Sleep Medicine Reviews 14 (2010) 299–305

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

THEORETICAL REVIEW

Electrical stimulation of the hypoglossal nerve in the treatment of obstructive sleep apnea☆

Eric J. Kezirian [a,e], An Boudewyns [b,*], David W. Eisele [a,f], Alan R. Schwartz [c,g], Philip L. Smith [c,h], Paul H. Van de Heyning [b,i], Wilfried A. De Backer [d,j]

[a] Department of Otolaryngology, Head and Neck Surgery, University of California, San Francisco School of Medicine, San Francisco, California, United States
[b] Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Antwerp, Belgium
[c] Johns Hopkins Sleep Disorders Center, Johns Hopkins School of Medicine, Baltimore, Maryland, United States
[d] Department of Pulmonary Medicine, University Hospital Antwerp, Belgium

ARTICLE INFO

Article history:
Received 27 July 2009
Received in revised form
24 October 2009
Accepted 26 October 2009
Available online 29 January 2010

Keywords:
Obstructive sleep apnea syndrome
Upper airway
Genioglossus
Hypoglossal nerve
Electrical stimulation

SUMMARY

Upper airway occlusion in obstructive sleep apnea has been attributed to a decline in pharyngeal neuromuscular activity occurring in a structurally narrowed airway. Surgical treatment focuses on the correction of anatomic abnormalities, but there is a potential role for activation of the upper airway musculature, especially with stimulation of the hypoglossal nerve and genioglossus muscle. We present evidence from research on upper airway neuromuscular electrical stimulation in animals and humans. We also present results from eight obstructive sleep apnea patients with a fully implanted system for hypoglossal nerve stimulation, demonstrating an improvement in upper airway collapsibility and obstructive sleep apnea severity. Future research, including optimization of device features and stimulation parameters as well as patient selection, is necessary to make hypoglossal nerve stimulation a viable alternative to positive airway pressure therapy and upper airway surgical procedures.

Introduction

Sleep-disordered breathing results from a combination of factors affecting upper airway patency and the control of ventilation.[1] Although positive airway pressure therapy is the primary treatment for patients with moderate to severe obstructive sleep apnea syndrome, poor compliance and/or refusal is an issue in up to 40–50% of these patients.[2] Alternatives to positive airway pressure therapy include mandibular repositioning appliances or surgical procedures that treat either soft tissue (resection, repositioning, or stiffening) or bony anatomy.[3] Both modalities aim to correct specific anatomic abnormalities that may play a role in upper airway narrowing and collapse during sleep. Although the mechanisms underlying upper airway collapse are incompletely understood, there is clearly a decline in pharyngeal neuromuscular activity during sleep compared to wakefulness in obstructive sleep apnea patients.[1] This knowledge has supported the notion that stimulation of upper airway muscles may prove effective.

Previous reports have indicated that various upper airway dilator muscles, especially the genioglossus, play a role in maintaining upper airway patency during sleep. Investigators have considered tensor veli palatini function in animals [4] and humans,[5] but the majority of research related to electrical stimulation of upper airway musculature has described the tonic and reflexive activation of the genioglossus muscle during wake and sleep.[1] Consequently, methods have been explored to stimulate selectively upper airway dilator muscles, particularly the genioglossus.

Animal studies

Miki et al. conducted some of the first animal experiments in this area and inserted needle electrodes perorally into the genioglossus of awake and spontaneously breathing dogs.[4] A decrease in upper

☆ Portions of the research described in this manuscript were supported by Medtronic. Inspire™ is a trademark of Inspire Medical Systems, Inc.
* Corresponding author. Tel.: +32 3 821 33 85; fax: +32 3 825 05 36.
E-mail addresses: ekezirian@ohns.ucsf.edu (E.J. Kezirian), an.boudewyns@uza.be (A. Boudewyns), deisele@ohns.ucsf.edu (D.W. Eisele), aschwar2@jhmi.edu (A.R. Schwartz), plsmith@jhmi.edu (P.L. Smith), paul.van.de.heyning@uza.be (P.H. Van de Heyning), wilfried.debacker@ua.ac.be (W.A. De Backer).
[e] Tel.: +415 353 2479; fax: +415 353 2603.
[f] Tel.: +415 502 0498.
[g] Tel.: +410 550 0572; fax: +410 550 3374.
[h] Tel.: +410 550 2507; fax: +410 550 2612.
[i] Tel.: +32 3 821 47 90; fax: +32 3 821 44 51.
[j] Tel.: +32 3 821 34 47; fax: +32 3 821 44 47.

1087-0792/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.smrv.2009.10.009

Nomenclature

AHI	apnea/hypopnea index
EEG	electroencephalogram
EMG	electromyogram
EOG	electrooculogram
HGN	hypoglossal nerve
NREM	non-REM sleep
Pcrit	critical closing pressure
Pes	esophageal pressure
PN	nasal pressure
REM	rapid eye movement sleep
SaO_2	oxygen saturation
$V_I$max	maximal inspiratory airflow

airway resistance was observed with progressively increasing stimulation frequencies up to 50 Hz. Schwartz et al. investigated the influence of bilateral supramaximal hypoglossal nerve (HGN) stimulation on upper airway mechanics in the feline upper airway (isolated, anesthetized, and unanesthetized).[5] A graded increase in maximal inspiratory airflow ($V_I$max) was observed with increasing stimulation frequency. The improvement in $V_I$max could be attributed to lower upper airway collapsibility (reflected by a decrease in the critical closing pressure, or *P*crit), but the result was partially offset by a concomitant increase in upstream airway resistance in the unanesthetized group.

