ORIGINAL ARTICLE

Therapeutic Electrical Stimulation of the Hypoglossal Nerve in Obstructive Sleep Apnea

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Background: Hypoglossal nerve stimulation has been demonstrated to relieve upper airway obstruction acutely, but its effect on obstructive sleep apnea is not known.

Objective: To determine the response in obstructive sleep apnea to electrical stimulation of the hypoglossal nerve.

Methods: Eight patients with obstructive sleep apnea were implanted with a device that stimulated the hypoglossal nerve unilaterally during inspiration. Sleep and breathing patterns were examined at baseline before implantation and after implantation at 1, 3, and 6 months and last follow-up.

Results: Unilateral hypoglossal nerve stimulation decreased the severity of obstructive sleep apnea throughout the entire study period. Specifically, stimulation significantly reduced the mean apnea-hypopnea indices in non–rapid eye movement (mean±SD episodes per hour, 52.0±20.4 for baseline nights and 22.6±12.1 for stimulation nights; $P<.001$) and rapid eye movement (48.2±30.5 and 16.6±17.1, respectively; $P<.001$) sleep and reduced the severity of oxyhemoglobin desaturations. With improvement in sleep apnea, a trend toward deeper stages of non–rapid eye movement sleep was observed. Moreover, all patients tolerated long-term stimulation at night and did not experience any adverse effects from stimulation. Even after completing the study protocol, the 3 patients who remained free from stimulator malfunction continued to use this device as primary treatment.

Conclusion: The findings demonstrate the feasibility and therapeutic potential for hypoglossal nerve stimulation in obstructive sleep apnea.

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OBSTRUCTIVE sleep apnea affects 2% to 4% of the adult population[1] and is most commonly seen in middle-aged, overweight men.[2] It is caused by recurrent episodes of upper airway obstruction during sleep that lead to periodic oxyhemoglobin desaturations and arousals from sleep.[3,4] Disturbances in sleep and oxygenation are believed to be responsible for the major clinical manifestations of this disorder, which include daytime hypersomnolence, arterial and pulmonary hypertension, and cardiopulmonary failure. The primary goal of therapy is to avert or alleviate the clinical sequelae of this disorder by relieving upper airway obstruction during sleep.[5] Various methods have been used to relieve upper airway obstruction in apneic patients, including nasal continuous positive airway pressure,[6-9] weight reduction,[10,11] positional maneuvers,[12] pharmacologic interventions,[13-15] dental appliances,[16,17] and upper airway reconstructive or bypass surgery,[18-22] all with varying degrees of success. Thus, no single treatment is certain to provide complete relief of upper airway obstruction in all patients during sleep.

The cause of upper airway obstruction is related to a decline in genioglossus muscle activity during sleep and is not addressed by current therapy.[3,23] In previous studies, investigators have demonstrated that short-term stimulation of the genioglossus can prevent the tongue from prolapsing into the pharynx[24-26] and relieve upper airway obstruction during sleep.[26-28] Recently, a novel implantable hypoglossal nerve-stimulating device has been developed to provide more prolonged genioglossal stimulation during sleep. In the present clinical trial, we report responses in sleep and breathing patterns to nightly stimulation for at least 6 months after implantation of a hypoglossal nerve–stimulating device in 8 apneic patients.

The affiliations of the authors appear in the acknowledgment section at the end of the article.

PATIENTS AND METHODS

PATIENT SELECTION

Patients with sleep apnea were eligible if they had more than 10 apneas per hour during non–rapid eye movement (NREM) sleep with predominantly obstructive apneas on a screening overnight sleep study. Patients with concomitant medical illness or neuromuscular or otolaryngologic disease were excluded. A total of 8 men were enrolled; baseline anthropometric characteristics are presented in **Table 1**. Three patients (patients 1-3) were also selected from 1 center on the basis of nocturnal pharyngeal manometric studies[29] indicating that they had predominantly retroglossal obstruction during sleep. The trial was approved by the research ethics committees in all participating centers and by competent authorities in the 4 centers' countries. Informed consent was obtained for each patient.

INITIAL AND FOLLOW-UP EVALUATION

Each patient also underwent a screening history, a physical examination, and an otolaryngologic examination. A standard overnight sleep study was performed to characterize each patient's sleep and breathing patterns. In brief, standard polysomnographic methods were used, which included monitoring of surface C3-A2 and C3-O1 electroencephalograms, submental electromyograms, and bilateral electro-oculograms for staging of sleep and assessment of sleep-wake state. Respiratory patterns were assessed by monitoring oxyhemoglobin saturation with pulse oximetry, oronasal airflow by thermistor or pneumotachogram, and thoracic and abdominal efforts by either piezoelectrodes or esophageal manometry. The patient's electrocardiogram rhythm was also monitored continuously throughout the night. Sleep studies were scored for sleep-wake state,[30] presence and type of apneas or hypopneas (obstructive, mixed, or central), changes in oxygen saturation, and arousals.[31] Apnea and hypopnea were defined using previously published criteria.[15]

