Hypoglossal Nerve Stimulation: Effective Long-term Therapy for Obstructive Sleep Apnea

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Obstructive sleep apnea (OSA) is a worldwide health problem. Historically, OSA was believed to be primarily anatomical in origin due to excess tissue obstructing the airway. Uvulopalatopharyngoplasty, the most common surgical approach, was aimed at resecting or ablating this tissue but failed to resolve OSA in 59% of patients. Contemporary research focuses on physiologic contributors to OSA, such as impaired airway dilator activity and failure of the neuromuscular feedback loop. Hypoglossal nerve stimulation is a new treatment option for eligible patients that addresses this neurofeedback-loop dysfunction. The hypoglossal nerve stimulator (Inspire Medical Systems, Maple Grove, MN) includes an implantable pacemaker-sized pulse generator that senses chest wall movement during sleep and contracts the genioglossus muscle via stimulation of the hypoglossal nerve. Genioglossus contraction gently protrudes the tongue, which enlarges the retrolingual and retropalatal levels of the airway. Early studies of the efficacy of hypoglossal nerve stimulation showed that apnea-hypopnea index scores decreased by 68% 12 months after stimulator implantation, with recipients reporting decreased sleepiness and OSA effects, and improved quality of life. Four-year follow-up results indicate ongoing effectiveness of therapy with regard to subjective measures of quality of life. To date, this device has been implanted in more than 1,800 patients.

Keywords: Hypoglossal nerve stimulation, obstructive sleep apnea, upper airway stimulation.

Objectives
1. Describe physiologic factors contributing to airway collapse in obstructive sleep apnea.
2. Describe the role of the hypoglossal nerve and genioglossus muscle in relation to pharyngeal patency during sleep.
3. List physiologic indications and contraindications to hypoglossal nerve stimulator implantation.
4. Describe the implantation procedure for a hypoglossal nerve stimulator, along with key anesthesia requirements.
5. Discuss factors affecting care of patients after hypoglossal nerve stimulator implantation and how this device may support and limit future perioperative care.

Introduction
Obstructive sleep apnea (OSA) is estimated to affect 7% to 16% of adults in the United States, although the actual incidence is likely much higher because many cases go undetected.\textsuperscript{1,2} Historically, airway obstruction was believed to be primarily anatomical, with soft tissue obstruction occurring at the level of the tongue, soft palate, or both.\textsuperscript{3} Uvulopalatopharyngoplasty involving substantial tissue resection was the most common surgical approach but resolved OSA in only 41% of patients.\textsuperscript{3} Of the patients without resolution, 84% still had major airway obstruction at the palate or oropharynx despite substantial tissue resection.\textsuperscript{3}

Because of these poor outcomes in surgical treatment of OSA, there has been increased focus on the physiologic factors in airway collapse such as intraluminal negative pressure forces and airway dilator muscle activity.\textsuperscript{4} The upper airway from the posterior nasal septum to the epiglottis has little bony or rigid support, leading to its comparison to and function as a collapsible tube.\textsuperscript{4} Two primary forces tend to promote airway collapse: negative intraluminal pressure generated by the diaphragm during inspiration, and positive extraluminal pressure exerted by tissue surrounding the airway lumen.\textsuperscript{4} To maintain a patent airway, these 2 collapsing forces must be offset by the action of the pharyngeal dilator muscles.\textsuperscript{4}

The primary pharyngeal dilator is the genioglossus
(GG) muscle, which forms the bulk of the tongue body. In patients without OSA, the GG responds to negative intraluminal airway pressure and collapse during sleep with increased dilatory activity to maintain a patent airway. In many patients with OSA, however, this neurofeedback loop is dysfunctional, allowing airway collapse and obstruction. Continuous positive airway pressure (CPAP) therapy ideally prevents this airway collapse by maintaining positive intraluminal pressure, but a large number of CPAP users are intolerant or noncompliant with its use. It is estimated that only 39% to 50% of patients use CPAP effectively on a long-term basis. Many others with OSA do not seek treatment at all because of few alternatives, leaving a great number of people inadequately treated.

**Hypoglossal Nerve Stimulation**

Hypoglossal nerve stimulation (HNS) is a Food and Drug Administration–approved treatment option for eligible patients with OSA. It targets the pharyngeal neuromuscular dysfunction of OSA by selectively stimulating the hypoglossal nerve, which elicits contraction of the GG muscle. Contraction of the GG muscle causes anterior advancement of the tongue body and stiffness of the anterior pharyngeal wall, which prevents pharyngeal collapse and obstruction, and directly enlarges the retroglossal airway.

Because of structural pharyngeal interconnections, HNS enlarges the retropalatal space along with the retrolingual space, thus providing multilevel treatment of OSA in appropriate patients (Figure 1). After implantation of a hypoglossal nerve stimulator, the retropalatal and retrolingual areas were found to increase by 180% and 130%, respectively. Early studies of HNS efficacy showed that the median apnea-hypopnea index (AHI) scores decreased by 68% at 12 months after implantation, from 29.3 to 9 events per hour. The AHI is an indicator of OSA severity, with 5 to 15 indicating mild; 15 to 30, moderate; and more than 30, severe. The oxygen desaturation index, the number of times per hour of sleep that blood oxygen levels decrease by 4 or more percentage points from baseline, decreased nearly 70% from 25 to 7 events per hour. Patients also reported decreased sleepiness and negative OSA effects and improved quality of life.