Oliven et al. studied pressure-flow relationships of the upper airway during selective stimulation of the HGN in anesthetized dogs.[6] Stimulation resulted in a significant decrease in upper airway resistance and an increase in *P*crit and $V_I$max compared to controls. Eisele et al. conducted studies in the isolated feline upper airway to investigate how upper airway mechanics were altered by differential electrode placement along the HGN and the ansa cervicalis.[7] From these data, it was concluded that any substantial decrease in upper airway collapsibility by HGN stimulation is dependent upon the activation of the genioglossus and that electrode placement on the proximal or distal segment of the HGN results in comparable improvements in $V_I$max. Bishara et al. confirmed the importance of electrode placement and stimulation of specific upper airway muscles; in anesthetized but spontaneously breathing dogs. Selective stimulation of the genioglossus with intramuscular fine wire electrodes was more effective in reducing upper airway resistance and eliminating upper airway obstruction than stimulation of other upper airway muscles.[8]

Bailey et al. have examined selective versus whole HGN stimulation in anesthetized rats to evaluate the differential effects of activation of protrusor muscles versus coactivation of protrusor and retrusor muscles, respectively.[9] Both methods showed increases in upper airway stiffness, suggestive of decreases in *P*crit, although the effects varied depending on baseline airway dimensions.[9] Fregosi also showed that both coactivation and selective protrusor activation lowered *P*crit in anesthetized rats, with a slightly greater improvement with selective stimulation of protrusor muscles.[10] Finally, Bailey et al. also showed that coactivation occurred under conditions of physiologic HGN stimulation (e.g., hypercapnea) in anesthetized, spontaneously breathing rats.[11]

Goding et al. reported data on chronic stimulation of the HGN in dogs.[12] These authors followed six dogs in which a cuff electrode (Medtronic, Inspire™ 3990 lead) was implanted bilaterally around the HGN. At 4 weeks after implantation, night-time HGN stimulation occurred for 8 h per day, 7 days a week, for 8 weeks, although it was only delivered to one hypoglossal nerve on a given night. At the conclusion of the 8 weeks, a tracheotomy was performed, and hypoglossal electrical stimulation resulted in improvement in airflow during induced airway obstruction. One of the most important findings, however, was the absence of any damage to the nerve secondary to chronic stimulation. These results suggested that long-term stimulation of the HGN in humans might be safe.

Yoo et al. compared the functional effect of selective and nonselective HGN stimulation in anesthetized beagles implanted with a flat interface nerve electrode.[13] This electrode allows for selective stimulation of nerve branches innervating different upper airway muscles (geniohyoid, genioglossus, hyoglossus, and styloglossus). During inspiration, whole nerve stimulation and selective stimulation with coactivation of the genioglossus and hyoglossus/styloglossus resulted in a significant improvement of airway collapsibility as reflected by a decrease in the critical closing pressure. During expiration, whole nerve stimulation yielded a significantly greater increase in upper airway caliber than selective stimulation of the geniohyoid or genioglossus muscle. From these experiments it was deduced that both nonselective whole HGN stimulation and selective stimulation with coactivation of tongue protrusor (genioglossus) and retrusor (hyoglossus/styloglossus) muscles improve upper airway stability in beagles.

Human studies

The first attempts to improve upper airway patency in humans by transcutaneous submental and intraoral electrical stimulation of upper airway muscles were made by Guilleminault et al.[14] These first experiments, however, were considered to be a failure. About 10 years later, Miki et al. reported their experience with genioglossus intramuscular stimulation using an apnea-demand type stimulator in obstructive sleep apnea patients.[15] A decrease in apnea index and an improvement in sleep architecture could be documented. Later, these investigators used a portable airflow-demand-type submental stimulator and reported similar findings.[16] In this second study, however, it was acknowledged that only a partial improvement could be obtained with a decrease in the apnea index from 53.8 ± 7.0 to 27.3 ± 5.7 ($p < 0.05$) and persistence of sleepiness.

The Miki et al. early favorable results, however, could not be reproduced by subsequent studies in other centers. Successful stimulation of upper airway muscles and relief of upper airway obstruction without causing arousal from sleep could not be obtained with either submental or intraoral stimulation,[17] by submental electrodes or fine wire electrodes placed into the neurovascular bundle,[18] or by transcutaneous electrical stimulation applied in the submental or infrahyoid regions.[19]

Smith et al. also failed to obtain a significant improvement in airway patency without causing arousal when transcutaneous stimulation was applied through the submandibular region.[20] When transoral fine wire electrodes were inserted into the genioglossus, however, tongue protrusion and contralateral deviation (consistent with genioglossus activation) were obtained during wakefulness. Posterior, rather than anterior, placement of the electrodes resulted in tongue retraction due to activation of the styloglossus and hyoglossus (retrusor) muscles.[20]

Selective stimulation of upper airway muscles during sleep has been performed using transoral, intramuscular fine wire electrodes in patients with obstructive sleep apnea.[21] Stimulus bursts were first applied during single inspirations with application of low levels of nasal continuous positive airway pressure. A significant improvement in maximal inspiratory airflow from 288.1 ± 176.2 ml/s to 501.4 ± 195 ml/s ($p < 0.001$) was obtained during protrusor (genioglossus) stimulation, whereas a significant decrease in $V_I$max was obtained with retrusor (hyoglossus/styloglossus) stimulation. In these studies, stimulation did not cause arousal from sleep. Although no attempts were made to measure upper airway collapsibility (critical

pressure, *P*crit) in these studies, the observed increase in $V_I$max during genioglossus stimulation implied a fall in *P*crit of approximately 4.8 cm H_2O.[22] When stimulation was applied during consecutive inspirations, a significant decrease of sleep-disordered breathing episodes without worsening of sleep architecture was observed.

