2–4] Untreated moderate-severe obstructive sleep apnea has been strongly linked to neurocognitive impairment, motor vehicle accident risk, and increased health risks.[5,6] The risk of hypertension, fatal and nonfatal cardiovascular events, as well as all-cause mortality is significantly increased in patients with untreated moderate-severe OSA.[6–8] Recent evidence has demonstrated that the risk of cancer mortality and ischemic stroke carry a dose-response association with the severity of sleep disordered breathing (SDB).[9,10] Untreated OSA poses a significant public health concern in the form of driving risk, loss of workplace productivity, cardiovascular disease, and the associated increased health care costs.[11,12]

NEED FOR NEW THERAPEUTIC OPTIONS

The current treatment paradigm positions continuous positive airway pressure (CPAP) as first-line therapy given its well-documented efficacy and overall low morbidity. Compared to other treatment modalities, CPAP by far has the most data of effectively managing OSA particularly for multilevel and multifactorial pathophysiology and for more severe disease. CPAP has been shown to improve snoring, subjective sleep symptoms, neurocognitive function, daytime sleepiness, driving risk, and sleep related quality of life measures.[13,14] In large longitudinal cohort studies such as the Sleep Heart Health Study, CPAP has also been shown to mitigate cardiovascular risk in those with moderate-severe disease.[6]

Despite its documented efficacy, adherence rates are suboptimal. Two recently published, well-conducted, multicenter trials (The Apnea Positive Pressure Long-term Efficacy Study, or APPLES, and HomePAP), reported CPAP adherence rates of only 39–50%.[15–17] A number of factors can limit adherence. Issues related to the chronic use of a nasal or oronasal interface are common.[18] As a result, when only CPAP therapy is considered, a large portion of the sleep apnea population remains inadequately treated.

Other treatment options are available, including oral appliance therapy, positional therapy, weight loss, behavioral modifications, and upper airway reconstructive surgery. Although these options also have documented effectiveness in the properly selected patients, the treatment effect is frequently incomplete. In addition, the potential benefits of traditional upper airway surgical procedures must be cautiously weighed against potential risk and morbidity, particularly in light of the lack of high-quality data and the heterogeneity of many surgeries. New treatment options are needed.

NEUROMUSCULAR PATHOPHYSIOLOGY

OSA is frequently a complex and multifactorial condition. In addition to anatomic factors (e.g., skeletal structure, pharyngeal anatomy, nasal airway), neuromuscular control of breathing during sleep (e.g. central respiratory output, tonic activity of pharyngeal dilator activity, arousal threshold loop gain) plays a key role in OSA pathophysiology.[19,20] The pharyngeal dilator muscles (e.g., genioglossus) must counteract the dual forces of negative intraluminal pressure from diaphragmatic excursion and positive extraluminal tissue pressure. Patients with OSA exhibit elevated genioglossus muscle electromyography (EMG) activity during wakefulness compared to healthy controls.[21] This phenomenon in patients with OSA has long been attributed to compensation for a narrower and more collapsible airway. Recent data suggest that it is a

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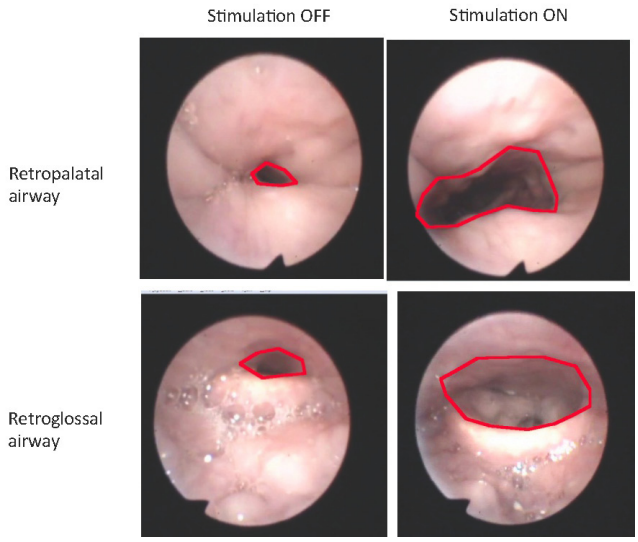

Figure 1—Multilevel upper airway improvement with stimulation during drug-induced sedation endoscopy. The outlined areas demonstrate the increase in cross-sectional area of both the retropalatal and retrolingual portions of the upper airway with hypoglossal nerve stimulation.

