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Editorial

Hypoglossal nerve stimulation—Optimizing its therapeutic potential in obstructive sleep apnea

Obstructive sleep apnea is characterized by recurrent periods of upper airway obstruction (apneas and hypopneas) during sleep, leading to nocturnal hypercapnia, repeated oxyhemoglobin desaturations and arousals [1]. It is a highly prevalent condition affecting 4 to 24% of men and 2 to 9% of women, and well over 50% of obese individuals [2–6]. Obstructive sleep apnea is a major cause of morbidity and mortality in Western society [7–11], and contributes significantly to the development and progression of neurocognitive, metabolic, cardiovascular, and oncologic diseases [2,8,12–21]. Sleep apnea treatment is plagued by poor adherence to nasal continuous positive airway pressure (CPAP) [22] despite efficacy in the sleep laboratory. Alternatively, surgical or medical weight loss strategies can offer definitive treatment, although responses in sleep apnea to weight loss are variable, and significant sleep apnea remains in nearly 50% of patients even after massive weight loss [23–27]. Moreover, despite advances in understanding neurochemical control of ventilation and pharyngeal patency during sleep [28], effective pharmacologic treatments and alternatives to CPAP are still lacking.

The development of pharyngeal obstruction during sleep has been widely attributed to a loss of pharyngeal neuromuscular activity. Initially, investigators focused on the role of dilator muscles, viz., the genioglossus, in maintaining pharyngeal patency by preventing the tongue from prolapsing into the pharynx [29]. This concept gave rise to the development of electrical pacemakers for the hypoglossal nerve to treat sleep apnea by augmenting genioglossus activity during sleep [30]. In early pre-clinical trials, investigators demonstrated that hypoglossus and direct genioglossus electrical stimulation led to marked decreases in pharyngeal collapsibility [31] and relief of airflow obstruction during sleep [32,33]. These proof-of-concept studies in humans and animals spurred the development of fully implantable hypoglossal nerve stimulating systems for therapeutic purposes [34].

To date, therapeutic efficacy of several implantable hypoglossal stimulating systems has been examined in several early stage "feasibility" trials [34–38] and one "pivotal" trial [39]. Despite differences in patient selection, implantation site and stimulating paradigms, these studies have demonstrated consistent improvements in sleep apnea, as reflected by decreases in the apnea–hypopnea index, a major metric of disease severity. Nevertheless, significant residual sleep apnea has been observed in these trials with approximately a third of patients failing to demonstrate adequate responses to hypoglossal nerve stimulation therapy [39]. The reasons for suboptimal responses to hypoglossal stimulation, however, remain unclear.

In an effort to optimize responses to hypoglossal stimulation, investigators employed a variety of strategies to refine patient inclusion criteria. One approach has been to restrict enrollment in clinical trials to patients with only mild to moderate obesity, in whom elevations in pharyngeal collapsibility are less pronounced than those with severe obesity [40–44]. Another approach has been to exclude patients with the most severe sleep apnea [37,39], who may require dramatic improvements to fully treat their disorder. In these patients, hypoglossal stimulation may not stiffen the airway sufficiently to overcome marked elevations in pharyngeal collapsibility, thereby limiting the improvement pharyngeal patency during sleep [42,45]. Investigators have suggested that such patients can be identified by the predominance of complete rather than partial airway obstruction (obstructive apneas vs. hypopneas) on routine sleep study [35]. Alternatively, investigators have suggested that the site and pattern of pharyngeal collapse [34], as assessed during drug-induced sleep endoscopy, could predict responders to hypoglossal stimulation [39]. It is possible that anterior movement of lingual structures during hypoglossal stimulation produces greater responses in those with retroglossal rather than retropalatal obstruction [34]. The primary site of obstruction is usually located in the retropalatal airway [46,47], which could account for residual sleep apnea during hypoglossal nerve stimulation in many patients. Nevertheless, some improvements in pharyngeal patency and sleep apnea can still be observed in patients with retropalatal obstruction, particularly in those demonstrating a high degree of mechanical linkage or "coupling" between tongue and palatal structures [48–50]. Lingual–palatal coupling could also account for the development of pharyngeal collapse predominantly in the antero-posterior rather than lateral dimension during drug-induced sleep endoscopy [37,50]. In contrast, concentric collapse of the pharyngeal lumen in both the antero-posterior and lateral dimensions has been identified as a potentially important negative predictor of responses to hypoglossal stimulation [37]. Nonetheless, considerable work is still required in large numbers of implanted patients to optimize selection criteria and predict responses to hypoglossal stimulation.