The effect of coactivation of tongue protrusors and retractors on pharyngeal collapsibility was further studied in subjects with obstructive sleep apnea during natural sleep (using surface intraoral electrodes) and during propofol sedation (using a combination of surface and intramuscular electrodes).[23] In both experimental conditions, electrical stimulation of tongue retractors (hyoglossus) was found to increase *P*crit and upstream resistance whereas combined genioglossus and hyoglossus stimulation resulted in a decrease in *P*crit. During natural sleep, surface electrode genioglossus stimulation had no effect on *P*crit, whereas during propofol sedation intramuscular stimulation produced a similar drop in *P*crit to combined genioglossus and hyoglossus stimulation. There are multiple potential explanations for the differential effects of surface electrode stimulation during natural sleep vs. intramuscular stimulation during propofol sedation. The authors suggest that surface intraoral stimulation activates the superior, vertically-oriented fibers that do not produce the anterior displacement of the tongue that is seen with the anteroposterior fibers in the inferior and middle portions of the muscle that can be activated with intramuscular electrodes. Other factors such as differences in the effect of stimulation during natural sleep or propofol sedation or difficulties with proper positioning of surface electrodes might contribute as well.

Parameters influencing stimulation efficacy

A multicenter collaboration supported in part by Medtronic Inc. (Minneapolis, Minnesota, USA) culminated in the development of a permanent, implanted electrode for HGN stimulation during sleep. Our work in HGN electrical stimulation has considered stimulation parameters, stimulation timing, and patient selection and their effect on outcomes. Selected relevant studies utilizing direct intramuscular stimulation are included in this discussion.

Stimulation frequency

Stimulation frequency, amplitude and pulse duration should be great enough to produce tetanic contraction of the muscle. Generally, a stimulation frequency of >30 Hz is required for this purpose. Thereafter, increases in frequency, amplitude, or pulse duration all produce progressively increasing levels of muscle recruitment. Frequency-pressure curves for the diaphragm [24] and for skeletal muscles [25] have been published and were found to be very similar. Muscle force is almost maximal at stimulation frequencies above 50 Hz. Therefore, it has been speculated that the frequency force curve of the genioglossus would be similar and that adequate stimulation frequency to obtain maximal airway opening would lie between 50 and 100 Hz.[4] Schwartz et al. also demonstrated a frequency-dependent effect of continuous stimulation on upper airway function.[5] Hida et al. studied pressure-volume relationships in an animal model during continuous electrical stimulation of the HGN.[26] At a stimulation frequency of 10 Hz, the results were similar to those without stimulation. At frequencies of 30 Hz or greater, a decrease in the slope of the pressure-volume curve was observed, indicating a decrease in upper airway compliance or stiffening of the pharynx. This effect plateaued at frequencies above 50 Hz.

Stimulation amplitude

Decker et al. used fine wire electrodes or submental stimulation with large amplitudes (10–20 V), a frequency of 50 Hz, and a pulse duration of 0.2 m sec.[18] They found that the amplitude needed to induce EEG arousal from sleep was significantly higher than that producing barely tolerable sensation during wakefulness. Nevertheless, both levels of electrical stimulation during apneic events caused interruption of apnea only 22 and 23% of the time. It is worth noting that the study by Guilleminault et al. that showed no benefits of electrical stimulation utilized high stimulation amplitudes up to 20 V for transcutaneous submental stimulation and up to 15 V for intraoral stimulation.[17] Although not proven, it is likely that these high voltages may have contributed to stimulation related arousals, as Miki et al. reported no evidence of arousals with intramuscular stimulation at amplitudes of 15–40 V.

Pulse duration

When stimulating skeletal muscles directly, a marked increase in muscle tension can be obtained with increasing pulse duration to a range of 0.2–1.0 ms.[27] Pulse duration is limited by the fact that longer pulse duration typically causes discomfort.

Timing of the stimulation with respect to the respiratory pattern

In the studies by Miki et al., an apnea-demand type stimulator was used for timing of surface submental stimulation.[15] Stimulation began 5 s after apnea onset and switched off when airflow resumed or after 10 s, whichever came first. No stimulation was applied during periods of decreased airflow (hypopneas), and the timing of stimulation was not dependent on the respiratory cycle. Decker et al. also applied surface submental stimulation solely during apneas.[18] Guilleminault et al. stimulated at different phases of the respiratory cycle with submental and intraoral electrodes, including during obstructive events or before the onset of events; none of these stimulation paradigms was found to be successful.[17] Our experience suggests that (intramuscular) stimulation at the onset of inspiration, as used by Schwartz et al., seems to be the most successful in obtaining an improvement in airflow.[21] This work demonstrated that airflow returns to baseline at offset of stimulation, and there is no hysteresis effect on the upper airway, requiring stimulation with the onset of each inspiratory effort.[21]

Prevention of arousal

When patients arouse during stimulation, the observed increase in airflow may be attributed to a generalized activation of the pharyngeal muscles rather than to an isolated recruitment of the stimulated muscle. Hypoglossal nerve stimulation is less likely to produce arousal because the nerve is pure motor, as opposed to the sensory stimulation associated with direct intramuscular stimulation. The greater success reported in Schwartz et al. [21] compared to other studies may be explained by the former's use of intramuscular stimulation techniques that allowed for more selective recruitment of the genioglossus muscle to occur without sensory activation or arousal.

Patient selection according to the primary site of upper airway obstruction

In the isolated feline upper airway preparation, the flow limiting site is located at a discrete locus slightly upstream to the free edge of the soft palate.[5] The improvement in $V_I$max obtained by HGN stimulation in these animals could be explained by a decrease in the pressure exerted by the tongue on the ventrolateral surface of the soft palate, suggesting that tongue protrusion may improve upper airway function through an indirect effect on the soft palate position.

