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Back to the Future or Forward to the Past?

Commentary on Eastwood et al. Treating obstructive sleep apnea with hypoglossal nerve stimulation. SLEEP 2011;34:1479-1486.

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The report by Eastwood and colleagues[1] in this issue of *SLEEP* on the efficacy and safety of a new generation hypoglossal nerve stimulator for treating patients with obstructive sleep apnea (OSA) reminded me of the movie "Back to the Future" in which Marty McFly uses a plutonium-powered DeLorean time machine to travel back in time and then return to the present. The concept of hypoglossal nerve stimulation to prevent airway collapse received a flurry of attention over a decade ago but since then has languished. Now, a new generation hypoglossal nerve stimulator promises to propel us from that past into the future development of a potentially new treatment option for patients with OSA. Have we found our "time machine" that will allow hypoglossal stimulation to finally achieve clinical application?

Many patients with OSA are unable to tolerate positive airway pressure treatment. Alternative treatments have failed to gain widespread clinical application. Weight loss, oral mandibular advancement devices, and surgical procedures to widen and stiffen the pharyngeal airway often fail to reduce the apnea-hypopnea index (AHI) to clinically acceptable levels.[2-4] Investigators in the past have attempted to treat patients with OSA by electrical stimulation of pharyngeal muscles during sleep. Although the potential feasibility and efficacy of this approach have been demonstrated in studies dating back to at least 1994, the technology was never successfully developed to the point that allowed its use in clinical practice. Interest in this potential treatment is now re-emerging perhaps due to technological advances.[1,5]

The implanted neurostimulator tested by Eastwood et al.[1] in this single-arm interventional trial transmits electrical signals to an implanted cuff electrode on the ipsilateral hypoglossal nerve allowing selective activation of the tongue protrudor muscles. The device monitors respiration via implanted thoracic leads that sense changes in bioimpedance with chest wall motion, delivering stimulation immediately prior to and during the inspiratory phase of respiration, when the upper airway is most vulnerable to sleep related narrowing and collapse. Stimulation was normally set to start automatically according to a predefined time-of-day schedule, but it can also be operated in a manual mode depending on patient preference. Twelve of the 18 participants (67%) who performed a post-operative polysomnogram at 6 mo had a reduction of the AHI to < 20 events/h (the cut-off for inclusion) and a > 50% reduction of AHI from baseline. For the whole group, the mean AHI decreased by 55% to 19.5 events/h at 6 mo. This reduction in AHI was associated with a significant subjective improvement in daytime sleepiness and daytime function.

The 1978 landmark study of Remmers et al.[6] reporting the direct relationship between loss of genioglossus muscle activation during sleep and upper airway closure in patients with OSA led to early attempts to treat the disorder by electrically stimulating pharyngeal muscles used transcutaneous, intraoral, and intramuscular electrodes. Transcutaneous delivery of the stimulus using submental electrodes has the advantage of being non-invasive but causes a non-specific, localized activation of underlying muscles and the stimulus can cause arousals.[7] Intramuscular wire electrodes and intra-oral transmucosal electrodes have similar disadvantages. None of these techniques have been evaluated as chronic treatments. Eisele et al.[8] and Schwartz et al.[9] were the first to show that hypoglossal nerve stimulation could decrease the severity of OSA without arousing patients from sleep. Although these reports demonstrated the feasibility of the technique, technical limitations with the device stalled its further development. Returning to this past, the new generation hypoglossal stimulator tested by Eastwood and colleagues[1] may jump-start this intervention into a new treatment option for patients with OSA.

As with any invasive procedure, safety of an implanted nerve stimulator is of primary importance. Potential concerns about this are partially allayed by the considerable experience gained with vagal nerve stimulators.[10] In the 21 patients enrolled by Eastwood et al.,[1] 2 (10%) developed serious device-related adverse events: an infection requiring device removal and a stimulation lead cuff dislodgement requiring replacement. Although at least one adverse event related to the implantation procedure or therapy occurred in the majority of the participants, these were relatively minor and transient. The rate of freedom from system (device or therapy) or procedure-related serious adverse events at 3 mo was 90.2% (19/21 participants) and at 6 mo was 85.2% (18/21 participants). Further studies are needed to assess the long term safety of this novel treatment approach, particularly if it is extended to bilateral stimulation in an effort to further improve the treatment's efficacy.