HYPOGLOSSAL NERVE–STIMULATING DEVICE

A stimulating device was designed to synchronize the delivery of stimulus bursts with the patient's inspiration using the Inspire I stimulating system (Medtronic Inc, Minneapolis, Minn). Unilateral stimulation was chosen in this study for reasons of safety. The hypoglossal nerve–stimulation system consisted of an implantable intrathoracic pressure sensor, a programmable pulse-generating system, and a stimulating electrode. The pulse-generating unit provided an excitation current for the sensor and monitored the sensor signal to predict the onset of inspiration. Independent threshold and slope parameters were used to detect the inspiratory and expiratory onset from the intrathoracic pressure sensor waveform. These timing parameters were then used to begin stimulation just prior to inspiratory onset and to continue stimulation for the duration of the inspiration, provided that a previously programmed expiratory refractory period had elapsed.

The pulse-generating unit delivered bursts of electrical impulses at a set voltage amplitude, pulse width, and frequency. Stimulus parameters and inspiratory sensing algorithms could be addressed using an external programming unit. Impulses were delivered to the hypoglossal nerve via a lead and half-cuff silicone-insulated, guarded, bipolar platinum electrode. A self-controlled programming unit was provided for patients to initiate and terminate electrical stimulation at will. Stimulation was set to begin after a preset delay of 0 to 30 minutes to allow patients to initiate sleep before the start of electrical stimulation.

DEVICE IMPLANTATION PROCEDURE

The patients received general anesthesia, and no long-acting muscle relaxants were used intraoperatively. Cefazolin was given perioperatively and every 6 hours for the first 24 hours postoperatively. An upper neck incision was made, and the main trunk of the hypoglossal nerve was identified by dissection between the submandibular gland and the digastric tendon. The nerve was dissected peripheral to a large inferior distal branch to the genioglossus muscle.

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RESULTS

BASELINE CHARACTERISTICS

Patients were middle-aged, moderately overweight men with moderate to severe obstructive sleep apnea during NREM and rapid eye movement (REM) sleep (Table 1). Two patients (patients 2 and 5) had previously undergone uvulopalatopharyngoplasties. All patients had been using nasal continuous positive airway pressure but discontinued its use at the start of the trial.

STIMULUS PARAMETERS DURING INTERVENTION

Stimulus parameters are shown for the group over the trial period in **Table 2**. A significant increase in stimulus voltage ($P=.047$) and frequency ($P=.02$) was required, particularly within the first 3 months of stimulation, without any significant change in pulse width. Interval assessments of stimulation were performed at 1 month (mean±SE, 38±15 days; n=8), 3 months (103±16 days; n=7), 6 months (219±31 days; n=8), and last follow up (345±97 days; n=6).

SLEEP RECORDINGS DURING HYPOGLOSSAL NERVE STIMULATION

In **Figure 1**, breathing patterns are illustrated at the onset of hypoglossal nerve stimulation during a period of continuous NREM sleep. Prior to the initiation of electrical stimulation (Figure 1, left), 3 obstructive hypopneas were evident (airflow and esophageal pressure tracings). These events were associated with oxyhemoglobin desaturations (oxyhemoglobin saturation waveform) and with arousals from sleep during which the submental electromyogram amplitude and tidal airflow increased. After stimulation was started (intermittent stimulus bursts in electromyogram recording, Figure 1, right), tidal airflow stabilized at

A peripheral branch was chosen for stimulation for reasons of safety and because stimulating the peripheral or proximal hypoglossal nerve produced comparable increases in airflow during sleep.[26] A half-cuff electrode was placed unilaterally around this branch and secured. The electrode was connected to a pulse generator to confirm proper nerve branch placement by observing tongue protrusion and contralateral deviation.[28] A midline lower-neck Kocher incision was made to expose the manubrium, and a pressure transducer was placed via a drill hole through the superior manubrium. The implantable pulse generator was placed in an infraclavicular subcutaneous pocket. The electrode lead and intrathoracic sensing lead were tunneled subcutaneously and connected to the pulse-generating unit. Before the patient left the operating room, the function of the entire implanted system was confirmed by observing appropriate tongue movement with stimulation.

STIMULATION PROTOCOL AND FOLLOW-UP SLEEP STUDIES

After implantation, stimulation was not initiated for 4 weeks to avoid disrupting hypoglossal nerve contact with the cuff electrode. Patients then returned for sleep studies at 1, 3, and 6 months postoperatively. When possible, for extended follow-up an additional sleep study night beyond the 6-month time point was added for selected patients.

On the first stimulation night at 1 month postoperatively, tongue function was assessed clinically. The motor recruitment and pain thresholds were then determined during wakefulness with intermittent stimulation (91 microseconds; pulse width, 33 Hz) at 0.1-V increments. After the onset of sleep, stimulation was started at the motor recruitment threshold, and stimulus parameters were increased to maximize tidal inspiratory airflow and to alleviate sleep-disordered breathing episodes without electroencephalographic arousal.