In humans, pattern of obstruction has not shown a consistent relationship with response to genioglossus stimulation. Edmonds et al. used CT scans to investigate the effect of voluntary tongue protrusion on upper airway dimensions in humans.[19] A borderline significant enlargement of the velopharynx was observed that was attributed to anterior tension exerted on the palatoglossus and the body of the soft palate. Moreover, in the experiments with genioglossus stimulation in obstructive sleep apnea patients conducted by Schwartz et al., two patients were thought to have primarily oropharyngeal/hypopharyngeal obstruction, and five patients were felt to have primarily velopharyngeal obstruction.[21]

This is in accordance with more recent data published by Oliven et al. who found that the presumed location of pharyngeal collapse did not affect the response to electrical stimulation of the genioglossus.[28] In a subsequent study, Oliven et al. investigated the effect of genioglossus intramuscular stimulation in obstructive sleep apnea patients under deep propofol sedation (unresponsive to painful stimuli).[29] Measurement of upper airway pressure/flow relationships was combined with fiberoptic endoscopy during genioglossus stimulation. Under propofol unconscious sedation, the velopharynx was a primary site of collapse in all study patients. Genioglossus electrical stimulation lowered *P*crit at both the oropharynx (decrease 4.2 ± 2.9 cm H_2O) and velopharynx (decrease 2.3 ± 1.9 cm H_2O), with a statistically significant greater reduction in the oropharynx. Anterior displacement of the tongue base during stimulation (visualized on endoscopy) was associated with greater reduction in velopharyngeal *P*crit. One potential explanation is that tongue prolapse contributes to palatal collapse through a direct mechanical effect. The authors observed similar changes in *P*crit in patients with a sagittal narrowing of the velopharynx and in those with a more transverse narrowing (indicating lateral wall collapse) and suggested that genioglossus electrical stimulation may also exert a mechanical effect on the lateral pharyngeal walls.

Although one would intuitively expect that genioglossus activation would be effective only for patients with tongue base obstruction, these observations support the presence of a non-neural interaction between upper airway segments and indicate that the lingual musculature modulates collapsibility at multiple pharyngeal segments. Whether the site of upper airway obstruction is a major determinant of the success of stimulation requires further investigation. Oliven et al. found that genioglossus electrical stimulation responses were related neither to obstructive sleep apnea severity (in terms of apnea-hypopnea index or baseline *P*crit) nor to the site and pattern of upper airway closure or pharyngeal compliance.[29] Most of these studies of electrical stimulation and airway collapsibility (measured by *P*crit) were performed under conditions of propofol sedation or general anesthesia, with low or absent upper airway dilator muscle activity (passive *P*crit). Because natural sleep includes greater levels of dilator muscle activity, the effects on disordered breathing events and upper airway collapsibility during natural sleep (active *P*crit) may differ substantially. Since only horizontally and diagonally oriented genioglossus muscle fibers can advance the posterior part of the tongue, it was suggested that stimulation methods might be improved by focusing on stimulation of relevant genioglossus fibers rather than by selection of patients with specific patterns of obstruction.[29]

Another mechanism that may modulate the association between response to hypoglossal or genioglossus electrical stimulation and either site of obstruction or upper airway collapsibility is the importance of ventilatory control factors such as loop gain.[30]These factors may play a major role in the pathophysiology of sleep disordered breathing (varying in importance for individual patients), and improvements in upper airway mechanics alter control mechanisms.[31]

Functional electrical stimulation of the hypoglossal nerve by an implantable device: the Inspire™ I system

Description of the system

A stimulating device was designed to synchronize HGN stimulation with inspiration using the Inspire™ I system (Medtronic Inc., Minneapolis, Minnesota, USA). Eight patients were included in a feasibility study, and those results are presented below. Full details have been published previously.[32]

This system (Fig. 1) consisted of the following:

- *A half-cuff stimulation lead*. The electrode cuff consisted of molded silicone rubber and has a tripolar electrode design. This tripolar design confined the stimulation current to the electrode cuff and prevented unwanted current spread. The electrode was connected via a subcutaneous lead with the implantable pulse generator.
- A custom designed *implantable pulse generator* was placed subcutaneously in the region of the pectoralis muscles. This programmable unit was capable of sensing intrathoracic pressure and synchronizing stimulation with inspiration.
- A *respiratory pressure sensor* was implanted through a hole drilled in the midline of the manubrium and connected with the implantable pulse generator by means of a subcutaneous lead.
- The investigators used a *programming system* to determine the optimal stimulus parameters. The most important parameters were 1) stimulation amplitude; 2) pulse width; 3) stimulation frequency.
- The patient received a *patient programmer* that allowed her/him to switch the stimulation on prior to sleep and off upon awakening.

The device was implanted under general anesthesia and the electrode was placed unilaterally on a peripheral branch of the HGN that innervated the genioglossus muscle and distal to the anterior branch of the ansa hypoglossi. Stimulation was triggered by the patient's respiratory pattern and stimulation started just prior to onset of inspiration and continued for the duration of inspiration, provided that a previously programmed expiratory refractory period had elapsed.