manifestation of neuromuscular dysfunction with EMG patterns similar to denervation/renervation injury.[22] The etiology of the neuromuscular dysfunction is unclear but may be related to intermittent hypoxia, systemic inflammation, or possibly vibrational trauma from snoring. A hypoglossal nerve conduction study in 16 patients with OSA reported delayed distal latency in 75% and low motor amplitude in 100%, compared to normative data, suggesting that neuromuscular dysfunction of the upper airway may be part of the pathophysiology and/or a consequence of untreated OSA.[23]

During sleep, normal healthy controls have been shown to predictably increase genioglossus EMG activity in response to intraluminal negative pressure, whereas patients with OSA may not.[19,20] This defective negative pressure reflex in patients with OSA, at least in part, lays the biologic foundation for research with nocturnal hypoglossal nerve stimulation to augment the neuromuscular activity of the upper airway.

ELECTRICAL STIMULATION OF THE UPPER AIRWAY

Animal Studies

In 1989, Miki et al.[24] isolated the upper airway from the lower airway by performing tracheotomy in six dogs and examined the relationship between the frequency of stimulation of the genioglossus and upper airway resistance. They demonstrated stability in upper airway patency with graded increases in stimulation frequencies of the genioglossus muscle in awake, spontaneously breathing canines. In 1992, Schwartz et al.[25] implanted bilateral hypoglossal nerve stimulators in 18 decerebrate felines and illustrated that increases in stimulation frequencies bear a direct relationship with $V_I$max via decreases in critical closing pressure (Pcrit). These findings were corroborated by Oliven et al.[26] in anesthetized canines.

Animal studies have confirmed that the genioglossus muscle is the primary upper airway dilator and tongue protrusor, whereas the hyoglossus and styloglossus are tongue retrusor muscles that contribute to airway collapse.[27–30] In addition, Yoo et al.[31] studied the effects of a multicontact nerve cuff electrode to determine if activation of selective segments of the hypoglossal nerve in the beagle model would yield greater benefit to airflow compared to non-selective hypoglossal nerve stimulation. During expiration, nonselective stimulation yielded the greatest benefit; on inspiration, both nonselective and coactivation of the genioglossus + hyoglossus/styloglossus muscles produced significant improvement.

Preliminary Human Studies

Initial human studies examining the tolerability of transcutaneous upper airway stimulation in the asleep, supine state bore mixed results.[32–36] Schwartz et al.[37] reported in 1996 the feasibility and efficacy of lingual musculature stimulation without causing arousals. Fine-wire Teflon-coated electrodes were used for intramuscular stimulation of the lingual muscle in nine participants with OSA. Tongue muscle stimulation in consecutive breaths decreased the frequency of obstructive episodes in a subset of participants without causing arousal.

Oliven et al.[26] demonstrated the airway effects of selective stimulation of protrusor and retrusor muscles. Selective intramuscular stimulation of the genioglossus significantly lowered Pcrit (more stable airway), whereas selective stimulation of the styloglossus and hyoglossus increased Pcrit (more collapsible airway). Coactivation of both protrusor and retrusor muscles resulted in a net improvement in airflow and reduction in Pcrit.[38] Nasopharyngoscopy was used to demonstrate that genioglossus stimulation can result in enlargement and stabilization of not only the retrolingual portion of the airway but also the retropalatal space (Figure 1). Because OSA frequently involves multilevel collapsibility, this was a key observation suggesting that hypoglossal nerve stimulation has the potential to affect multiple levels of the pharyngeal airway rather than the tongue base alone.

IMPLANTABLE UPPER AIRWAY STIMULATION TECHNOLOGY

Human Pilot Study

Implantable nerve stimulation technology has been available and applied successfully in other medical conditions: sacral nerve stimulation for incontinence, vagal nerve stimulation for seizures, spinal cord stimulation for pain, and deep brain stimulation for tremors.[38–41] In 2001, a pilot study reported the results of eight participants receiving an implantable hypoglossal nerve stimulator (Inspire I, Inspire Medical Systems, Maple Grove, MN) for OSA.[42] The system was composed of three components: tripolar half-cuff nerve stimulation electrode, implantable pulse generator, and respiratory pressure sensor. The respiratory piezoelectric pressure sensor placed against the pleura detected respiratory effect. The signal of "end expiration" to the implantable pulse generator, in turn, activated the hypoglossal nerve stimulation electrode at the onset of inspiration. Implantation was unilateral and stimulation was limited to inspiration to avoid neuromuscular fatigue. Implantation occurred under general anesthesia using an upper neck incision for access to hypoglossal nerve, midline lower neck incision followed by drilling the superior manubrium to place

