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Origins of and Implementation Concepts for Upper Airway Stimulation Therapy for Obstructive Sleep Apnea

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Abstract

Upper airway stimulation, specifically hypoglossal (CN XII) nerve stimulation, is a new, alternative therapy for patients with obstructive sleep apnea hypopnea syndrome who cannot tolerate positive airway pressure, the first-line therapy for symptomatic patients. Stimulation therapy addresses the cause of inadequate upper airway muscle activation for nasopharyngeal and oropharyngeal airway collapse during sleep. The purpose of this report is to outline the development of this first-in-class therapy and its clinical implementation. Another practical theme is assessment of the features for considering a surgically implanted device and the insight as to how both clinical and endoscopic criteria increase the likelihood of safe and durable outcomes for an implant and how to more generally plan for management of CPAP-intolerant patients. A third theme is the team building required among sleep medicine and surgical specialties in the provision of individualized neurostimulation therapy.

Introduction

Obstructive sleep apnea (OSA) is a prevalent (9–17% in the United States) adult human sleep disorder caused by episodes of complete or partial collapse (obstruction) of the upper airway during sleep^{1,2}. Repetitive apneas and hypopneas produce sleep hypoxemia and sleep

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Conflict of interest

Kingman P. Strohl served as a site Principal Investigator for the STAR trial and advisor to the FDA application in 2014 for the Inspire Medical System and received research grants from the VA Research Service and the National Institute of Health. Other authors have no conflict of interest.

fragmentation, which if left untreated, leads to a number of cognitive, behavioral, and cardiovascular morbidities¹.

The properties of the oropharynx and/or velopharynx are under dynamic neuromuscular control. Sleep is essential for the well-being, and OSA occurs because failure of functional patency³. Patency is compromised by a diminished drive to the upper airway muscles, combined with a collapsible airway¹. Sleep-related loss of upper airway muscle tone is partly responsible^{4,5}. This general reduction not only affects the genioglossus muscle but other upper airway muscles, such as the ala nasi, which affects the patency of the anterior nares^{6,7}. Reductions in drive in the absence of a collapsible airway will result in non-obstructive apnea, referred to as central apnea and/or central hypopnea. Thus, it is the anatomy that determines whether obstruction or near-obstruction (hypopnea) occurs when airway tone and activation falls below a threshold that can maintain patency⁸. Meanwhile, it is upper airway activation that reopens the closed airway, with or without arousal from sleep⁹. Then, once the airway reopens, a period of recovery occurs, determined by activation. In 80% of the time, an arousal from sleep occurs, with maintenance of sufficient drive in the upper airway muscles for unobstructed ventilation, before neuromuscular drive falls again as gas exchange recovers and the patient falls back to sleep. If the drive is insufficient for the anatomy, another obstructive event will ensue. Cycle extremes are determined by the gain of the control and controlled system of the ventilatory system, a property called “loop gain”^{8,10}. These recurrent apneas are clinically important and lead to the development of OSA syndrome.

To summarize, 4 pathways, acting in combination, contribute to the pathophysiological mechanism and underlie the clinical treatment of OSA (Figure 1). These are anatomy (small airway size and high pharyngeal compliance), low activation levels and reflex responses of muscles that keep the airway open (inadequate upper airway muscle drive), loop gain (controls on overshoot and undershoot of ventilatory responses), and sleep itself (specifically the arousal threshold)^{11,12}. These pathways can be measured in human subjects¹³ and estimated from elements in the polysomnogram^{14–16}, and will be used to individualize therapy in the future.

The first and most common treatments are focused on the pathway of an inadequately stiff and large upper airway, that is, the anatomy. Continuous positive airway pressure (CPAP) takes advantage of the ability of positive pressure to inflate the collapsible site of upper airway obstruction, keeping the channel open, thus preventing OSA and its associated sleep disruption^{17,18}. CPAP secondarily reduces upper airway muscle activity⁶ and, by lung inflation, loop gain¹, and permits uninterrupted sleep. Despite efficacy in the polysomnography laboratory, chronic use is limited by patient tolerance and adherence, rather than by direct side effects of the mask and tubing¹⁹. When adherence is defined as greater than 4 hours of nightly use, about a third of patients with moderate to severe OSA have been reported to be non-compliant to treatment^{19,20}.