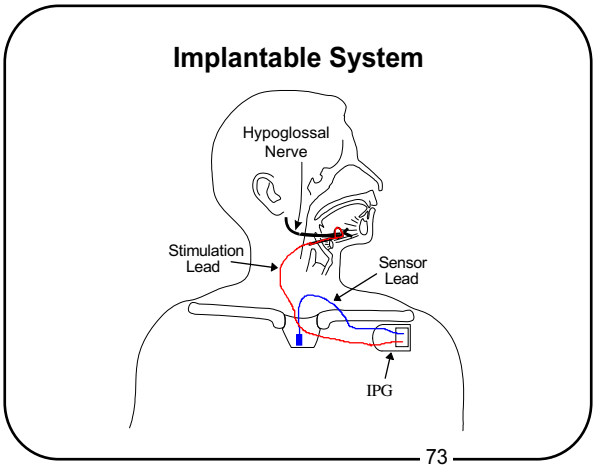

Fig. 1. Schematic representation of the Inspire™ I system for hypoglossal nerve stimulation in OSA patients. The stimulator (implantable pulse generator–IPG) is connected to the respiratory sensor by means of a sensor lead. A stimulation lead connects the stimulator to the half-cuff electrode around the hypoglossal nerve.

Clinical results

Eight patients at 4 participating centers were implanted between 1996 and 1997 (Johns Hopkins University Hospital, Baltimore ($n = 3$), Antwerp University Hospital, Belgium ($n = 3$), Sahlgrenska University Hospital Goteborg, Sweden ($n = 1$), Phillips University of Marburg, Germany (n = 1)).

Patients were middle-aged (range 36–57 years), overweight men (body mass index 28.4 ± 4.5 kg/m^2) with moderate to severe obstructive sleep apnea syndrome (NREM AHI 52.0 ± 20.4 and REM AHI 48.2 ± 30.5). Before implantation, each patient was using nasal continuous positive airway pressure treatment, and this was discontinued at the start of the trial. Two patients had previously undergone uvulopalatopharyngoplasty.

The patients were followed for a period of at least six months ($n = 8$) with polysomnography at intervals of 1, 3, and 6 months following implantation. A last follow-up polysomnography was performed in 6 patients with functioning devices after 345 ± 97 days.

Stimulation was initiated 4 weeks after implantation and stimulus parameters were adjusted over time depending on motor recruitment threshold, pain threshold, and the obtained alleviation of sleep-disordered breathing episodes without EEG arousals. The effect of stimulation on airflow and sleep architecture is illustrated in Fig. 2.

In an intention-to-treat analysis, the entire night's recording was evaluated with exception of the initial 30–60 min period, required for adjustment of stimulus parameters. These data demonstrate a significant decrease in the AHI from a baseline value of 52.0 ± 20.4 to 22.6 ± 12.1 during NREM sleep ($p < 0.001$) and from 48.2 ± 30.5 to 16.6 ± 17.1 during REM sleep ($p < 0.001$). The effect of stimulation on AHI at different follow-up times is illustrated in Fig. 3.

Sleep stage analysis demonstrated a trend towards improved sleep architecture, including a reduction in stage 1 NREM sleep and an increase in slow wave sleep during stimulation. There was no evidence of arousals from sleep related to stimulation. Occasionally, the onset of stimulation was associated with a brief arousal from sleep, as documented by polysomnography. However, this did not prevent the patient from continuing to sleep, and frequent arousals or awakenings from sleep were not observed.

The chronic use of HGN stimulation did not cause any detectable alterations in the tongue (atrophy, hypertrophy or fasciculations). None of the patients reported discomfort during sleep because of the stimulation or in the morning upon awakening. The patients did not have problems using the patient programmer.

The implantable stimulating device was well tolerated by the patients, who reported good treatment compliance with continuous use of the stimulator on a nightly basis for at least six months. Device malfunction occurred in 5 patients; in all cases this occurred more than 6 months following implantation. Because financial support for replacement parts had been withdrawn from the study, stimulation treatment was suspended in these cases and was abandoned after the internal power supply had been depleted in the remaining patients.

Effect of HGN stimulation on upper airway function

Previous experiments in the isolated feline upper airway demonstrated that the improvement in $V_I$max with HGN stimulation could be attributed to a decrease in upper airway collapsibility.[5] The effect of HGN stimulation on upper airway function was studied in 5 of the 8 patients treated with the fully implantable Inspire™ I system.[28]

The response to electrical stimulation was studied by evaluating the changes in upper airway pressure-flow relationships during sleep following a standardized protocol.[33] Airflow was measured at multiple levels of nasal pressure, and upper airway collapsibility was defined as the nasal pressure below which airflow ceased (the critical pressure, *P*crit). Measurements were made during stage II-III NREM sleep and during periods with and without stimulation. Stimulation parameters were those that had previously been used to treat the patient at home.

Stimulation of the HGN resulted in a significant decrease of *P*crit from -1.32 ± 1.97 to -5.30 ± 3.30 cm H_2O ($p < 0.05$) without altering upstream resistance 19.80 ± 7.93 versus 20.04 ± 6.27 cm H_2O/L/s.