the pressure transducer, and a right infraclavicular incision for tunneled placement of the pulse generator. Sleep studies were performed at 1, 3, and 6 mo postoperatively and apnea-hypopnea index (AHI) results were reported individually for nonrapid eye movement (NREM) and rapid eye movement (REM) sleep. Seven of the eight participants had significant reductions in their AHI and in the overall group, NREM sleep AHI dropped from 52.0 ± 20.4 to 22.6 ± 12.1 ($P < 0.001$). All participants tolerated stimulation once parameters were appropriately adjusted and no adverse effects were observed. Despite the encouraging results, electrode breakage and sensor malfunction occurred in five of eight participants, precluding use beyond the 6-month study period.

Feasibility Studies

Following the published technical limitations of the human pilot study, multiple investigators and medical device companies spent a decade improving the product prior to the launch of two larger trials with results available as of 2011.[43, 44] Eastwood et al.[43] reported on the safety and effectiveness in a Phase II trial of a new generation implantable hypoglossal nerve stimulator (HGNS) therapy system (HGNS, Apnex Medical Inc, St Paul, MN, USA) at four Australian sites. Participants (n = 21) had moderate-severe OSA, were surgically naïve, and unable to tolerate CPAP. Similar to the Schwartz pilot study, sleep studies were performed at 1, 3, and 6 mo. The surgical technique was made less invasive such that dual respiratory sensing leads were tunneled subcutaneously along the costal margin as opposed to drilling the superior manubrium. These sensors function as transthoracic impedance sensors used to determine respiratory effort. Intraoperative fluoroscopy was used to confirm placement of the electrode cuff by demonstrating an expansion of the retroglossal airway with device activation. Nineteen of the 21 participants in the study had baseline and 6-mo polysomnography (PSG). There was a significant improvement ($P < 0.05$) from baseline to 6 mo in: AHI (43.1 ± 17.5 to 19.5 ± 16.7) and Epworth Sleepiness Scale (ESS) (12.1 ± 4.7 to 8.1 ± 4.4). The investigators reported two adverse events: an infection requiring device removal and a stimulation lead cuff dislodgement requiring replacement.

Van de Heyning et al.[44] carried out two consecutive open prospective studies with another device, reporting their results in 2012. The Inspire II Upper Airway Stimulation (UAS) system (Inspire Medical Systems) was implanted similar to the HGNS with the exception that this device only has a single respiration sensor (Figure 2). In lieu of intraoperative fluoroscopy, electrode placement was confirmed by observing tongue protrusion with stimulation. In Part I of the study, the therapeutic feasibility and safety of upper airway stimulation in participants with OSA were assessed and predictive factors for therapeutic success were analyzed. For Part II, patient selection was based on the positive predicting factors from Part I. PSGs were obtained 2, 4, and 6 mo post-implantation. Three participants exited the study prior to the 6 mo PSG: lost to follow-up (n = 1); device-related infection (n = 1); inability to activate the tongue with amplitude in the allowable range (n = 1). Unlike the previous two feasibility studies, the composite AHI of the study population did not change between baseline and 6-mo visits. Six participants had significant improvements in AHI

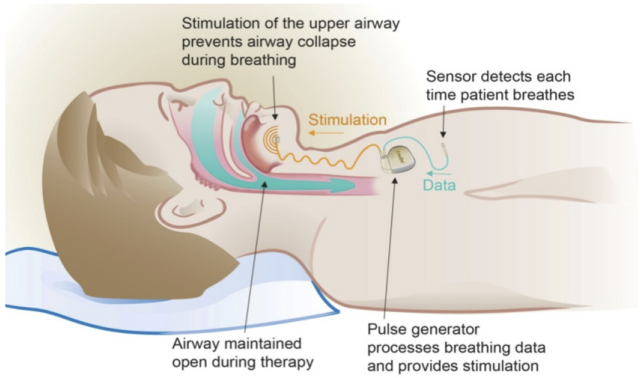

Figure 2—Implantable hypoglossal nerve stimulation system. The hypoglossal nerve stimulation system consists of three implanted components: (1) an implantable pulse generator in a subcutaneous pocket in the right upper chest, (2) a stimulation lead with a cuff electrode placed on the medial branch of the hypoglossal nerve in the right submandibular space, and (3) a sensing lead to detect ventilatory effort placed in the intercostal space facing the pleura. (Inspire Medical Systems, Minneapolis, MN).