Oral appliance therapy is an alternative approach designed to fit over the teeth and hold or advance the mandible and tongue forward, thereby creating greater or stiffer pharyngeal airway space. Clinical effectiveness is similar to that of CPAP and, like CPAP, reports of use

are better initially but decline over time²¹. However, therapy is less consistently effective in patients with more severe OSA, and therapy can result in pain in the temporomandibular joint and teeth movement in approximately 20% of patients²². Critical closing pressure (anatomy) is improved with oral appliance therapy²², but whether or not it is also accompanied by muscle activation is not known. Effects on sleep are reported for those that improve, but whether oral appliance therapy results in changes in the arousal threshold is not known.

Site-selective surgery on soft tissues or bony structures when effective improves OSA and critical closing pressure²³. While no data exists for how it might affect other pathways, it could improve sleep stability and respiratory drive, as well as the structural properties prior to falling asleep. Surgical alternatives, except for bariatric surgery and possibly mandibulomaxillary advancement, are not highly predictable, possibly because the site of obstruction is not addressed or the other pathways are unchanged²⁴. Thus, patients with moderate to severe OSA hypopnea syndrome, therefore, may remain untreated despite surgical effort²⁵.

This review of upper airway stimulation as a therapy for those who fail prior therapy is not a comprehensive appraisal, and the reader is directed to recent, detailed reviews of experimental results from preclinical trials and physiological studies in early application of this technology before approval for general use in human subjects^{26,27}. These reports discuss in great detail physiology, acute responses, and stimulation approaches in animal and preclinical human studies, and the proof that acute restoration of hypoglossal drive decreases flow resistance and improves patency, indicating its potential value.

Historical Roots

The first publication in 1988 was from Japan and described the effect of transcutaneous stimulation with polysomnographic studies during all-night sessions²⁸. Submental stimulation was shown to reduce OSA by using several respiratory metrics. A more in-depth study followed, indicating that stimulation decreased apnea episodes and promoted deeper sleep without accompanying serious side effects. Furthermore, the technology was a demand-type stimulator based on tracheal breath sounds²⁹. When the stimulator was optimally placed in the proximal half of the submental region with surface electrodes 1 cm apart, decreasing supraglottic inspiratory and expiratory resistance in OSA patients and inspiratory resistance in age-matched people without OSA were observed. The magnitude of improvement in inspiratory but not expiratory values was shown to be dependent on stimulation frequency and voltage³⁰.

Other groups started to apply muscle therapy with mixed results. With their approach to muscle stimulation therapy, Verse et al found that daytime sleepiness improved significantly as did snoring. However, the apnea-hypopnea index (AHI), the defining metric of OSA, decreased modestly from approximately 29/hr before to approximately 21/hr after therapy. These data suggest that transcutaneous stimulation therapy could be safe and relatively easy but that its effectiveness in regard to reducing apneic events needs further evaluation. A positive study, reported in abstracts^{31,32}, showed that submaxillary electrical stimulation was

effective for reducing apneas overnight and suggested that it pushed the tongue “ahead,” thereby opening the pharyngeal region. Piao et al³³ reported in an abstract that transcutaneous stimulation was effective, but also noted, as anticipated, that the technology failed to improve central sleep apnea.