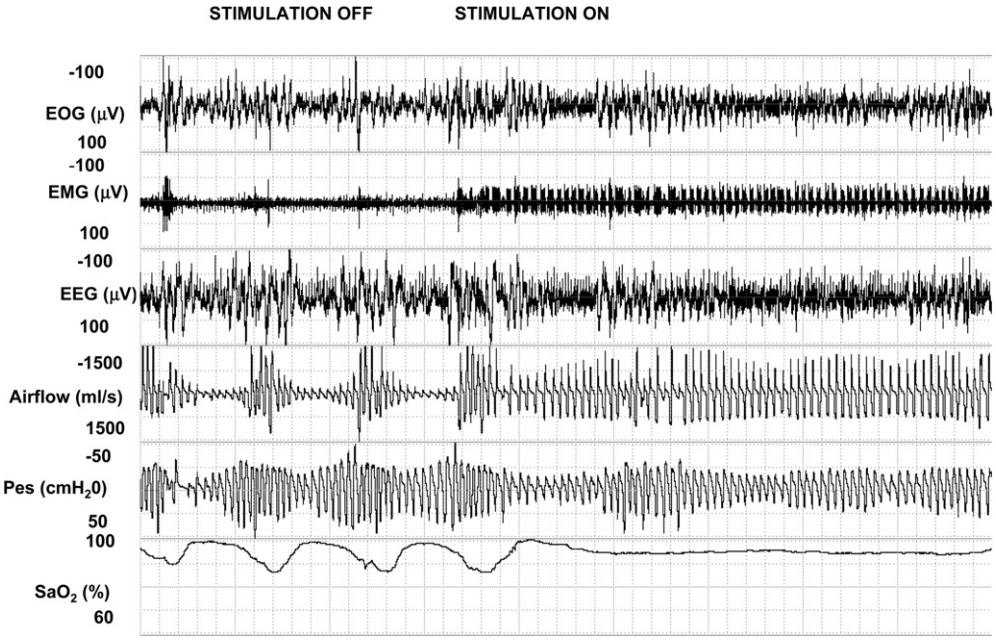

Fig. 2. Effect of hypoglossal nerve stimulation on sleep and respiratory parameters. From top to bottom: Electrooculogram (EOG), Chin Electromyogram (EMG), Electroencephalogram (EEG), Airflow, Esophageal pressure (Pes), oxygen saturation (SaO_2). At the left hand of the figure, breathing without HGN stimulation is shown with repeated hypopneas, arousals and drops in oxygenation. At the right hand, the effect of stimulation is evidenced with normalization of respiration and oxygen saturation. Note the stimulus artifact on the EMG tracing and the absence of arousals on the EEG tracing during stimulation.

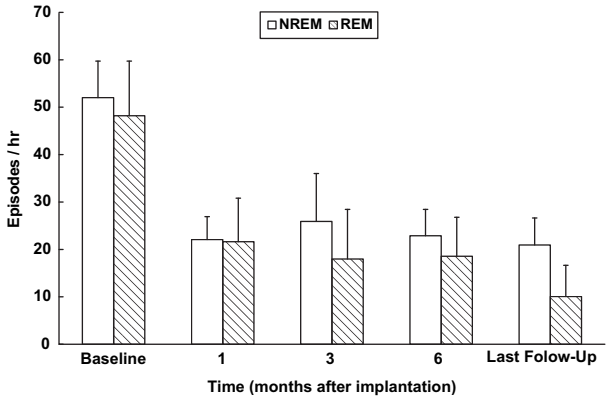

Fig. 3. Effect of HGN stimulation on AHI. NREM and REM AHI at baseline, 1 month, 3 months and 6 months after implantation and at last follow-up.

The difference in *P*crit between stimulated and unstimulated conditions was 3.98 ± 2.31 cm H_2O. The decrease in upper airway collapsibility during stimulation resulted in a marked improvement of $V_I$max from 75.8 ± 98.4 ml/s at baseline to 261.4 ± 123.8 ml/s. The effect of hypoglossal nerve stimulation upon upper airway collapsibility in a representative patient is illustrated in Fig. 4.

The response to stimulation was determined by the baseline *P*crit and the magnitude of the *P*crit fall with stimulation. When *P*crit fell below ~ -4 cm H_2O, there was resolution of disordered breathing events. Patients who will be most likely to respond to stimulation will be those with an initial *P*crit in the range of 0 to -4 cm H_2O, given the mean decrease of ~ 4 cm H_2O during HGN stimulation.[34–37]

Based on animal studies and data from temporally implanted patients, it was predicted that HGN stimulation would result in a fall of *P*crit by about 5 cm H_2O.[20] The present results confirm this prediction and suggest the clinical utility of HGN stimulation in patients with a near atmospheric *P*crit at baseline.

In contrast to the experience with direct genioglossus stimulation, there was an association between the site of obstruction and outcomes, in that the greatest improvements were seen in three patients with primarily retroglossal obstruction on pressure transducer catheter testing and one patient who had not responded to previous uvulopalatopharyngoplasty.[31] However, patients with retropalatal obstruction also demonstrated notable improvements in $V_I$max during HGN stimulation, underscoring the important role of the tongue in pharyngeal airflow and the pathogenesis of sleep-related breathing disorders.

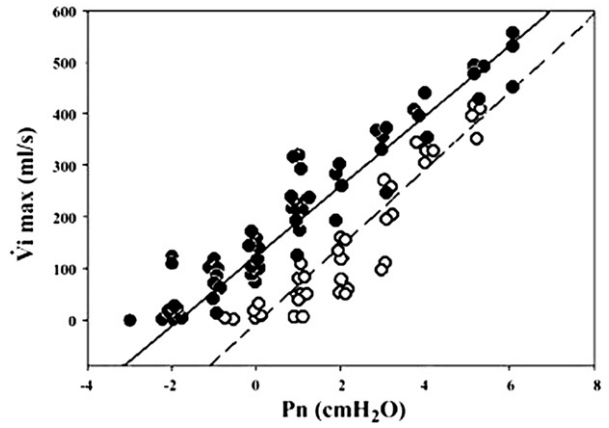

Fig. 4. Pressure-flow relationships over the range of flow limitation in a representative OSA patient before (open circles) and after (closed circles) hypoglossal nerve stimulation. NREM AHI decreased from 80.8 at baseline to 10.0 episodes/hr during continuous stimulation and NREM *P*crit dropped from -0.4 cm at baseline to -2.4 cm H_2O during HGN stimulation. $V_I$max, maximal inspiratory flow. Pn=nasal pressure.