consistently over the 6-mo follow-up, whereas the remaining 14 participants did not demonstrate significant changes. Based on the analysis of responders and nonresponders from Part I, the participants selected for Part 2 of the study met the following criteria: body mass index (BMI) ≤ 32 kg/m^2, AHI between 20–50/h and absence of complete concentric pattern of palatal collapse on drug-induced sedation endoscopy (DISE). In the eight participants prospectively enrolled in Part 2 with the aforementioned selection criteria, AHI was reduced significantly from a baseline of 38.9 ± 9.8 to 10.0 ± 11.0 ($P < 0.01$) at the 6-mo postimplant visit. Across all participants in study Part 1 and Part 2, both ESS and Functional Outcomes of Sleep Questionnaire (FOSQ) improved significantly from baseline.

Selective Nerve Segment Stimulation and Respiratory Coordination of Stimulation

Stimulation of the HGN causes contraction of both the retrusor (styloglossus and hyoglossus) and protrusor (genioglossus) muscles of the tongue. Oliven[45] demonstrated that selective stimulation of the protrusors only resulted in increased airflow and reduced collapsibility of the pharynx, whereas retrusor stimulation resulted in increased collapsibility of the pharynx. Furthermore, improved anterior displacement of the tongue was achieved with selective stimulation of the deeper and more horizontally oriented genioglossus fibers compared to the superficial and more obliquely oriented genioglossus fibers. These findings follow the anatomic principles that the lateral branching point of the hypoglossal primarily innervated the retrusor muscles and stimulation distal to this retrusor branch point selectively stimulated the protrusor muscles resulting in anterior tongue displacement (Figure 3).

Hypotheses behind a respiratory effort-sensing lead are to coordinate stimulation during the most vulnerable portion of the respiratory cycle–from end-expiration through the inspiratory period–and to avoid neuromuscular fatigue. Both Apnex and Inspire systems use various sensors to achieve this

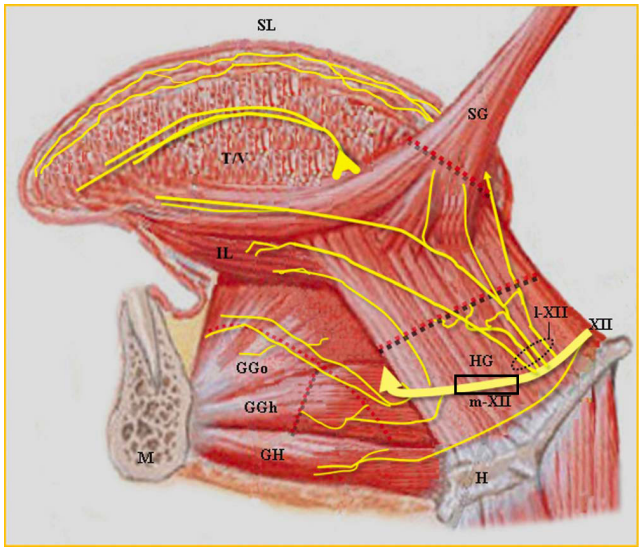

Figure 3—Neuroanatomy of the tongue. Sagittal illustration of the tongue showing lateral branches (I-XII) of the hypoglossal nerve supplying the retrusor muscles: styloglossus (SG) and hyoglossus (HG). The deeper medial branches (m-XII) selectively innervate the genioglossus muscle, which is the primary protrusor muscle and upper airway dilator. Ideal cuff electrode placement is distal to the lateral branching point as indicated by the rectangle. GG, genioglossus; GGh, genioglossus horizontal; GGo, genioglossus oblique; IL, inferior longitudinal; SL, superior longitudinal; T/V, transverse and vertical. (With permission, John Wiley and Sons)

purpose. Another neurostimulation device, Imthera aura6000, uses a continuous nerve stimulation without a respiratory sensing lead, but rotates the stimulation through different electrode configurations to rest some neuromuscular groups while others are being stimulated.[46] None of the devices uses intercostal muscle activation. A more detailed discussion of advantages/disadvantages is premature and beyond the scope of this manuscript.