Negative studies appeared and tempered enthusiasm. Therapy was demonstrated to induce electroencephalographic (EEG) arousals, and application of submental subcutaneous stimulation resulted in more contractions of the platysma than the movement of the tongue³⁴. In comparison, an alternative intraoral approach induced anterior tongue movement with increases in the size and shape of the posterior oropharyngeal airway. However, each time a submental stimulation broke an apnea, a time-linked alpha EEG arousal occurred. The results suggest intraoral electrodes as a viable approach. Another study³⁵ addressed whether transcutaneous stimulation affected airway collapsibility or size, and detected no change in size with stimulation applied at 50% and 100% of the maximal tolerated intensity. By contrast, voluntary protrusion of the tongue increased the cross-sectional area of the oropharyngeal, hypopharyngeal, and velopharyngeal segments. When applied during sleep, however, transcutaneous stimulation failed to prevent or improve either sleep-disordered breathing or the sleep architecture. Work on this approach continues³⁶.

Neural Stimulation Therapy

Hypoglossal nerve stimulation (HNS) emerged as an alternative approach to muscle stimulation. Nerve stimulation is less bothersome than muscle stimulation because selective stimulation occurs at very low amplitudes, below perception or at least below a certain sensory threshold that might interfere with sleep. HNS could activate all intrinsic and extrinsic muscles of the tongue. This treatment addresses the role of inadequate neural activation, rather than the anatomy-passive mechanical properties treated by CPAP, site-selective surgery, or oral appliances¹¹. In 1993, studies demonstrated that HNS was capable of keeping the airway open during sleep in OSA patients but could not break an apnea once it was established³⁷. The initial trial of efficacy was reported in 2001³⁸. Over the past 10–12 years, HNS was developed commercially as therapy for OSA²⁷. Three years ago, 3 companies, namely ImThera, Inspire, and Apnex, worked toward clinical studies, each with a different approach (Table 1). Apnex reported its phase II safety study³⁹, but the study was halted when it did not appear to reach efficacy thresholds in a phase III trial, and investors suspended the trial.

ImThera and Inspire technologies have been available in Europe since 2013 and are offered with required post-marketing monitoring. In regard to regulatory status in the United States, the pivotal trial of Inspire therapy was completed in late 2013 and gained Food and Drug Administration (FDA) approval in April 2014. ImThera is currently in an FDA-monitored phase III trial.

In Inspire therapy, a three-electrode wrap cuff is placed intraoperatively on more-distal (medial) branches of the hypoglossal nerve in order to stimulate the anterior tongue protusors (primarily the genioglossus). This approach opens the retrolingual pharyngeal airway but also affects the opening of the retropalatal pharynx⁴⁰. Stimulation of the muscles

of the tongue base that might cause backward movement of the tongue are to be minimized by placement selectivity and optimized by post-implant stimulation adjustments. Activation is synchronized with the inspiratory phase of respiration by sensing intrathoracic pressure, ideally triggered by its fall with inspiration. The example shown in Figure 2 is a recording where Inspire therapy is turned off briefly, resulting in immediate obstructed efforts; when the stimulator is again turned on, OSA is resolved.

The ImThera system does not synchronize stimulation with respiration and relies on a different activation strategy. The device has a multi-contact cuff electrode that is placed more proximally on the hypoglossal nerve catching branches to all lingual muscles, including tongue retrusors. The ImThera approach considers the tongue as a muscular hydrostat with its ability to produce coordinated and independent actions among several muscles to the posterior tongue (tongue base) and to the anterior (oral) tongue. Several muscles of the tongue have no bony attachment or are attached to only one floating bone. As such, the tongue easily can change its shape and form to accommodate its functions (e.g., speech, masticatory aid, deglutition, and negative pressure resistance). The tongue base (as distinct from the oral tongue) is proposed to have a specific role in OSA treatment in terms of its interface with the palate and pharynx.

Proponents of ImThera technology propose that an effective innervation should capture a greater cross-section of lingual muscles by employing a multicontact electrode that can take advantage of the topographic organization of the hypoglossal nerve. Six contacts extend around the circumference of the nerve, and each can be tested against one another to determine which arrangement is associated with the greatest pharyngeal airway opening (using respiratory metrics). When favorable effects are identified, the programming rotates between stimulating different contacts in the array. This approach prevents fatigue in muscles, which would occur if the same muscle was always stimulated. By chronically stimulating muscles in the tongue (which could include retrusors and protrusors), the system could likely activate fatigue-resistant type I and IIa fibers in the tongue base. It is proposed that this approach creates a stronger lingual platform, which by virtue of its pharyngeal and palatal attachments, positively influences pharyngeal patency well beyond the retrolingual airway.