On the second study night at 1 month postoperatively, optimal parameters were used to stimulate the hypoglossal nerve for the entire night. Stimulation was discontinued during awakenings of longer than 3 minutes and resumed once patients reinitiated NREM sleep. During follow-up sleep studies at 3 and 6 months postoperatively, stimulus parameters were incremented as needed in the initial 30 to 60 minutes of sleep to normalize breathing patterns and maintained for the remainder of the night. During all sleep studies, patients were allowed to sleep on their side or back in an unrestrained fashion.

DATA ANALYSIS

Sleep studies were scored for sleep and breathing patterns at baseline; 1, 3, and 6 months after implantation; and on the last available study night with electrical stimulation. Two separate analyses were performed to account for physiologic and device-related variability in response to stimulation. In an intention-to-treat analysis, the entire night was evaluated with the exception of the initial 30- to 60-minute period required for adjustment of stimulus parameters. A further analysis of the polysomnographic recording was performed to account for periods of stimulator malfunction and "off" time. In this analysis, only prolonged periods of repeated, synchronous stimulation were assessed for the purpose of characterizing sleep and breathing responses. The longest uninterrupted NREM period in which no device malfunction was apparent constituted a period of continuous stimulation.

Outcome variables included stimulus parameters and nocturnal sleep and respiratory indices. Mixed-model generalized linear regression was used to analyze responses (Minitab Inc, State College, Pa). A nested study design was used to determine the response to electrical stimulation during treatment vs baseline nights and to determine the response to electrical stimulation across treatment nights. In this model, treatment and treatment night were considered to be fixed factors, and the patient was considered to be a random factor. When significant differences in the response were detected over time, Bonferroni post hoc comparisons were performed to test for significant differences between stimulation and baseline study nights. $P<.05$ was considered significant.

higherlevels, and arousals and oxyhemoglobin desaturations abated.

SLEEP-DISORDERED BREATHING

Apnea-hypopnea indices in NREM and REM sleep are illustrated for baseline; 1, 3, and 6 months; and last follow-up night of stimulation (**Figure 2**). Hypoglossal nerve stimulation was associated with a significant decrease in apnea-hypopnea indices from baseline across all treatment nights ($P<.001$). In **Table 3**, sleep-disordered breathing indices are reported for baseline, for entire-night studies, and for continuous-stimulation recording periods. During entire-night recordings, the mean±SD apnea-hypopnea index decreased from a baseline value of 52.0±20.4 to 22.6±12.1 episodes per hour in NREM sleep ($P<.001$) and from 48.2±30.5 to 16.6±17.1 episodes per hour in REM sleep ($P<.001$). During periods of continuous stimulation, further, nonsignificant ($P>.99$) decreases in apnea-hypopnea indices to 15.5±15.2 and 12.0±17.6 episodes per hour were observed for NREM and REM sleep, respectively. In addition, there were increases from control night in the NREM baseline oxyhemoglobin saturation level ($P=.03$) and in the mean low oxygen saturation ($P=.001$) during disordered-breathing episodes for both the entire-night and continuous-stimulation periods. In REM sleep, the baseline oxyhemoglobin saturation level was unchanged from the control night ($P=.71$), whereas the mean low oxygen saturation level was increased ($P=.047$) during both stimulation conditions compared with baseline.

In **Figure 3**, NREM apnea-hypopnea indices are illustrated for baseline, entire-night, and continuous-stimulation recording periods for each patient. Although no significant differences in apnea-hypopnea indices were observed between the entire-night and continuous-stimulation conditions, responses to the 2 stimulation conditions differed in selected patients. For the entire-night recording, the apnea-hypopnea index decreased markedly in 7 of 8 patients during NREM sleep and in

Table 1. Baseline Anthropometric and Sleep-Disordered Breathing Indices*

			NREM			REM		
				Sao_2, %			Sao_2, %	
Patient No./Sex/Age, y	Neck, cm	BMI, kg/m²	AHI, Episodes/h	Baseline	Low	AHI, Episodes/h	Baseline	Low
1/M/57	43.5	31.4	65.6	91.9	90.1	45.7	94.6	88.4
2/M/54	46.5	34.4	17.1	92.4	91.7	8.0	95.0	92.4
3/M/55	41.0	25.8	57.8	91.4	88.7	66.7	88.9	85.9
4/M/52	45.7	34.9	58.0	97.3	86.6	60.0	96.8	75.7
5/M/36	41.3	24.5	60.7	93.0	87.6	69.7	93.3	89.9
6/M/38	39.4	27.2	80.8	97.4	93.6	88.4	97.0	93.7
7/M/54	39.5	23.1	46.5	98.1	93.1	47.1	98.0	94.7
8/M/53	40.0	26.0	29.7	91.2	85.9	0.0	NA	NA
Mean ± SD	42.1 ± 2.8	28.4 ± 4.5	52.0 ± 20.4	94.1 ± 3.0	89.7 ± 2.9	48.2 ± 30.5	94.4 ± 3.1	88.7 ± 6.5
(range)†	(39.4-46.5)	(23.1-34.9)	(17.1-80.8)	(91.2-98.1)	(85.9-91.7)	(8.0-88.4)	(98.0-88.9)	(94.7-75.7)

*BMI indicates body mass index; NREM, non–rapid eye movement; AHI, apnea-hypopnea index; Sao_2, oxyhemoglobin saturation; REM, rapid eye movement; and NA, not applicable.
†For age, 49.9 ± 8.1 (36-57) years.

each of the 6 patients with significant apnea during REM sleep. During the continuous-stimulation recording period, a further decrease in NREM apnea-hypopnea index was observed in selected individuals (patients 1, 5, and 6) compared with the entire night. These decreases could be attributed to periods of intermittent device malfunction or asynchronous stimulation that were excluded from the analysis of continuous-stimulation recordings in these patients.