Stimulation Parameters

The level of stimulation frequency, stimulation amplitude, and pulse duration for skeletal muscle, such as the genioglossus, is directly correlated with muscle recruitment.[47] Increasing levels of these parameters, however, may lead to patient discomfort and arousals. The canine literature has shown that stimulation frequency of the genioglossus between 50 Hz and 100 Hz produces maximal airway opening.[24] The Schwartz pilot study successfully utilized frequencies between 33–38 Hz.[42] In this report, stimulation amplitude was increased by 0.1 V during successive calibrations from 2.2 V to 3.0 V though voltages as high as 40 V in other studies have been shown be tolerated during sleep.[24] Increases in pulse duration correspond to increased muscle tension with an average pulse width range between 94.3–110.5 μsec and were well-tolerated in the 2001 human pilot study.

Effect of Hypoglossal Nerve Stimulation on Airflow, Fluoroscopy and DISE in Implanted Individuals

Schwartz et al.[48] studied 30 participants implanted with the HGNS system. Holding fixed the frequency and pulse-width, current was increased stepwise during NREM sleep. At each current level, stimulation was applied on alternating breaths, and responses in maximal inspiratory airflow ($V_I$max) and inspiratory airflow limitation (IFL) were assessed. With increasing current from 1.05 mA to 1.46 mA, HGNS demonstrated linear increases in $V_I$max across all participants. IFL was eliminated in 57% of participants. Of note, all participants attained normal or near-normal levels of $V_I$max at 400 mL/sec or greater.

Goding et al.[49] sought to determine objective fluoroscopic measures in 26 participants implanted with the HGNS system. Under general anesthesia, they examined changes in the anterior-posterior dimension of the retropalatal and retrolingual airway spaces and hyoid bone position with stimulation. All participants had an increase in retrolingual airway (9 ± 3 mm), whereas 65% of participants had enlargement of the retropalatal airway in whom the average increase was 5 ± 3 mm. There was a trend (not reaching significance) toward increased BMI in those participants having failed to show expansion of the retropalatal airway. Anterior displacement of the hyoid occurred in 92% of participants.

In 2013, Vanderveken et al.[50] studied the predictive value of DISE in assessing therapeutic response to implanted UAS for participants with OSA. Using midazolam and/or propofol, the pharyngeal collapse patterns were visualized using a flexible fiberoptic nasopharyngoscope in 21 participants. The results of the DISE were scored based on three factors: the level (palate, oropharynx, tongue base, hypopharynx/epiglottis), the direction (anteroposterior, concentric, lateral), and the degree of collapse (none, partial, or complete). The authors concluded that the absence of palatal complete circumferential collapse during DISE may predict therapeutic success with implanted UAS therapy.

Multicenter Prospective Studies

The basic science experiments and feasibility studies served as the basis for multicenter prospective studies. The largest prospective trial to date is the Stimulation Therapy for Apnea Reduction (STAR) trial.[51] Eligible implant participants had moderate-severe OSA (AHI 20–50), CPAP intolerance, BMI ≤ 32, and absence of a complete circumferential pattern of palatal obstruction on DISE. After a rigorous screening clinical evaluation, PSG, and DISE, 126 participants underwent surgical implantation of the hypoglossal nerve stimulation system and were followed for at least 12 mo to assess effectiveness and adverse events. Devices were titrated in the sleep laboratory during full-montage attended PSG, similar to CPAP titration, to optimize comfort and effectiveness. Primary outcome measures (AHI, 4% oxygen desaturation index) and secondary outcomes measures (ESS, FOSQ) all demonstrated clinically and statistically significant improvements at 12 mo (Figure 4). Two thirds of the implanted participants were considered complete responders to therapy by previously published surgical success criteria and had successful management of their OSA with a decrease in median AHI from 30 to 6.

Risk and morbidity data were favorable with no permanent hypoglossal nerve weakness, no serious device-related infection requiring explantation, and significantly less postoperative discomfort compared to traditional pharyngeal or skeletal

sleep apnea surgeries. One third of the participants reported minor tongue discomfort due to stimulation itself or abrasion of the tongue on an adjacent tooth. Most of these local side effects resolved with adjustment of stimulation parameters or in some cases a dental guard. Adherence, which is essential to success with any medical device therapy, was excellent by self-report (86% of participants using the therapy nightly at the 12-mo mark) but detailed objective data monitoring was limited.