- **Device Components.** A hypoglossal nerve stimulator (Inspire Medical Systems, Maple Grove, MN) has 3 implantable components: a pulse generator, one sensing lead, and one stimulation lead (Figure 2). The implantable pulse generator (IPG) is similar in size and appearance to a standard pacemaker and is able to be activated by the patient immediately before sleep and deactivated during wakefulness. The IPG is connected to a sensing lead that is implanted over the rib cage and to a stimulation lead that is affixed to a submental branch of the hypoglossal nerve. The sensing lead sends information regarding inspiratory and expiratory chest wall motion to the IPG, which then triggers electrical stimulation of a distal hypoglossal nerve branch at end-expiration, thus preventing collapse before its onset. This direct stimulation of the hypoglossal nerve results in GG contraction and visible anterior movement of the tongue, which maintains patency of the retrolingual and retropalatal pharyngeal airway. Although direct electrical stimulation of the tongue would be painful, there is no discomfort or arousal with HNS because the hypoglossal nerve is a pure motor nerve and has no sensory component.

- **Selection Criteria.** Currently, HNS is indicated for patients with moderate OSA (AHI 15-30) to severe OSA (AHI > 30). Patients must also have a body mass index (BMI) of 32 kg/m² or less, failure of CPAP therapy, and a specific pharyngeal collapse pattern, as described below. A BMI above 32 kg/m² is a relative contraindication because patients with higher BMIs are less likely to respond to therapy. These patients usually have complex OSA dynamics with altered lung volumes, tracheal traction forces, and fat deposition in airway tissues.

- **Velopharyngeal Collapse Pattern.** Evaluation for HNS includes examination of the candidate’s velopharyngeal collapse pattern. The velopharynx is the smallest, most collapsible part of the airway and includes the pharynx, lateral walls, and uvula at the level of the soft palate. Collapse in this area can be anterior-posterior (AP), lateral (LC), or complete concentric (CCC; Figure 3). With AP collapse, anterior structures move toward the posterior pharyngeal wall, creating an oblong banana-
shaped lumen. In pure LC, which is rare, the lateral walls collapse toward midline with no AP movement. Complete concentric collapse is a combination of both AP and LC, with all of the velopharyngeal walls collapsing toward midline. On endoscopic examination, CCC is visualized as a circular squeezing of the velopharyngeal structures toward the center of the airway.

Identifying the pattern of velopharyngeal collapse is critical because HNS is indicated only in AP collapse patterns. Hypoglossal nerve stimulation moves anterior structures forward, which opens the airway in AP collapse but allows increased room for lateral structures to fall inward in LC or CCC patterns. Therefore, HNS will likely worsen OSA if the device is implanted in patients with an incorrect collapse pattern.

Drug-Induced Sleep Endoscopy

The velopharyngeal collapse pattern is best assessed in patients with active obstruction of their airway during sleep. Because this is not easily assessed during natural sleep, a fiberoptic nasolaryngoscopy is done at a level of anesthesia that mimics the pharyngeal muscle tone of natural sleep and resultant upper airway obstruction. A drug-induced sleep endoscopy allows dynamic examination of the airway during conditions that more closely resemble the reduced airway dilator muscle activity and loss of control of breathing that occurs during natural sleep. This sleep study evaluates upper airway structures and collapse patterns in patients with OSA, starting at the nasal septum and ending at the supraglottic larynx. For patients considering HNS therapy, a drug-induced sleep endoscopy is required to document their velopharyngeal collapse pattern.

Device Implantation

For patients who meet HNS criteria, implantation is a 60- to 90-minute surgical procedure involving subcutaneous insertion of 3 components: sensing lead, pulse generator, and stimulation lead. Patients receive a general anesthetic with no postinduction paralysis to allow intraoperative nerve stimulation and device testing. A roll is placed under the patient’s right torso to create a left tilt, and the arms are tucked bilaterally. This position provides access to the right lateral chest wall for sensing lead placement. A shoulder roll is also placed to extend the neck, improving submental access for stimulation lead placement. Fine wire electrodes are placed intraorally in the GG, hyoglossus, and styloglossus muscles for intraoperative assessment of tongue movement during stimulation. Isolation and stimulation of the incorrect nerve can retract the tongue and worsen OSA.

After sterile preparation and draping, an incision is made in the submandibular area and a hypoglossal nerve branch is isolated. Nerve stimulation is used to selectively choose the distal tongue protrusor muscle branches, which supply the GG muscle. The stimulation cuff electrode is placed around the appropriate nerve branches and secured.

A second incision is made in the right lateral aspect of the chest wall for placement of the respiratory sensing lead. The sensor is placed between the external and internal intercostal muscles at the fifth or sixth intercostal space and is secured to the chest wall.