FDA Approval for Inspire Therapy in the United States: April 2014

At the moment, the Inspire system is approved for clinical use in the United States. In the pivotal FDA study⁴¹, a study in which we at Case Western Reserve University participated, upper airway stimulation of the hypoglossal nerve was timed with the breathing cycle by using the Inspire implantable neurostimulator (Inspire Systems, Minnesota, MN). Results suggested that this approach was an effective and safe treatment for selected patients with moderate to severe OSA who have failed or are intolerant of CPAP therapy^{41–43}. The selection criteria for implant were based tested in the phase II experience⁴⁴ and led to the inclusion criteria used in the FDA-monitored phase III-body mass index (BMI: <32 kg/m²), AHI (20–50/hr), and drug-induced sedation endoscopy (DISE), which most notably included the absence of a complete concentric collapse of the velopharynx. In a multicenter,

prospective, single-group, cohort study, the surgically implanted upper airway stimulation device was placed and, 1 month later, activated.

The primary outcomes of the Inspire trial were the AHI and oxygen desaturation index (ODI). For instance, the median AHI score at 12 months decreased by 68%, from 29 to 9/hr ($P < 0.001$; Figure 3). The AHI effect was not explained by sleep stage effects, positional effects, or a change in weight. Secondary outcome measures, which included subjective measures of sleepiness and wakefulness, improved (Figure 3). In a sub-study at 12 months, improvements in respiratory measures and quality of life were reversed by brief cessation of therapy and were thus temporally related to the therapy⁴². One-year results met expected prespecified thresholds for success, and the technology obtained FDA approval in late April 2014. There are now 36-month outcomes, and the effects appear durable in general. Furthermore, the stimulation amplitudes needed to maintain effectiveness were similar at 36 and 12 months, suggesting no effects on the electrode-nerve interface. The 36-month outcomes were largely unchanged from the 18-month values (Figure 3).

Non-serious adverse events are encountered within the first month of device implantation and are the result of the procedure⁴¹. After 12 months, there was an elective device removal due to non-effectiveness and one due to concerns for a cause for septic arthritis, which was adjudicated as non-device related. Numbness at the incisional sites occurred in 3 patients for longer than 12 months but were not present by 36 months. Discomfort due to electrical stimulation was encountered more in the first year but continued to emerge in the second and third year of the follow-up. Tongue abrasions caused by movement of the tongue over the mandibular dentition occurred in the first year ($n = 28$). In most cases, this could be managed by changing stimulation parameters. Four patients had occasional problems in the third year. Twelve patients needed to construct a plastic dental guard, most for temporary use. None of these problems resulted in any of the patients discontinuing therapy. Two additional device- or disease-unrelated deaths (a cardiac arrest after a fall and a homicide) occurred. A detailed list of adverse events is provided in the Supplemental Appendix to the report⁴⁵.

Therefore, device-related serious adverse events are rare. The approach is effective in these selected patients with an AHI responder rate of $>66\%$, with durable improvements in behavioral sleepiness and quality-of-life measures.

At 36 months, 69% of the patients who met “responder” rates were also responders at the 12- and 18-month evaluations⁴⁵. This observation is consistent with the concept that addressing the pathway of insufficient upper airway muscle activation results in control of sleep apnea. Looking from the other side of the results, there were 25 non-responders at 36 months, 7 (28%) of whom became responders at both 12 and 18 months, while only 9 were non-responders at all time points.

We suspect non-responders, and intermittent responders could differ due to the influences of the other pathways (see Figure 1) and to differences in the functional linkage between the unilateral HNS and nasopharyngeal patency⁴⁰. In terms of predictive characteristics, unilateral correlations were found with age, AHI, ODI, and a prior

uvulopalatopharyngoplasty on a less desirable outcome. However, in multivariate analyses, none of the factors reached significance. The stimulation approach, implant positioning, or some other anatomical factors, all not captured by screening, could affect outcomes with the Inspire system.