SLEEP ARCHITECTURE

Sleep stage distribution is represented in **Table 4** for the entire study period. Trends toward a reduced percentage of stage I (transitional) NREM sleep ($P=.16$) and an increased percentage of slow wave (deep) NREM sleep ($P=.14$) were observed during the stimulated nights compared with baseline, but were not statistically significant. There were no significant differences in sleep stage distribution among the treatment nights over the course of the study.

CLINICAL FOLLOW-UP

The implantable stimulating device operated well in all patients, was well tolerated, relieved symptoms of sleep-disordered breathing, and replaced nasal continuous positive airway pressure as the sole treatment modality in these patients for at least 6 months. All patients reported continuous use of the stimulator on a nightly basis. Patients' body mass index values (calculated as weight in kilograms divided by the square of height in meters) remained stable throughout the study period (mean±SD, 29.3±4.6 and 29.5±4.4 at baseline and 6 months, respectively). At each follow-up time point, the tongue was thoroughly examined, and no abnormalities in lingual appearance or function (abnormal tongue deviation, atrophy, hypertrophy, fasciculations, pain, numbness, inflammation, alterations in speech and swallowing) were detected in any patient.

Subsequent device malfunction included pulse generator failure (patients 5 and 7), intermittent sensor shutdown (patient 6), transient asynchronous stimulation due to sensor signal artifact (patients 4 and 8), and electrode breakage (patients 3 and 8). At the time this article was written, 3 patients were still using the stimulating system (patients 1, 2, and 4) as their sole treatment.

Table 2. Stimulation Parameters*

Time After Implantation, mo	Stimulus Amplitude, V†	Frequency, Hz‡	Pulse Width, µs
1	2.2 ± 0.5	33.9 ± 2.5	94.3 ± 9.2
3	2.6 ± 0.4	35.0 ± 3.4	107.7 ± 24.6
6	2.7 ± 0.7	35.6 ± 3.6	105.6 ± 23.5
Last follow-up	3.0 ± 1.0	37.7 ± 3.6	110.5 ± 25.7

*Values are mean ± SD.
†$P=.047$.
‡$P=.02$.

COMMENT

The major finding of the present study was that nightly stimulation in patients with moderate to severe obstructive sleep apnea markedly diminished apnea severity without arousing patients from sleep. Specifically, the frequency of obstructive apneic and hypopneic episodes decreased, and the severity of oxyhemoglobin desaturations improved significantly. With improvement in sleep apnea, a trend toward deeper stages of NREM sleep was observed. Moreover, all patients tolerated long-term stimulation at night, and none experienced any adverse effects from stimulation throughout the entire observation period. The 3 patients remaining free from any stimulator malfunction continued to use this device as a primary treatment for their apnea even after completing the study protocol. Thus, these findings demonstrated that nightly unilateral hypoglossal nerve stimulation is both feasible and of potential therapeutic benefit for patients with obstructive sleep apnea.

Because of the temporary nature of the stimulator used, previous studies on hypoglossal nerve stimulation have shown only short-term relief of upper airway obstruction