It is possible that chronic electrical stimulation of the hypoglossal nerve during sleep may lead to beneficial alterations in tongue structure and function. Previous studies show an improvement in AHI with electrical activation and exercise of the pharyngeal muscles but the explanation for this improvement is unknown.[11-13] A recent study reports that fat content of the

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tongue is directly related to body mass index.[14] In contrast, no relationship was found between body mass index and the fat content of the sternocleidomastoid and psoas muscles. This differential fat deposition in the tongue may help explain its increased volume in patients with OSA that predisposes to pharyngeal airway collapse. One can speculate that repetitive, daily electrical stimulation of the tongue muscles may mobilize these fat deposits, decrease tongue volume, and thereby reduce the likelihood of pharyngeal airway collapse during sleep. This hypothesis could be tested by assessing changes in tongue fat content with MRI following weeks to months of the hypoglossal nerve stimulation treatment and correlating this with changes in AHI without hypoglossal stimulation.

The concept of hypoglossal nerve stimulation is not new but its application in this novel device will hopefully allow this intervention to achieve its long intended clinical application. At present, however, its potential role in clinical treatment has once again been raised, but its future remains uncertain. Given the prevalence of OSA, this invasive and therefore relatively expensive treatment, is unlikely to ever become a primary treatment for OSA. However, treatment options other than positive airway pressure are needed. Hopefully, the new generation hypoglossal stimulator will be the vehicle we have been looking for to propel us from the past into the future.

CITATION

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REFERENCES

1. Eastwood PR, Barnes MB, Walsh JH, et al. Hypoglossal nerve stimulation and sleep apnea. Sleep 2011;34:1479-86.
2. Foster GD, Sanders MH, Millman R, et al. Obstructive sleep apnea among obese patients with type 2 diabetes. Diabetes Care 2009;32:1017–9.
3. Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. Sleep 2006;29:244–62.
4. Caples SM, Rowley JA, Prinsell JR, et al. Surgical modifications of the upper airway for obstructive sleep apnea in adults: a systematic review and meta-analysis. Sleep 2010;33:1396–1407.
5. Kezirian EJ, Boudewyns A, Eisele DW, et al. Electrical stimulation of the hypoglossal nerve in the treatment of obstructive sleep apnea. Sleep Med Rev 2010;14:299–305.
6. Remmers J, deGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. J Appl Physiol 1978;44:931–8.
7. Steier J, Seymour J, Rafferty GF, et al. Continuous transcutaneous submental electrical stimulation in obstructive sleep apnea: a feasibility study. Chest Epub ahead of print, 1 April 2011.
8. Eisele DW, Smith PL, Alam DS, Schwartz AR. Direct hypoglossal nerve stimulation in obstructive sleep apnea. Arch Otolaryngol Head Neck Surg 1997;123:57–61.
9. Schwartz AR, Bennett ML, Smith PL, et al. Therapeutic electrical stimulation of the hypoglossal nerve in obstructive sleep apnea. Arch Otolaryngol Head Neck Surg Obes Relat Dis 2001;2011:1216–1223.
10. Kamath MV, Thomson MS, Gaitonde S, Upton A. Longer-term effects of implanted vagal nerve stimulation. J Long Term Eff Med Implants 2010;20:251–67.
11. Randerath WJ, Galetke W, Domanski U, Weitkunat R, Ruhle K. Tongue-muscle training by intraoral electrical neurostimulation in patients with obstructive sleep apnea. Sleep 2004;27:254–9.
12. Puhan MA, Suarez A, Lo Cascio C, Zahn A, Heitz M, Braendi O. Didgeridoo playing as alternative treatment for obstructive sleep apnoea syndrome: randomised controlled trial. Brit Med J 2006;332:266–70.
13. Guimaraes KC, Drager LF, Genta PR, Marcondes BF, Lorenzi-Filho G. Effects of oropharyngeal exercises on patients with moderate obstructive sleep apnea. Am J Respir Crit Care Med 2009;179:858–9.
14. Nashi N, Kang S, Barkdull GC, Lucas J, Davidson TM. Lingula fat at autopsy. Laryngoscope 2007;117:1467–73.