Making a Center: Practice Experience and Implementation

Nerve stimulation therapy has produced a reappraisal of how CPAP-intolerant OSA is managed. The clinical trial program can be considered as a pilot plan for assessment of patients who might have failed oral appliance or anatomical surgery as a second option¹. Specifically, nerve stimulation, as currently envisioned, is an appropriate consideration for those who are unable to use or cannot tolerate CPAP, as opposed to a therapy that can be a lifestyle choice or desire for the “next new thing.” The initial conversation with the patient has to be an extended one. The discussion should include a review of all forms of attempted and available therapy to assure that the patient is informed about options, cost, and benefit. This is where a multidisciplinary team is needed. Professionals in sleep medicine, otolaryngology, and oromaxillofacial specialists, and dentistry provide expertise and key inputs so that all therapies are considered and available. Allied health sleep professionals are needed to manage patients over time. Implementation of short assessment protocols such as a nap with a CPAP device helps to determine whether the patient is truly intolerant or just needs education, a change of equipment, and/or interface adjustment. The process of rehabilitation when primary therapy fails would require a close collaboration among specialists to develop a strategy to achieve an optimal outcome, specifically in regard to new treatment options.

Once it has been determined that the patient is unable to tolerate positive pressure therapy and that an alternative mode of therapy is neither tolerated, feasible nor desirable, the discussion can turn toward the tests leading up to and following implantation (Figure 4). Eligibility and cost assessment also should be discussed during this part of the evaluation⁴⁶. Consideration needs to be given to the fact that the current device may interfere with future magnetic resonance imaging, although efforts have been made in this regard to improve both imaging and device materials so that this can be done safely.

Specialists with anatomical expertise and knowledge of inclusion and exclusion criteria will perform a detailed upper airway examination and DISE. Along the path from initial assessment to a decision that the candidate is appropriate for implantation are several opportunities to reinstate CPAP or an alternative strategy. In the STAR trial, more than 900 patients were screened but only approximately 135 met the criteria, as many did not meet the severity, DISE, or anatomical criteria.

A case management plan needs to be developed and coordinated across the several involved administrative and clinical structures in the medical/surgical center. A center offering stimulation therapy requires leaders who has an understanding of the role for this therapy in the broader context of treatments of OSA. Co-leaders could be a surgeon who has or gains expertise in implant placement and in DISE, and a sleep physician who will be engaged in longitudinal management of OSA before and after an implant. There should be a daytime

health-care associate to address patient concerns and issues, and a trained sleep technologist to perform the titration study. Practice and hospital administrators will need education about the purpose, manner, and cost of therapy. For a center to become highly competent and sustainable, a plan to perform about 30 implants a year will be needed, which means that the referral population is substantial. For a new center, the more time spent on planning, and on the recruitment and identification of appropriate candidates will result in a payoff in the rapid accrual of expertise. The suggestion is that the startup includes about 5 patients in the first month so that the procedures are tested and expertise is developed locally. Too large a gap between patients often requires retraining and readjustments in the program if key personnel are not engaged. Finally, there are financial considerations for the patient, the center, and the practitioners, and prior authorization, procurement logistics, DISE and operating room readiness, and scheduling are issues that vary from center to center.

Opportunities for Research

By this time, we expect the reader to have identified a number of questions relating to clinical utility and outcomes of upper airway stimulation as an approach to treat moderate-to-severe OSA. We have also identified some areas for consideration.

The indications and assessments are not currently based or assessed by measures in all the pathways that could lead to recurrent apneas and then OSA (Figure 1). For instance, what precisely is the anatomical problem, and does DISE identify airway closure relevant to “sleep” apnea? Is this really a prerequisite for successful upper airway stimulation? The failed Apnex trial and the current ImThera trial did not include DISE measures, so the value step may not be independently determined. However, the procedure has some independent value. For instance, it may be useful before and after a surgical treatment to stabilize the lateral walls of the nasopharynx⁴⁷. If possible, it should be used more routinely for assessment of non-surgical therapy.