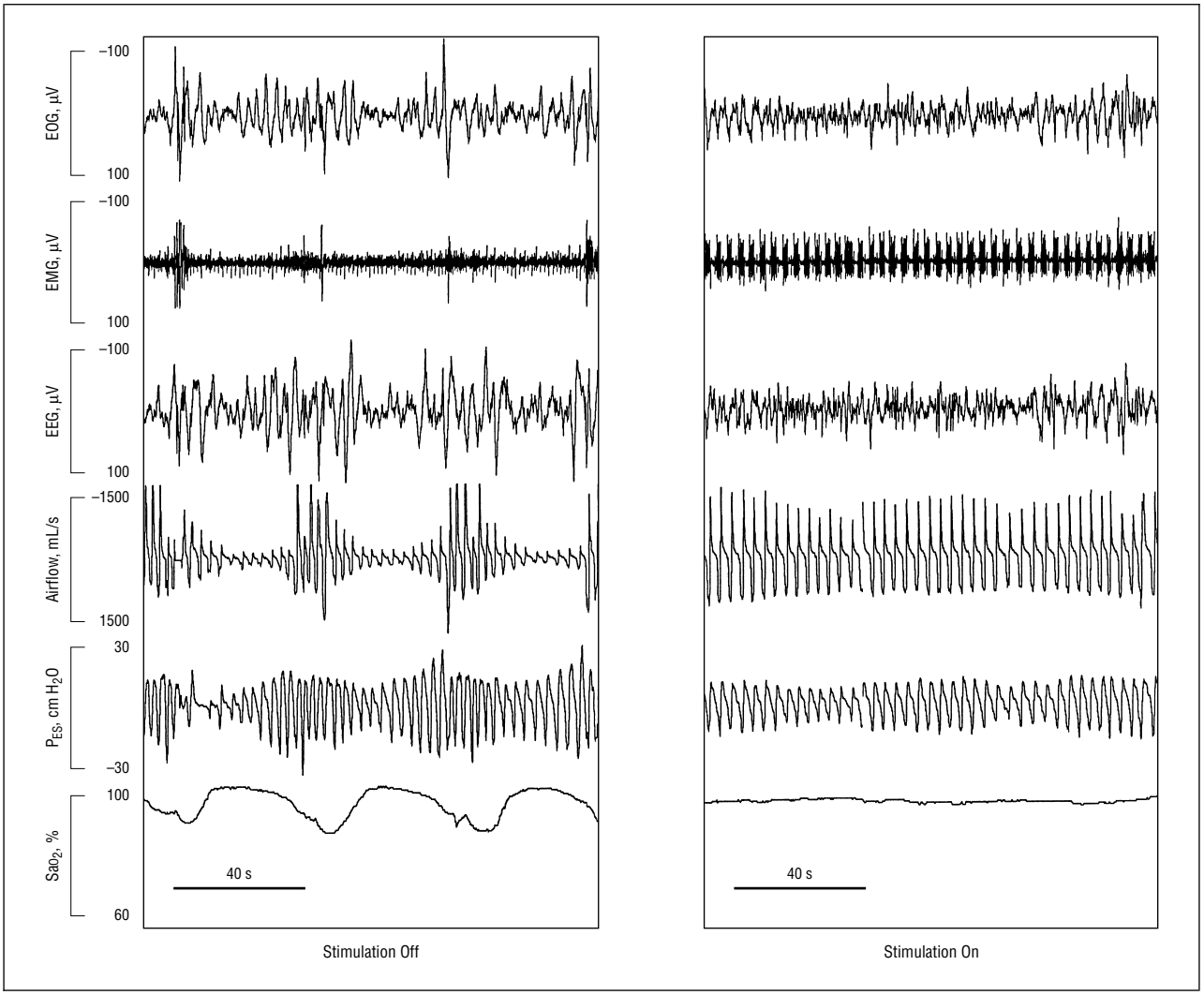

Figure 1. Representative recording example in 1 patient showing response in breathing pattern at the onset of hypoglossal stimulation during a continuous period of non–rapid eye movement sleep. Left, Before stimulation was started, 3 obstructive hypopneas were evident, with periodic reductions in airflow terminated by microarousals from sleep (rise in submental electromyogram [EMG] amplitude with resumption of tidal airflow) and oxyhemoglobin desaturations. Right, Approximately 20 seconds after the onset of the stimulus, tidal airflow stabilized, esophageal pressure swings were reduced, and arousals and oxyhemoglobin desaturations were abolished. EOG indicates electro-oculogram; EEG, C3-A2 electroencephalogram; P_{ES}, esophageal pressure; and Sao_2, oxyhemoglobin saturation.

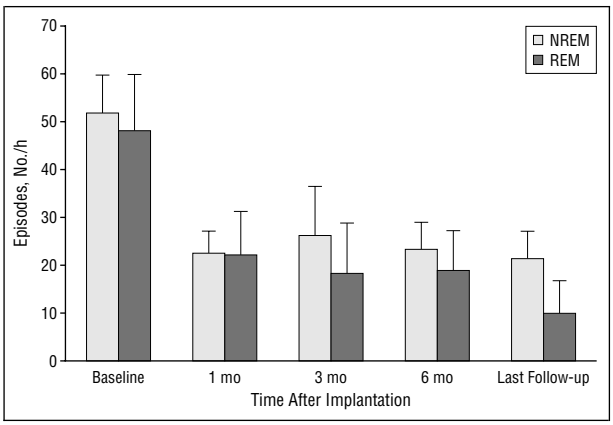

Figure 2. Apnea-hypopnea indices during non–rapid eye movement (NREM) and rapid eye movement (REM) sleep at baseline; at 1, 3, and 6 months; and at last follow-up after implantation of the hypoglossal nerve–stimulating device. A significant treatment effect ($P<.001$) was observed without any significant change in the response to stimulation over time. All values are mean ± SE.

during sleep.[26] With the development of a fully implantable stimulating system, we were able to examine the effect of nightly stimulation in the present study, and marked improvements in the severity of obstructive sleep apnea were observed. We believe that such improvements were primarily the result of activating the genioglossus muscle, since the tongue protruded and deviated contralaterally during unilateral stimulation.[24,25] Indeed, selective activation of the genioglossus was confirmed by noting such movement both intraoperatively and postoperatively throughout the trial. Moreover, recruitment of the genioglossus muscle during sleep led to prompt increases in inspiratory airflow (Figure 1), a finding previously attributed to a decrease in upper airway collapsibility[27] or critical closing pressure. However, apnea was not eliminated entirely in our patients, and intermittent inspiratory flow limitation (snoring) remained.

