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THEORETICAL REVIEW

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

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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

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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