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Hypoglossal-Nerve Stimulation for Obstructive Sleep Apnea

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Obstructive sleep apnea has well-established neurocognitive and cardiovascular sequelae.¹ Conservative estimates suggest that approximately 13% of men and 6% of women in North America have clinically important obstructive sleep apnea.² Despite the transformative benefits in some patients who receive therapy with continuous positive airway pressure (CPAP),³ many patients remain inadequately treated owing to inconsistent levels of adherence to existing therapies. Thus, further research is required to allow new therapeutic options to evolve.

Traditionally, obstructive sleep apnea has been defined by anatomical compromise in which soft tissues and craniofacial structures around the pharyngeal airway lead to increased airway collapsibility.⁴ Because of protective reflexes, the pharyngeal airway maintains patency during wakefulness, but, during sleep, loss of these reflexes reduces the activity of the pharyngeal dilator muscle, causing collapse of the susceptible airway.¹ Instability of ventilatory control, in which fluctuations in output from the central pattern generator in the brain stem lead to variable output to the diaphragm and upper-airway muscles, also contributes to obstructive sleep apnea.^{5,6} Recent findings suggest that therapies can be directed in an individualized manner to treat specific subgroups of patients with obstructive sleep apnea.⁷ For example, patients with obstructive sleep apnea due primarily to velopharyngeal compromise may have a good response to palatal surgery, whereas those with unstable ventilatory control may improve with agents such as oxygen or acetazolamide, which can stabilize the breathing pattern. In theory, strategies that increase activity in the pharyngeal dilator muscles should be effective for patients who have dysfunction in these muscles.⁸ Thus, a concept is emerging that personalized medicine may be applied to obstructive sleep apnea on the basis of underlying mechanisms.¹

In this issue of the *Journal*, Strollo et al.⁹ report the results of a study that tested the hypothesis that hypoglossal-nerve stimulation may be an effective therapy for patients who have obstructive sleep apnea possibly related to ineffectiveness in the pharyngeal dilator muscles. In this industry-sponsored, uncontrolled, prospective trial, the authors investigated the effect of hypoglossal-nerve stimulation on the severity of obstructive sleep apnea among patients who had moderate-to-severe obstructive sleep apnea and had not had a response to CPAP therapy. They identified patients with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 32 or less and further screened for the

nature of pharyngeal collapse by means of endoscopy performed while the patient was under propofol-induced anesthesia. Hypoglossal-nerve stimulation was associated with significant improvement in the primary outcomes, including reduction in the frequency of respiratory events (29.3 events per hour at baseline to 9.0 events per hour at 12 months) and the oxygen desaturation index score (the number of times per hour of sleep that the blood oxygen level dropped by ≥ 4 percentage points from baseline; 25.4 to 7.4 events per hour).

The authors also performed a randomized, therapy-withdrawal trial to assess the effects of hypoglossal-nerve stimulation among patients who had had a response, and they found that the reduction in the severity of obstructive sleep apnea was maintained among those who continued the therapy, as compared with those who had it withdrawn (whose severity metrics reverted toward baseline values). Thus the proportion of patients who had a response to hypoglossal-nerve stimulation is unclear, but a subgroup of patients had clear improvement with therapy. Although hypoglossal-nerve stimulation required surgical implantation, serious adverse events were uncommon (occurring in $<2\%$ of the patients), and the side effects were not particularly bothersome to most patients.

Several points deserve emphasis. First, the population studied was carefully selected, and only a minority of screened patients underwent implantation. Although one could question the generalizability of the study, a substantial proportion of patients would probably benefit from the therapy, on the basis of the known patho-physiology of obstructive sleep apnea. Second, some residual disease was seen during the therapy, as shown by a score on the apnea-hypopnea index (the number of apneas plus hypopneas per hour of sleep) of 9.0 events per hour at 12 months, leading to an interpretation that obstructive sleep apnea was reduced but not eliminated by hypoglossal-nerve stimulation. Although the elimination of apnea would clearly be desirable, the observed reductions are probably similar to the benefits observed with CPAP, particularly when one considers the variability of adherence to CPAP therapy. Third, the experimental design was an unblinded, prospective, open-label study, without a concomitant control group. Diet, exercise, or other unmeasured factors may have changed during the course of the study and could have contributed to the observed reduction in obstructive sleep apnea. Indeed, a competing trial (ClinicalTrials.gov number, NCT01446601) failed to show a between-group difference in the reduction of sleep apnea, owing to major unanticipated improvements in the control group. However, the results of the randomized, therapy-withdrawal trial provide reassurance that the benefits from hypoglossal-nerve stimulation observed by Strollo et al. were real.

Fourth, the cost-effectiveness of the therapy must be considered. Clearly, the consequences of untreated apnea may be considerable, and thus the cost of hypoglossal-nerve stimulation may be justifiable if major complications of untreated apnea, such as stroke and motor vehicle accidents, could be avoided.^{10,11} Furthermore, surgical procedures that are currently performed for obstructive sleep apnea without major benefits may be replaced by hypoglossal-nerve stimulation over time. Fifth, to refine patient selection, sophisticated analyses of airflow signals and other focused biomarkers may ultimately make it possible to identify before implantation patients with pharyngeal-muscle dysfunction who might benefit from hypoglossal-nerve stimulation.

Despite possible limitations, the new data provide the rationale to consider therapy with hypoglossal-nerve stimulation for selected patients with obstructive sleep apnea who have difficulties with CPAP therapy and to design more definitive randomized, controlled studies or comparative-effectiveness trials focused on hard outcomes in the future.

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