Although our data from chronic stimulation in dogs [12] as well as our clinical experience in patients with obstructive sleep apnea [32] indicate that long-term HGN stimulation by the Inspire™ I system is safe, concern has been risen that chronic nerve stimulation would cause damage to the HGN.[38] This was not our experience with the Inspire™ I system, as no tongue neuromuscular changes occurred grossly. One potential alternative, should this occur, would include an approach taken with diaphragmatic pacing and phrenic nerve stimulation: stimulation of distinct portions of the nerve with special electrodes that enabled variation in the location of stimulation.

Another treatment option requiring further investigation is the use of non-invasive, sublingual surface electrical stimulation. Oliven et al. reported a significant increase in peak inspiratory flow rate and a decrease in pharyngeal resistance for both healthy subjects and OSA patients.[39] In addition, electrical stimulation of the genioglossus muscle resulted in a similar decrease of upper airway collapsibility with a fall of *P*crit by 3.18 ± 1.70 cm H_2O during HGN stimulation.[28]

Conclusions

Both direct intramuscular and HGN stimulation result in activation of the genioglossus muscle and a predictable improvement in upper airway collapsibility, reflected by decreases in *P*crit. Functional electrical stimulation of the hypoglossal nerve by the Inspire™ I system results in an improvement of sleep-related breathing disorders in carefully selected patients. HGN stimulation may be considered as an alternative to positive airway pressure therapy in patients with obstructive sleep apnea, especially in those with moderately increased upper airway collapsibility.

Practice points

Selective stimulation of the hypoglossal nerve during sleep may

- offer a surgical treatment alternative in whom positive airway pressure therapy is unsuccessful or not tolerated
- result in a physiological approach to treat obstructive sleep apnea based on the restoration or improvement of upper airway dilator muscle activity during sleep
- provide insight into upper airway function during sleep in obstructive sleep apnea

Research agenda

- The long-term safety, feasibility, and efficacy of HGN stimulation in humans needs to be established
- Techniques must be developed to allow for optimal placement of the electrode around the hypoglossal nerve in order to avoid nerve injury or recruitment of muscle fibers that result in tongue retrusion or have no benefit
- The possible role of coactivation of various upper airway muscles must be explored
- Optimal stimulus parameters must be investigated and refined
- Investigation of methods to select patients that are most likely to benefit from HGN stimulation, with a focus on obstructive sleep apnea severity, site of obstruction and the degree of collapsibility (*P*crit)

Financial disclosures

Kezirian: Apneon (consultant), Apnex Medical (medical advisory board, consultant), Medtronic (consultant), Pavad Medical (consultant).

Boudewyns: Inspire Medical Systems (investigator).

Eisele: Apnex Medical (consultant), Inspire Medical Systems (consultant).

Schwartz: Apnex Medical (medical advisory board, consultant).

Smith: Apnex Medical (medical advisory board, consultant).

De Backer: Inspire Medical Systems (consultant).

Van de Heyning: Inspire Medical Systems (consultant).

Acknowledgements

Dr. Kezirian is currently supported by a career development award from the National Center for Research Resources (NCRR) of the National Institutes of Health and a Triological Society Research Career Development Award of the American Laryngological, Rhinological, and Otological Society. This project was supported by NIH/NCRR/OD UCSF-CTSI Grant Number KL2 RR024130. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