Although airway collapsibility was not measured, comparable levels of stimulation have been associated pre-

Table 3. Sleep-Disordered Breathing Indices*

	NREM				REM			
			Sao_2, %				Sao_2, %	
	AHI, Episodes/h	Apnea, %†	Baseline	Low	AHI, Episodes/h	Apnea, %†	Baseline	Low
Baseline	52.0 ± 20.4	38.8 ± 36.5	94.1 ± 3.0	89.7 ± 2.9	48.2 ± 30.5	26.2 ± 32.6	94.4 ± 3.1	88.7 ± 6.5
Entire night	22.6 ± 12.1‡	28.2 ± 23.4	95.2 ± 2.2§	91.7 ± 2.0‖	16.6 ± 17.1‡	17.9 ± 19.3	94.8 ± 2.4	91.6 ± 2.2‖
Continuous stimulation	15.5 ± 15.2‡	34.7 ± 33.4	95.4 ± 1.9§	92.4 ± 2.9‖	12.0 ± 17.6‡	3.7 ± 6.3	94.3 ± 3.0	92.6 ± 3.0‖

*Values are mean ± SD. Means are averaged over the 1-, 3-, and 6-month nights and the last follow-up night. NREM indicates non–rapid eye movement; AHI, apnea-hypopnea index; Sao_2, oxyhemoglobin saturation; and REM, rapid eye movement.
†No. of apneas/(No. of apneas + No. of hypopneas).
‡$P \leq .001$ vs baseline.
§$P = .03$ vs baseline.
‖$P < .05$ vs baseline.

viously with a decrease in critical pressure of approximately 5 cm of water[32] and persistent airway obstruction.[26,28] On the basis of these findings, it is likely that the greatest improvement in apnea occurred in patients with the least collapsible airways (lowest critical pressure at baseline).[5,33,34] Alternatively, greater reductions in both the critical pressure and apnea severity might have been achieved with an increase in stimulus intensity or with bilateral stimulation in those patients with suboptimal responses. Given the apparent safety of unilateral stimulation in our patients, it might now be possible to stabilize the airway mechanically with more uniform bilateral hypoglossal nerve stimulation.

Broad selection criteria were adopted for this initial series and probably contributed to the variability in the response to stimulation. No single factor could be discerned that predicted an optimal outcome. Nevertheless, retroglossal obstruction appeared advantageous, since the most marked improvements in apnea occurred in patients 1, 2, and 3, in whom retroglossal obstruction had been demonstrated previously in a nocturnal pharyngeal manometric study.[29] Another patient (patient 5), who also had an excellent response to stimulation, was suspected of having retroglossal obstruction because he had not responded to uvulopalatopharyngoplasty.[35] Additional variability in the response to hypoglossal nerve stimulation may also have been caused by differences in anatomy or different patterns in pharyngeal and cervical muscle activity during sleep.[36] Additional studies of airway anatomy or physiology, however, have not been performed; thus, the factors required for optimal responses are unknown.

One general concern is that microarousals could have accounted for improvements in airway patency during stimulation.[3,4,28,37-39] We do not believe this to have been the case for the following reasons: First, cortical arousal was not apparent in electroencephalographic recordings spanning many nights.[31] Second, we and others have observed that cortical arousal is usually associated with sustained improvements in tidal airflow beyond the stimulus burst[28,37,38] (Figure 1). Third, if frequent arousals had occurred, disturbances in sleep architecture (consisting of an increase in stage I sleep and decreases in deeper stages of NREM [stages II-IV] and REM sleep) would have been expected. Rather, we found trends toward deeper stages of NREM sleep during stimulation nights (Table 4), and thus we believe that improvements in apnea were related to selective genioglossus muscle recruitment instead of arousal.

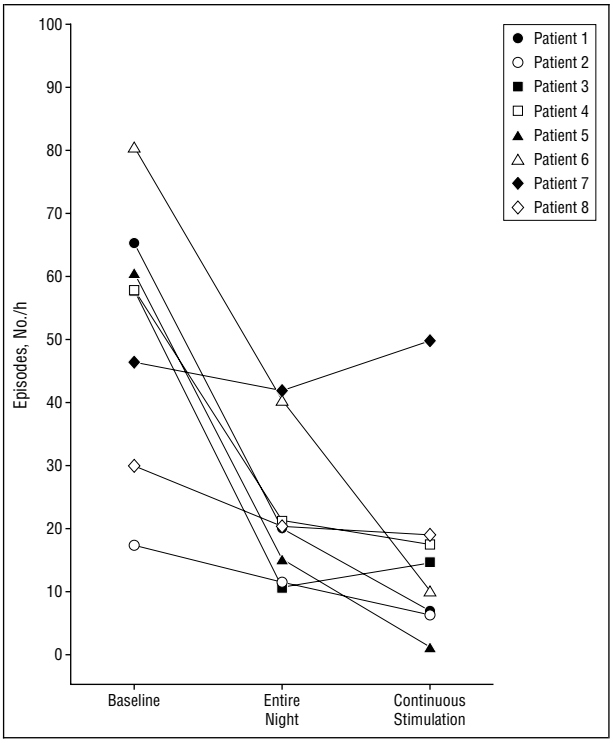

Figure 3. Non–rapid eye movement (NREM) apnea-hypopnea indices for a night without stimulation (baseline) and for entire-night and continuous periods with hypoglossal nerve stimulation. Patients' values for the entire night are the mean of values at 1, 3, and 6 months and last follow-up. A significant decrease in NREM sleep was observed between the entire night and baseline night and between continuous stimulation and baseline night ($P < .001$).