A second single-arm, prospective interventional trial was performed using the Apnex HGNS device. Kezirian et al.[52] reported on 12-mo outcomes on a group of 31 patients with moderate to severe OSA. Primary outcomes included both objective and subjective measures. Across all subjects, the AHI decreased from 45.4 to 25.3 ($P < 0.001$) and FOSQ score improved from 14.2 to 17.0 ($P < 0.001$). The subjects demonstrated excellent compliance with therapy, using therapy 86% of nights for an average of 5.4 h per night. Within the first 6 mo, three serious device-related adverse events occurred: an infection requiring device removal; and two stimulation lead cuff dislodgements requiring replacement. No adverse events were recorded in mo 6 and12.

DISCUSSION AND INSIGHTS FROM AN OTOLARYNGOLOGY PERSPECTIVE

Otolaryngologists are frequently faced with the challenge of helping patients who are frustrated with and unable to achieve benefit with positive pressure therapy. It is common for otolaryngologists to see patients who, despite years of struggling to make CPAP work, have essentially remained untreated with persistent symptoms and cardiovascular risk. Patients with CPAP intolerance and nonacceptance are very common in otolaryngology practices and have already placed themselves in a salvage situation having failed the standard first-line therapy. A universally accepted second-line therapy does not exist. The current approach to these patients typically involves phenotyping each individual's anatomy and pathophysiology and tailoring a personalized treatment plan that may include oral appliance therapy, weight loss, positional therapy, lowering nasal resistance, and/or airway reconstructive surgery–often in combination. Even with this variety of second-line options, many patients remain inadequately treated with residual symptoms and persistent health risks, and require an effective option.

Diagnostic advances such as DISE have improved the surgeon's ability to characterize the anatomical locations and pattern of airway closure and better predict proper surgical therapy.[53–56] Recent palatopharyngoplasty modifications (expansion sphincter pharyngoplasty, transpalatal advancement, anterior palatoplasty) employing more reconstructive and physiologically sound techniques have improved effectiveness and reduced morbidity over traditional excisional uvulopalatopharyngoplasty techniques.[57] Improved results have been demonstrated with multilevel surgical plans including the nose, palate, and tongue; however, the increase in the number of procedures also increases perioperative risk and potential complications.[58–60] Despite these advances, the data on tongue base procedures remain rather limited, whereas the potential risk and morbidity of hypopharyngeal and even skeletal advancement surgery remains relatively high.[61]

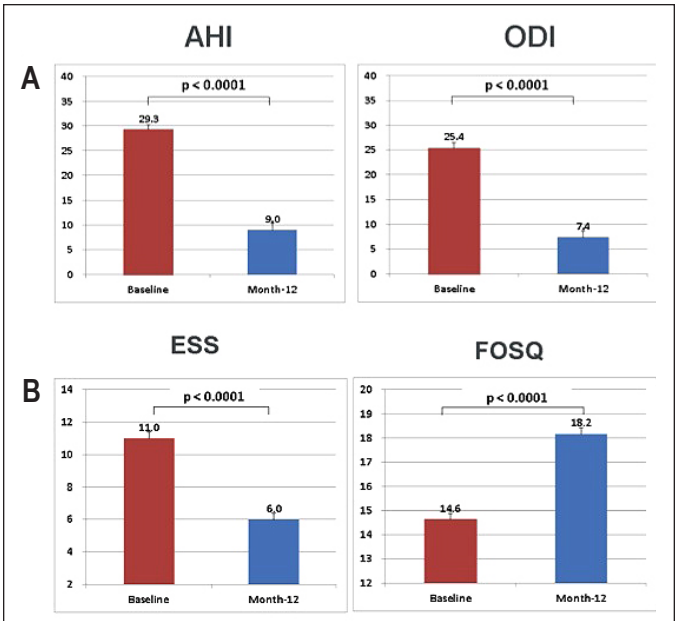

Figure 4—(A) STAR trial primary outcomes data (n = 124). With upper airway stimulation therapy, median apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) improved significantly from baseline to 12-mo follow-up. **(B)** STAR trial secondary outcomes data (n = 123). With upper airway stimulation therapy, median Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ) improved significantly from baseline to 12-mo follow-up.

UAS has several unique advantages compared to traditional OSA surgeries. First, successful hypoglossal nerve stimulation provides multilevel airway improvement with only one procedure. Studies using drug-induced sedation endoscopy or other imaging techniques have demonstrated enlargement of the retropalatal space as well as the retrolingual space. Second, upper airway stimulation therapy is a titratable and adjustable therapy, similar to CPAP or even oral appliances. Unlike other surgical procedures that provide a one-time result, hypoglossal nerve stimulation parameters can be modified postoperatively through a variety of configurations (e.g., bipolar versus monopolar, pulse width, amplitude, duration of stimulation) to optimize effectiveness as well as patient comfort/adherence. Further, the device can be specifically titrated in real-time during overnight PSG to directly assess the effect of stimulation. This may be particularly relevant because OSA is frequently a chronic long-term condition that requires continued reevaluation and management throughout the lifespan.