Are there methods other than DISE to evaluate anatomical patency and provide specificity as to the site and manner of closure? The clinical characteristics that currently predict the success or failure of upper airway stimulation are likely to map anatomical factors of airway size and compliance. One can postulate that the BMI cutoff of $<34 \text{ kg/m}^2$ lowers the risk of having a high critical closing pressure, and the AHI upper limit represents a high loop gain and high closing pressure³⁸. If one could routinely perform measures to prevent critical closing pressure, one might be able to assess this pathway in all patients who fail CPAP. Even the introduction of this measure into a DISE procedure might be used to assess function, even with temporary stimulation^{48–50}.

Finally, what is the role of this therapy in regard to health services. Economic considerations are important. In the United States, the acknowledged willingness-to-pay threshold is \$50,000–\$100,000/QALY. Modeling on this threshold, the relative costs and benefits suggest that upper airway stimulation could be a cost-effective therapy in this healthcare system⁵¹. However, the willingness-to-pay threshold is a function of median income, so that it may not be directly applicable to other countries or systems.

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Rationale for Stimulation Therapy

Figure 1.

The four pathogenic pathways that in combination lead to recurrent OSA and to the development of the syndrome. If inadequate muscle activation could be reversed, even by itself, recurrent sleep apnea could be reversed at least in a subset of patients. Upper airway muscle and nerve stimulations are collectively called neurotherapeutics.

Effects of Stimulation

Figure 2.

In this strip chart polysomnogram recording (approximately 2 minutes), the stimulator is turned ON (as verified by the bursting of the chin EMG and then turned OFF, and then turned ON again. Abruptly, when the stimulator is turned OFF, there is upper airway obstruction, as illustrated by the flat nasal pressure signal, continued respiratory efforts, and a fall in oxygen saturation. (The thermistor signal is a thermal drift.) EEG = electroencephalogram. EOG = electrooculogram or eye movements. EMG = chin electromyogram. Snore = snore signal by microphone. THERM = thermistor at the nose for airflow. Nasal = nasal pressure transducer for flow. Chest and Abdm = chest and abdomen efforts, respectively, by inductance methods. SaO₂ = oxygen saturation by oximetry.

Figure 3.

These bars represent the results of the STAR trial for the Inspire therapy from baseline to 36 months. The median values (as the data are not normally distributed) of the apnea-hypopnea index and oxygen desaturation index are provided in the bar graph on the right. The subjective outcomes of the Epworth Sleepiness Scale (ESS) and functional outcomes of sleep questionnaire are also shown. There are significant differences ($p < 0.001$) between the baseline and each of the time points. Further discussion of the results is in the review.

Figure 4.

The concepts for the development of a case management plan for a center in terms of patient flow (left column) and system issues (right column).

Table 1

Table of Similarities and Differences among XII Nerve Stimulator Approaches

	Type	Detection/Trigger	Selection	Status
Apnex Medical	Multiple contacts cuff electrode, with inspiratory based activation	Impedance sensing from chest electrode, with synchronization	Patient selection by BMI and AHI with recruitment of protrusors	Phase III trial suspended and company closed 2013
Inspire Medical Systems	3-electrode circumferential cuff electrode on distal, medial terminal branches, with fixed sequence more to activate protrusors	Pressure sensing of effort from costal lead, with synchronization	Patient selection by BMI and AHI, then absence of concentric collapse at palate on DIS E,	Phase III trial completed and FDA approved 0 4/2014
ImThera Medical	6-contact circumferential cuff electrode, more proximal placement with rotating stimulation of electrodes to activate retrusors and protrusors	None	AHI <20, no tonsillar hypertrophy, and Mallipatti 0–3	In Phase III FDA trial