Therapeutic responses to hypoglossal stimulation may depend on which lingual muscles are recruited by stimulating the hypoglossal nerve. These muscles are recruited dynamically along with other pharyngeal, cervical and respiratory pump muscles to integrate aerodigestive functions of the upper airway. Reductions in neuromuscular tone can increase airway collapsibility by decreasing caudal traction on pharyngeal structures [51] and/or by decompressing tissues around the pharynx [52]. Effects of lingual muscles on pharyngeal patency [53–55] have traditionally been largely attributed to the protrusor action of the genioglossus. This muscle can prevent the tongue from prolapsing into the pharynx, while unopposed action of the styloglossus and hyoglossus muscles retracts the tongue and occludes the pharynx [32]. When these muscles were activated physiologically

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or stimulated electrically, however, they acted in concert to stabilize tongue position and maintain retrolingual airway patency [56,57]. They also modulated retropalatal patency through the zone of apposition between the dorsum of the tongue and anterior surface of the soft palate, particularly in lean compared to obese individuals [49,58–60]. In further studies, investigators demonstrated heterogeneous responses to stimulating horizontally- and vertically-oriented genioglossus fibers. They found that horizontal fibers, which move the base of the tongue anteriorly, were more effective in restoring airway patency [61]. In fact, anterior tongue movement produced the greatest improvements in airway patency in subjects whose tongue and soft palate encroached more markedly on the pharyngeal lumen than did lateral pharyngeal wall tissues [61,62]. Actions of these extrinsic lingual muscles can be further modulated by intrinsic tongue muscles that markedly alter the conformation of the tongue. Thus, complex interactions of lingual and other muscles can modulate pharyngeal patency by controlling the shape, stiffness and position of the tongue [63].

Various combinations of lingual muscles can be recruited by stimulating specific segments of the hypoglossal nerve at different intensities. In general, proximal nerve stimulation recruits tongue protrusor and retractor muscles, whereas distal stimulation isolates the action of protrusor muscles [32,33]. These observations led investigators to suggest that stimulating the entire hypoglossal nerve distally instead of proximally conferred a therapeutic advantage [34], which was later confirmed in a follow-up study [37]. Distal stimulation, however, is also likely to recruit genioglossus fibers that depress the tongue, which counteract beneficial effects of muscle fibers that dilate the pharynx [55]. Stimulating the proximal nerve, on the other hand, likely activates muscles that both retract and protrude the tongue to variable degrees [33,55,64], making it difficult to predict its overall effect on pharyngeal patency. Thus, stimulating the distal and proximal hypoglossal nerve can activate combinations of lingual protrusor, retractor and depressor muscles that can attenuate responses in pharyngeal patency and sleep apnea severity.

In the current issue of the Journal of Neurological Sciences, Zaidi et al. describe methods for activating specific lingual muscles alone and in combination. Using an elegant multi-contact lead to stimulate specific sectors of the rat hypoglossal nerve, these investigators examined differential effects of targeted stimulation on tongue position, shape and airway size. Their approach was motivated by prior work suggesting topographic organization of nerve fibers within the hypoglossal nerve [65–69], despite the absence of well-defined histological fascicles [68]. A recent clinical report also demonstrated improvements in sleep apnea with multi-channel hypoglossal stimulation [70] that were comparable to those obtained with whole nerve stimulation [34,35,37,38]. In the present study, the investigators demonstrated unique recruitment patterns with differential activation of specific lingual muscles when specific nerve sectors were stimulated with a circumferential electrode array. They also achieved greater degrees of airway opening with selective stimulation of a relatively discrete group of proximal hypoglossal nerve fibers compared to stimulating the distal medial branch *en masse*, which innervates both lingual protrusor and depressor muscles. Moreover, these investigators demonstrated that responses could be independently titrated by steering current between two contacts, thereby recruiting combinations of tongue muscles innervated by specific nerve fibers in a graded fashion. Of note, unilateral stimulation also produced some degree of airway opening on the contralateral side. Finally, stimulation could be applied to specific electrodes in alternating cyclical fashion to minimize the risk of neuromuscular fatigue. Taken together, the investigators' findings suggest that selective stimulation of specific lingual muscles (or groups of muscles) both in isolation and in combination can achieve greater degrees of airway opening than stimulating the whole proximal or distal hypoglossal nerve.

The authors' findings in rats highlight the potential that selective stimulation of the hypoglossal nerve can optimally treat obstructive sleep apnea. The advantages of this approach could be further quantified if investigators also demonstrate improvements in upper airway function. Concomitant reductions in pharyngeal collapsibility [54,55,71–74] and/or increases in airflow [33,75,76] with stimulation would serve to stabilize ventilation and abolish obstructive apneas and hypopneas. Additional work is still required to develop methods for identifying combinations of lingual muscles that act synergistically to maintain airway patency during sleep. These methods may necessitate steering current between specific electrodes as well as novel approaches for visualizing effects of stimulation on tongue shape, position, and stiffness. Some 25 years of work on hypoglossal stimulation have clearly demonstrated its therapeutic potential, and have ushered in a new frontier designed to optimize effects on pharyngeal patency and obstructive sleep apnea.

Conflict of interest

Dr. Schwartz' laboratory currently receives research support from ImThera. Dr. Schwartz previously served as a scientific advisor to Medtronics and Apnex Medical on hypoglossal stimulation therapy.

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