Several technical issues with the current device limited its immediate application. First, poor synchronization in selected patients (patients 1 and 6) and device malfunction (patient 5) diminished the sustained improvement in apnea. Nevertheless, when the stimulation was well synchronized with inspiration, improvement in apnea was consistently observed. In one patient (patient 7), despite good synchronization, the apnea-hypopnea index did not fall, although stimulation partially restored this patient's airway patency as mani-

Table 4. Sleep Architecture*

	Total Sleep Time, min	Sleep Efficiency, %†	Stage I Sleep, %	Stage II Sleep, %	Slow Wave Sleep, %	REM Sleep, %
Baseline	307.8 ± 97.0	76.3 ± 23.2	33.9 ± 20.2	46.4 ± 14.5	8.7 ± 8.4	11.1 ± 7.7
Entire night	259.8 ± 66.0	70.8 ± 14.5	21.1 ± 9.4	51.7 ± 10.1	12.7 ± 11.3	14.5 ± 5.7
Continuous stimulation	227.4 ± 113.7	88.4 ± 13.5	20.2 ± 19.5	49.5 ± 14.2	15.9 ± 16.2	15.3 ± 9.3

*Values are mean ± SD. REM indicates rapid eye movement.
†Total sleep time/time in bed.

fested by increased hypopneas (partial airflow obstruction) instead of apneas (complete airflow obstruction). Second, small but consistent increases in stimulus parameters were also required early in the protocol to maintain responses in apnea-hypopnea indices.[40] However, it should be noted that little further increase in stimulus intensity was required beyond 3 months, suggesting that the electrode-nerve interface stabilized thereafter. Finally, electrode breakage and sensor malfunction (5 of 8 patients) compromised long-term stimulation beyond 6 months. Nevertheless, responses in the apnea-hypopnea index during entire nights and for continuous periods of stimulation suggest that the therapeutic potential for hypoglossal nerve stimulation will be fully realized once these technical issues are solved and stimulus parameters are optimized.

In summary, the present findings demonstrate the potential for hypoglossal nerve stimulation as a novel form of therapy for obstructive sleep apnea. Further studies will be required to optimize patient selection criteria based on baseline differences in upper airway function or the site of pharyngeal obstruction. It should also be noted that improvements in sleep-disordered breathing might be further augmented with bilateral hypoglossal nerve stimulation and/or stimulation of other upper airway and cervical muscles. Finally, the effect of nightly stimulation on measures of daytime performance, sleepiness, and cardiovascular function will have to be assessed before the role of hypoglossal nerve stimulation as a therapeutic option for treating obstructive sleep apnea can be established.

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REFERENCES

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328:1230-1235.
2. Redline S, Kump K, Tishler PV, Browner I, Ferrette V. Gender differences in sleep-disordered breathing in a community-based sample. *Am J Respir Crit Care Med*. 1994;149(3 pt 1):722-726.
3. Remmers JE, deGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol*. 1978;44:931-938.
4. Gastaut H, Tassinari CA, Duron B. Polygraphic study of diurnal and nocturnal (hypnic and respiratory) episodal manifestations of Pickwick syndrome [in French]. *Rev Neurol (Paris)*. 1965;112:568-579.
5. Gold AR, Schwartz AR. The pharyngeal critical pressure: the whys and hows of using nasal continuous positive airway pressure diagnostically. *Chest*. 1996;110:1077-1088.
6. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet*. 1981;1:862-865.
7. Reeves-Hoche MK, Meck R, Zwillich CW. Nasal CPAP: an objective evaluation of patient compliance. *Am J Respir Crit Care Med*. 1994;149:149-154.
8. Kribbs NB, Pack AI, Kline LR, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Respir Dis*. 1993;147:887-895.
9. Weaver TE, Kribbs NB, Pack AI, et al. Night-to-night variability in CPAP use over the first three months of treatment. *Sleep*. 1997;20:278-283.
10. Smith PL, Gold AR, Meyers DA, Haponik EF, Bleecker ER. Weight loss in mildly to moderately obese patients with obstructive sleep apnea. *Ann Intern Med*. 1985;103(6 pt 1):850-855.
11. Strobel RJ, Rosen RC. Obesity and weight loss in obstructive sleep apnea: a critical review. *Sleep*. 1996;19:104-115.
12. Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep*. 1984;7:110-114.
13. Brownell LG, West P, Sweatman P, Acres JC, Kryger MH. Protriptyline in obstructive sleep apnea: a double-blind trial. *N Engl J Med*. 1982;307:1037-1042.
14. Hanzel DA, Proia NG, Hudgel DW. Response of obstructive sleep apnea to fluoxetine and protriptyline. *Chest*. 1991;100:416-421.
15. Smith PL, Haponik EF, Allen RP, Bleecker ER. The effects of protriptyline in sleep-disordered breathing. *Am Rev Respir Dis*. 1983;127:8-13.
16. American Sleep Disorders Association. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances. *Sleep*. 1995;18:511-513.
17. Schmidt-Nowara W, Lowe A, Wiegand L, Cartwright R, Perez-Guerra F, Menn S.