It is also important to note that hypoglossal nerve stimulation differs greatly from other tongue surgeries such as midline glossectomy, transoral robotic tongue base reduction, radiofrequency ablation, tongue base suspension. The UAS surgical procedure is completely external to the pharynx, thus minimizing or even eliminating the traditional risks of severe throat pain or hemorrhage, dysphagia, change in taste, or other untoward side effects in the throat. Based on the published data and clinical experience, the UAS implant procedure is associated with significantly less discomfort, downtime, and recovery compared to other pharyngeal surgeries. Unlike most pharyngeal surgeries, the implant procedure is technically and potentially reversible.

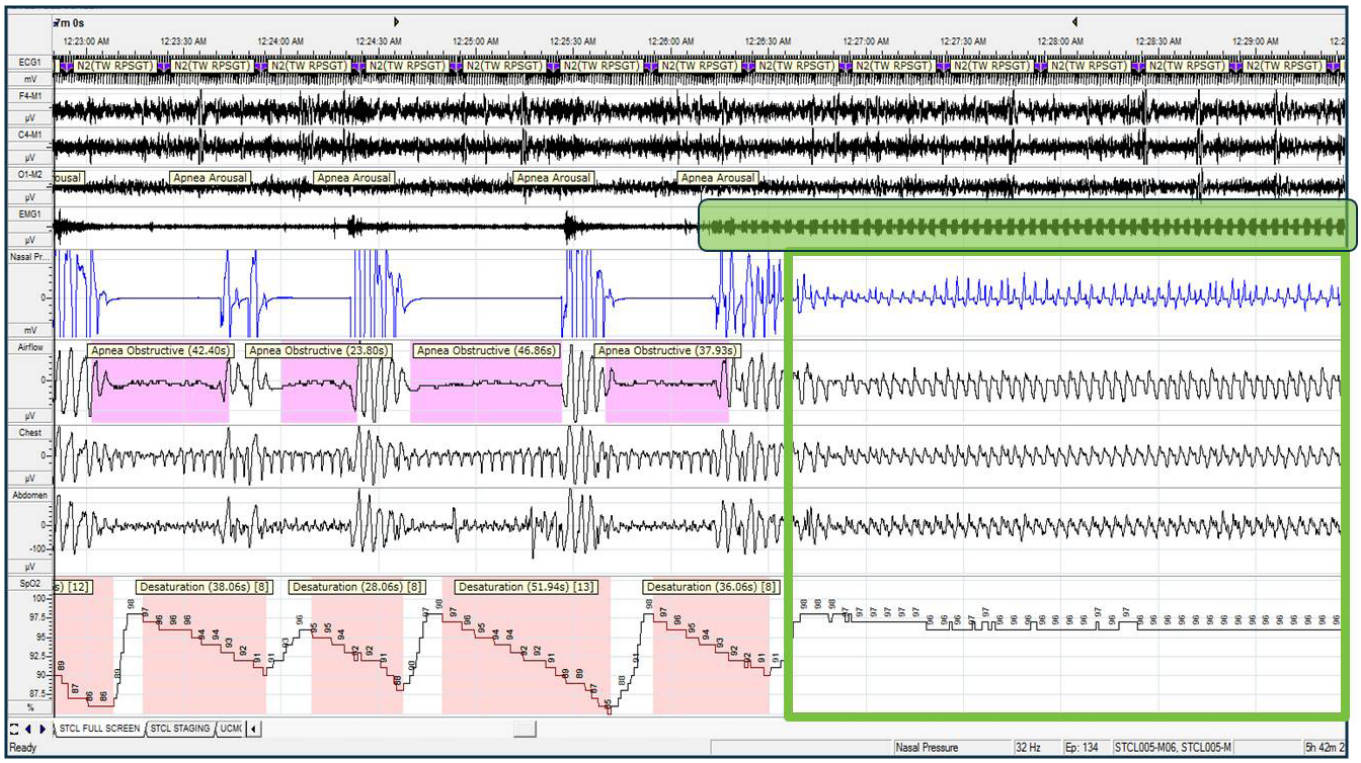

Figure 5—Titration of upper airway stimulation therapy during polysomnography (PSG). PSG snapshot showing an approximately 6-min respiratory window. The left side of the figure shows periodic airflow limitation, fluctuating respiratory effort, and associated oxygen desaturations consistent with obstructive sleep apnea. Device activation is illustrated by the vertical arrow. After the device synchronizes with ventilatory effort, immediate improvement in control of breathing and oximetry is observed.