References

1. White DP. Pathogenesis of obstructive and central sleep apnea. *Am J Respir Crit Care Med* 2005;**172**:1363–70.
2. Kribbs NB, Pack AI, Kline LR, Smith PL, Schwartz AR, Schubert NM, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Respir Dis* 1993;**147**:887–95.
3. Boudewyns AN, Marklund M, Hochban W. Alternatives for OSAHS treatment: selection of patients for upper airway surgery and oral appliances. *Eur Respir Rev* 2007;**16**:1–14.
4. Miki H, Hida W, Shindoh C, Taguchi O, Inoue H, Takishima T. Effects of electrical stimulation of the genioglossus on upper airway resistance in anesthetized dogs. *Am Rev Respir Dis* 1989;**140**:1279–84.
*5. Schwartz AR, Thut DC, Russ B, Seelagy M, Yuan X, Brower RG, et al. Effect of electrical stimulation of the hypoglossal nerve on airflow mechanics in the isolated upper airway. *Am Rev Respir Dis* 1993;**147**:1144–50.
*6. Oliven A, Odeh M, Schnall RP. Improved upper airway patency elicited by electrical stimulation of the hypoglosssus nerves. *Respiration* 1996;**63**:213–6.
*7. Eisele DW, Schwartz AR, Hari A, Thut DC, Smith PL. The effects of selective nerve stimulation on upper airflow mechanics. *Arch Otolaryngol Head Neck Surg* 1995;**121**:1361–4.
*8. Bishara H, Odeh M, Schnall RP, Gavriely N, Oliven A. Electrically-activated dilator muscles reduce pharyngeal resistance in anaesthetized dogs with upper airway obstruction. *Eur Respir J* 1995;**8**:1537–42.
9. Bailey EF, Fregosi RF. Pressure-volume behaviour of the rat upper airway: effects of tongue muscle activation. *J Physiol* 2003;**15**:563–8.
10. Fregosi RF. Influence of tongue muscle contraction and dynamic airway pressure on velopharyngeal volume in the rat. *J Appl Physiol* 2008;**104**:682–93.
11. Bailey EF, Jones CL, Reeder JC, Fuller DD, Fregosi RF. Effect of pulmonary stretch receptor feedback and CO_2 on upper airway and respiratory pump muscle activity in rat. *J Physiol* 2001;**15**:525–34.
*12. Goding GS, Eisele DW, Testerman R, Smith PL, Roertgen K, Schwartz AR. Relief of upper airway obstruction with hypoglossal nerve stimulation in the canine. *Laryngoscope* 1998;**108**:162–9.
13. Yoo PB, Durand DM. Effects of selective hypoglossal nerve stimulation on canine upper airway mechanics. *J Appl Physiol* 2005;**99**:937–43.
14. Guilleminault C, Hill MW, Simmons FB, Dement WC. Obstructive sleep apnea: electromyographic and fiberoptic studies. *Exp Neurol* 1978;**62**:48–67.
15. Miki H, Hida W, Chonan T, Kikuchi Y, Takishima T. Effects of submental electrical stimulation during sleep on upper airway patency in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1989;**140**:1285–9.
16. Hida W, Takishima T. The effect of submental electrical stimulation on sleep disordered breathing in patients with obstructive sleep apnea. *Sleep* 1993;**16**:S96–7.
17. Guilleminault C, Powell N, Bowman B, Stoohs R. The effect of electrical stimulation on obstructive sleep apnea syndrome. *Chest* 1995;**107**:67–73.
18. Decker MJ, Haaga J, Arnold JL, Atzberger D, Strohl KP. Functional electrical stimulation and respiration during sleep. *J Appl Physiol* 1993;**75**:1053–61.
19. Edmonds LC, Daniels BK, Stanson AW, Sheedy PF, Shepard JW. The effects of transcutaneous electrical stimulation during wakefulness and sleep in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1992;**146**:1030–6.
20. Smith PL, Eisele DW, Podszus T, Penzel T, Grote L, Peter JH, et al. Electrical stimulation of upper airway musculature. *Sleep* 1996;**19**:S284–7.
*21. Schwartz AR, Eisele DW, Hari A, Testerman R, Erickson D, Smith PL. Electrical stimulation of the lingual musculature in obstructive sleep apnea. *J Appl Physiol* 1996;**81**:643–52.
22. Gleadhill IC, Schwartz AR, Schubert NM, Wise RA, Permutt S, Smith PL. Upper airway collapsibility in snorers and in patients with obstructive hypopnea and apnea. *Am Rev Respir Dis* 1991;**143**:1300–3.
23. Oliven A, Odeh M, Geitini L, Oliven R, Steinfeld U, Schwartz AR, et al. Effect of coactivation of tongue protrusor and retractor muscles on pharyngeal lumen and airflow in sleep apnea. *J Appl Physiol* 2007;**103**:1662–8.
24. Moxham J, Morris AJ, Spiro SG, Edwards RH, Green M. Contractile properties and fatigue of the diaphragm in man. *Thorax* 1981;**36**:164–8.
25. Edwards RH. Physiological analysis of skeletal muscle weakness and fatigue. *Clin Sci Mol Med* 1978;**54**:463–70.
26. Hida W, Kurosawa H, Okabe S, Kikuchi Y, Midorikawa J, Chung YT, et al. Hypoglossal nerve stimulation affects the pressure-volume behavior of the upper airway. *Am J Respir Crit Care Med* 1995;**151**:455–60.
27. Hultman E, Sjoholm H, Jaderholm-Ek I, Krynicki J. Evaluation of methods for electrical stimulation of human skeletal muscle in situ. *Pflugers Arch* 1983;**398**:139–41.
*28. Oliven A, O'Hearn D, Boudewyns A, Odeh M, De Backer W, Van de Heyning P, et al. Upper airway response to electrical stimulation of the genioglossus in obstructive sleep apnea. *J Appl Physiol* 2003;**95**:2023–9.
29. Oliven A, Tov N, Geitini L, Steinfeld U, Oliven R, Schwartz AR, et al. Effect of genioglossus contraction on pharyngeal lumen and airflow in sleep apnoea patients. *Eur Respir J* 2007;**30**:1–11.
30. Wellman A, Malhotra A, Jordan AS, Stevenson KE, Gautam S, White DP. Effect of oxygen in obstructive sleep apnea: role of loop gain. *Respir Physiol Neurobiol* 2008;**162**:144–51.
31. Longobardo GS, Evangelisti CJ, Cherniack NS. Analysis of the interplay between neuromechanical control of respiration and upper airway mechanics producing upper airway obstruction in humans. *Exp Physiol* 2008;**93**:271–87.
*32. Schwartz AR, Benett ML, Smith PL, De Backer W, Hedner JA, Boudewyns A, et al. Therapeutic electrical stimulation of the hypoglossal nerve in obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg* 2001;**127**:1216–23.
33. Boudewyns A, Punjabi N, Van de Heyning P, De Backer WA, O'Donnell CP, Schneider H, et al. Abbreviated method for assessing upper airway function in obstructive sleep apnea. *Chest* 2000;**118**:1031–41.
34. Schwartz AR, Gold AR, Schubert NM, Stryzak A, Wise RA, Permutt S, et al. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1991;**144**:494–8.
35. Schwartz AR, Schubert NM, Rothman W, Godley F, Marsh B, Eisele DW, et al. Effect of uvulopalatopharyngoplasty on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1992;**145**:527–32.
36. Gold AR, Schwartz AR. The pharyngeal critical pressure. The whys and hows of using nasal continuous positive airway pressure diagnostically. *Chest* 1996;**110**:1077–88.
*37. Patil SP, Schneider H, Marx JJ, Gladmon E, Schwartz AR, Smith PL. Neuromechanical control of upper airway patency during sleep. *J Appl Physiol* 2007;**102**:547–56.
38. Mann EA, Burnett T, Cornell S, Ludlow CL. The effect of neuromuscular stimulation of the genioglossus on the hypopharyngeal airway. *Laryngoscope* 2002;**112**:351–6.
*39. Oliven A, Schnall RP, Pillar G, Gavriely N, Odeh M. Sublingual electrical stimulation of the tongue during wakefulness and sleep. *Respir Physiol* 2001;**127**:217–26.

*The most important references are denoted by an asterisk.