Oral appliances for the treatment of snoring and obstructive sleep apnea: a review. *Sleep*. 1995;18:501-510.
18. Conradt R, Hochban W, Brandenburg U, Heitmann J, Peter JH. Long-term follow-up after surgical treatment of obstructive sleep apnoea by maxillomandibular advancement. *Eur Respir J*. 1997;10:123-128.
19. Mickelson SA. Upper airway bypass surgery for obstructive sleep apnea syndrome [review]. *Otolaryngol Clin North Am*. 1998;31:1013-1023.
20. Fujita S, Conway W, Zorick F, Roth T. Surgical correction of anatomic abnormalities in obstructive sleep apnea syndrome: uvulopalatopharyngoplasty. *Otolaryngol Head Neck Surg*. 1981;89:923-934.
21. Shepard JW Jr, Olsen KD. Uvulopalatopharyngoplasty for treatment of obstructive sleep apnea [review]. *Mayo Clin Proc*. 1990;65:1260-1267.
22. Riley RW, Powell NB, Guilleminault C. Obstructive sleep apnea syndrome: a review of 306 consecutively treated surgical patients. *Otolaryngol Head Neck Surg*. 1993;108:117-125.
23. Safar P, Escarraga LS, Chang F. Upper airway obstruction in the unconscious patient. *J Appl Physiol*. 1959;14:760-764.
24. Abd-el-Malek S. A contribution to the study of the movements of the tongue in animals, with special reference to the cat. *J Anat*. 1938;73:15-30.
25. Bennett GA, Hutchinson RC. Experimental studies on the movements of the mammalian tongue. *Anat Rec*. 1946;94:59-72.
26. 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.
27. Schwartz AR, Thut DC, Russ B, et al. Effect of electrical stimulation of the hypoglossal nerve on airflow mechanics in the isolated upper airway. *Am Rev Respir Dis*. 1993;147:1144-1150.
28. 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;81:643-652.
29. Boudewyns A, Van de Heyning PH, De Backer WA. Site of upper airway obstruction in obstructive apnoea and influence of sleep stage. *Eur Respir J*. 1997;10:2566-2572.
30. Rechtschaffen A, Kales A. *A Manual of Standardized Terminology, Techniques and Scoring Systems for Sleep Stages of Human Subjects*. Washington, DC: National Institutes of Health; 1968. Publication NIH 204.
31. Atlas Task Force. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep*. 1992;15:174-184.
32. O'Hearn DJ, Schneider H, LeBlanc K, Schubert, O'Donnell CP, Smith PL, Schwartz AR. Effect of unilateral hypoglossal stimulation on upper airway function [abstract]. *Am J Respir Crit Care Med*. 1998;157:A284.
33. Schwartz AR, Gold AR, Schubert N, et al. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis*. 1991;144(3, pt 1):494-498.
34. Schwartz AR, Schubert N, Rothman W, et al. Effect of uvulopalatopharyngoplasty on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis*. 1992;145:527-532.
35. Launois SH, Feroah TR, Campbell WN, et al. Site of pharyngeal narrowing predicts outcome of surgery for obstructive sleep apnea. *Am Rev Respir Dis*. 1993;147:182-189.
36. Fuller DD, Williams JS, Janssen PL, Fregosi RF. Effect of co-activation of tongue protrudor and retractor muscles on tongue movements and pharyngeal airflow mechanics in the rat. *J Physiol (Lond)*. 1999;519:601-613.
37. Decker MJ, Haaga J, Arnold JL, Atzberger D, Strohl KP. Functional electrical stimulation and respiration during sleep. *J Appl Physiol*. 1993;75:1053-1061.
38. Edmonds LC, Daniels BK, Stanson AW, Sheedy PF III, Shepard JW Jr. The effects of transcutaneous electrical stimulation during wakefulness and sleep in patients with obstructive sleep apnea. *Am Rev Respir Dis*. 1992;146:1030-1036.
39. Guilleminault C, Powell N, Bowman B, Stoohs R. The effect of electrical stimulation on obstructive sleep apnea syndrome. *Chest*. 1995;107:67-73.
40. Goding GS Jr, Eisele DW, Testerman R, Smith PL, Roertgen K, Schwartz AR. Relief of upper airway obstruction with hypoglossal nerve stimulation in the canine. *Laryngoscope*. 1998;108:162-169.