DISCUSSION AND INSIGHTS FROM A SLEEP MEDICINE PERSPECTIVE

Although UAS involves a surgical procedure for device implantation, the therapy shares many similarities with positive pressure devices. There is no cutting or rearranging of tissues of the pharynx or jaw structure. Similar to CPAP, the patient has control of the device with the ability to turn it on and off for the sleep period, make adjustments for comfort within a preset range of parameters, and set a ramp or delay time to facilitate sleep onset. After device activation, the treatment is optimized through a titration study in the sleep laboratory in a similar method to CPAP titration (Figure 5). Wireless telemetry is employed to make adjustments in stimulation parameters during PSG from outside the patient's room and without disturbing the patient from sleep.

The adjustability and titratability of the treatment may facilitate long-term management as the patient and their sleep apnea change over time. Device interrogation in the office can provide feedback on hours of usage and stimulation settings akin to CPAP data download technology. UAS therapy puts the sleep medicine physician and the sleep laboratory technician at the center of this longitudinal care model.

LIMITATIONS AND FUTURE DIRECTIONS

Based on the available data, particularly the results of the STAR trial, UAS therapy has a very favorable risk-benefit profile and is well-positioned as a salvage treatment for patients with moderate-severe OSA. However, a number of questions remain unanswered and current limitations need to be addressed.

Although the STAR trial has collected data through 18 mo postoperatively, studies are needed on long-term adherence and effectiveness as OSA is a chronic, long-term condition. Prior clinical trials have identified some patient features, such as BMI and DISE findings, that may correlate with UAS success rates; however, more research is needed to better understand which anatomical and pathophysiologic patient phenotypes will respond best to therapy. With obesity rates dramatically increased over the past two decades and with obesity a common component of OSA pathophysiology, it will be important to better understand the potential role of UAS therapy in patients with a BMI higher than 32 kg/m^2.

Further work is needed to better define the most effective and appropriate stimulation parameters and titration protocols. Perhaps future technology development will provide autotitrating devices that would allow home portable titration. Preliminary cost-effectiveness data from the STAR trial demonstrate cost-effectiveness of UAS compared to no therapy using a willingness-to-pay threshold of $50,000–$100,000/quality-adjusted life-years.[62] The study authors incorporated the risk of myocardial infarction, stroke and motor vehicle accident over a 10-y horizon. Further data are needed to evaluate how the UAS procedure and follow-up compares to CPAP therapy, oral appliance therapy, and other surgical procedures. UAS has higher up-front costs compared to CPAP, related to screening and device implantation; however, it may compare

favorably when taking into account the long-term costs of CPAP replacement parts over time as well as the persistent public health costs and increased cardiovascular disease in patients who are CPAP intolerant and otherwise untreated.

Other limitations include incompatibility of the current technology with magnetic resonance imaging (MRI) and the need for three external incisions for implantation–two factors that may preclude a subset of patients from considering this therapy. Although the cumulative stimulation time is available from device interrogation, the current technology does not provide detailed nightly data monitoring as is available and standard with most of the current CPAP machines. Continued efforts to produce a smaller MRI-compatible pulse generator, more advanced and user-friendly patient programmer, and more sophisticated and comprehensive data recording technology will further advance the treatment. Finally, as is evident in other medical and surgical sleep apnea studies, there is likely a role for combination therapy. Future studies should explore the role of UAS in conjunction with other modalities such as oral appliance therapy, upper airway surgery, lowering nasal resistance, weight loss, and positional therapy.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
CPAP, continuous positive airway pressure
DISE, drug-induced sedation endoscopy
EMG, electromyography
ESS, Epworth Sleepiness Scope
FOSQ, Functional Outcomes of Sleep Questionnaire
HGNS, hypoglossal nerve stimulator
IFL, inspiratory airflow limitation
MRI, magnetic resonance imaging
OSA, obstructive sleep apnea
Pcrit, critical pressure
PSG, polysomnogram
SDB, sleep disordered breathing
STAR, Stimulation Therapy for Apnea Reduction
UAS, upper airway stimulation
$V_I$max, inspiratory airflow

DISCLOSURE STATEMENT

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