A third incision is made in the right subclavicular area and a pocket created for the IPG, which is similar in appearance to a pacemaker generator. The sensing and stimulation leads are tunneled into this pocket and connected to the IPG, which is then secured to the pectoral fascia.

The device is tested intraoperatively to confirm proper sensing with chest movement, electrical activation of the GG, and visible tongue protrusion. Tongue protrusion is subtle but can be visualized intraoperatively by positioning a dental roll behind the tongue to locate it more anteriorly in the mouth. In patients with a preexisting pacemaker, proper function of both devices when in...
the activated mode is verified. After testing is complete, the HNS generator is deactivated to allow postoperative edema to diminish before determining settings and thresholds. Most HNS recipients can be discharged home within a few hours given the absence of airway incisions, minimal to no opioid requirement, and absence of substantial obesity according to the screening criteria.

Device Activation
Approximately 4 weeks after insertion, patients return to the surgeon’s office or similar setting for device activation. Electrical thresholds and timing are established and programmed. Patients receive a remote control to activate the device before sleep and deactivate on awakening and are educated on how to use the therapy and titrate settings within an individual preprogrammed range. At bedtime, the device is activated by placing the remote controller over the IPG. After a predetermined delay to allow for sleep onset, usually 30 to 45 minutes, the GG muscle is rhythmically activated from end-expiration through end-inspiration. The remote allows patients to have complete control over therapy with on, off, pause, and amplitude adjustment available within their set range (Figure 4).

After 30 days of use and self-titration of therapy, a repeat polysomnography sleep study is done to objectively assess results and fine-tune settings for optimal effectiveness (Figure 5). Patients are followed long term to monitor adherence, side effects, and subjective outcomes. The current IPG battery life expectancy is 10 years, and the second-generation device currently available is compatible with magnetic resonance imaging of the head and extremities, as per manufacturer guidelines.

Outcomes Data
The first 126 recipients of a hypoglossal nerve stimulator were included in an ongoing prospective multicenter study evaluating both objective and subjective measures of clinical safety and effectiveness, known as the Stimulation Therapy for Apnea Reduction (STAR) Trial. Initial results at 12 months after implantation showed a 68% decrease in median AHI from 29.3 to 9 events per hour and a 70% decrease in the oxygen desaturation index from 25.4 to 7.4 events per hour. Subjective measures of therapy effectiveness included scores on the Functional Outcomes of Sleep Questionnaire (FOSQ) and Epworth Sleepiness Scale (ESS), which both included significant improvement at 12 months compared with baseline. The FOSQ scores showed mean increases of 2.9, with higher scores indicating better functioning. The ESS scores decreased from 11.0 to 6.0, with lower scores indicating less daytime sleepiness.

The most recent published data of the STAR Trial include follow-up for 48 months after HNS, with 91 of the original 126 recipients still participating. This multicenter longitudinal observational study continues to assess subjective measures of success through the FOSQ, ESS, and Subject and Bed-Partner Scoring Scale. Sleep-related quality of life as measured by FOSQ significantly improved compared with baseline, and daytime sleepiness as measured by ESS was significantly reduced. Soft snoring or no snoring was reported by 85% of bed partners. These results indicate ongoing effectiveness of HNS therapy with regard to subjective measures of quality of life.

Subsequent Surgery
During subsequent surgeries, patients with a hypoglossal nerve stimulator will present with their device in the off mode. The stimulator can be activated with the patient’s remote control for sedation or regional anesthesia.
cases in which intraoperative upper airway obstruction is likely. Because each device has a preset time delay, stimulation will not begin immediately. The device can be activated in the recovery period as well, but this delay of onset must be considered.

As with pacemakers, bipolar electrocautery is preferable to monopolar to avoid electrical interference, and grounding pads should be placed as far from the IPG as possible. If defibrillation is required, pad or paddle placement should ideally not be over the IPG to avoid delivering shocks directly to the device. Options for paddle placement include left side anterior-posterior or left and right axilla. The hypoglossal nerve stimulator should be interrogated by qualified personnel any time there is a concern for proper function.

Adolescent Trials

More than 1,800 hypoglossal nerve stimulators have been implanted in adults in the United States and Europe since 2014. In April 2015, a CPAP-intolerant tracheostomy-dependent adolescent with Down syndrome and OSA underwent implantation with a hypoglossal nerve stimulator. Postimplantation results showed an AHI decrease from 48 to 3 and allowed permanent tracheostomy removal for this teenager. Following this, a multicenter prospective pilot study of HNS implant safety and efficacy in adolescents with Down syndrome and persistent moderate to severe OSA after adenotonsillectomy began across 5 medical centers in the United States. Results of this trial have not yet been published.

Conclusion

Hypoglossal nerve stimulation has proved to be an effective long-term treatment for select patients with OSA. By targeting the pharyngeal neuromuscular dysfunction of OSA, it approaches the treatment of OSA in a novel way. Hypoglossal nerve stimulation not only offers improvement of OSA symptoms and quality of life but also may reduce the incidence of OSA-associated comorbidities.

REFERENCES


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DISCLOSURES

The author has declared no financial relationships with any commercial entity related to the content of this article. The author did not discuss off-label use within the article.

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