

Direct Hypoglossal Nerve Stimulation in Obstructive Sleep Apnea

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Objectives: To determine the motor responses resulting from direct electrical stimulation of the hypoglossal (HG) nerve and to correlate these responses to changes in upper airway patency during sleep.

Design: The motor effects of direct electrical stimulation of the main trunk of the HG nerve and the branch that supplies the genioglossus muscle during anesthesia and wakefulness were assessed visually. Responses in airflow during sleep to HG nerve stimulation were assessed with standard polysomnographic techniques.

Setting: University medical center.

Patients: Fifteen patients undergoing a surgical procedure that involved the neck that exposed the HG nerve and 5 volunteer patients with obstructive sleep apnea constituted the study population.

Interventions: The main trunk (n=3) and genioglossus branch (n=2) of the HG nerve were stimulated electrically with a half-cuff tripolar electrode.

Results: Stimulation of the branch of the HG nerve that innervates the genioglossus muscle caused protrusion and contralateral deviation of the tongue. Stimulation of the main trunk of the HG nerve caused slight ipsilateral deviation and retrusion of the tongue. The arousal threshold for stimulation exceeded the motor recruitment threshold by 0.8 ± 0.4 V. Inspiratory airflow increased in all patients by 184.5 ± 61.7 mL/s (mean $\pm$ SD; $P = .02$, analysis of variance) with stimulation.

Conclusion: Direct HG nerve stimulation below the arousal threshold can improve airflow in patients with obstructive sleep apnea.

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RECENT epidemiological data demonstrate that approximately 4% of men and 2% of women in the United States have obstructive sleep apnea (OSA).¹ Obstructive sleep apnea is caused by periodic pharyngeal obstruction during sleep.^{2,3} One proposed mechanism for pharyngeal occlusion in OSA is tongue prolapse into the pharynx. Tongue prolapse may be due to diminished neuromuscular activity in the genioglossus muscle, an extrinsic tongue muscle that is the principal tongue protusor muscle.³ Therefore, reduced activity of the genioglossus muscle may be responsible for pharyngeal occlusion in OSA.

Several previous investigations have attempted various methods to electrically stimulate the genioglossus muscle to improve pharyngeal patency in patients with OSA, unfortunately without proved favorable results.⁴⁻⁸ From these studies,

whether the genioglossus muscle was selectively stimulated with the stimulation techniques used is not clear. In addition, patients were often aroused with stimulation, and observed improvements in pharyngeal patency could have been related to pharyngeal musculature activation during arousal.⁶⁻⁸

During a previous study in which the tongue musculature was stimulated electrically with transorally placed wire electrodes in patients with OSA, we demonstrated both opening and closure of the upper airway depending on the location of the stimulating electrode.⁹ We believed that the differences in airway responses were due to the activation of different muscles. Specifically, we speculated

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MATERIALS AND METHODS

Fifteen patients undergoing a surgical procedure that involved the neck that exposed the HG nerve and 5 volunteer patients with OSA constituted the study population. All investigations were approved by The Johns Hopkins Joint Committee on Clinical Investigation and written informed consent was obtained from each patient.

INTRAOPERATIVE PROTOCOL: MOTOR RESPONSES

A half-cuff tripolar electrode (model 3990, Medtronic, Inc, Minneapolis, Minn) was used for nerve stimulation (**Figure 1**). This electrode was placed in contact with the main trunk of the HG nerve just distal to the ansa hypoglossi in 7 patients (**Figure 2**). In the other 8 patients, the electrode was placed on the distal HG nerve supplying the genioglossus muscle (**Figure 2**). The stimulating electrode was connected to a constant current electrical stimulator (Dynex transcutaneous electrical stimulator, Medtronic, Inc). The nerves were stimulated with stimulation variables consisting of a pulse width of 100 microseconds, frequency of 30 Hz, and burst duration of 1 to 1.5 seconds. Tongue movements resulting from site-specific stimulation were observed and recorded.

SLEEP LABORATORY PROTOCOL: EFFECT ON AIRWAY PATENCY IN OSA

In 5 sleep-deprived patients with OSA, the HG nerve was surgically exposed under local anesthesia using sterile technique, and the half-cuff tripolar electrode was placed in contact with the HG nerve. The wound was closed around the electrode and a sterile dressing was applied. The electrode was placed on the main trunk of the HG nerve in 3 patients and on the distal branch of the HG nerve supplying the genioglossus muscle in 2 patients (**Figure 2**). Selective stimulation of the nerve branch to the genioglossus muscle was confirmed by intraoperative stimulation by observing tongue protrusion and contralateral deviation, the same motor response observed with stimulation of the genioglossus muscle by intramuscular

electrode.⁹ Postoperatively, patients received oral oxycodone, 10 mg, for analgesia and oral triazolam, 0.25 mg, for sedation before going to sleep.

In these 5 apneic patients, respiratory responses to electrical stimulation during sleep were assessed with standard polysomnography performed during the afternoon of the day that nerve electrodes were placed. Surface C₃-A₂ and C₃-O₁ electroencephalographic electrodes, submental surface electromyographic electrodes, and left and right electro-oculograms were used to determine stages of sleep. Heart rate and rhythm were monitored with electrocardiographic electrodes. The patients breathed through a tight-fitting nasal mask with a fixed leak and a variable airflow source at the inflow port (Respironics, Murrysville, Pa). Pressure in the nasal mask (P_N) was measured with the catheter connected to a port in the mask and airflow was monitored with a pneumotachometer connected to the breathing circuit. An esophageal balloon was used to measure esophageal pressure. All pressures, flows, and polysomnographic variables were recorded continuously on a polygraph recorder.

Several variables were studied to determine whether electrical stimulation aroused the patient from sleep. Arousal was considered to have occurred if any change in electroencephalographic (ie, alpha rhythm, K complexes, or blocking artifact) or electromyographic amplitude or blocking artifact occurred during or immediately after the stimulation period. In addition, the effect of stimulation on airflow was studied.

The P_N was set to achieve steady state periods of inspiratory airflow limitation during non-rapid eye movement (REM) sleep. Stimulation was initiated at the onset of inspiration and was maintained for 1 to 1.5 seconds during the inspiration. Synchronization of stimulation with inspiration was achieved by triggering the stimulator when pressure in the hypopharynx or esophagus began to fall early in inspiration. Stimulation was performed during single inspirations. The level of maximal inspiratory airflow (V_I max) was then measured for each stimulated inspiration and for the inspirations immediately before and after stimulation. Repeated measures analysis of variance was used to detect significant changes in V_I max with stimulation. After stimulation and data acquisition during sleep, the stimulating electrode was removed from the nerve through the wound.

that airway opening during sleep in patients with OSA resulted from activation of the genioglossus muscle, whereas airway closure resulted from activation of the tongue retrusor muscles, the hyoglossus and styloglossus, and other pharyngeal muscles. Moreover, these different effects on airway patency correlated with specific observed motor responses during wakefulness. Our methods in this prior work, however, did not allow us to determine specifically which muscles produced the observed changes in pharyngeal patency. The purpose of the present study is to determine the motor responses resulting from direct electrical stimulation of the hypoglossal (HG) nerve and to correlate these responses with changes in airway patency during sleep in patients with OSA.

RESULTS

INTRAOPERATIVE PROTOCOL: MOTOR RESPONSES

The effect of direct stimulation of the HG nerve on tongue movement in the 15 patients undergoing a surgical procedure that involved the neck was dependent on the site of HG nerve stimulation. Stimulation of the branch of the HG nerve that supplies the genioglossus muscle resulted in selective recruitment of the genioglossus muscle because the tongue protruded and deviated contralaterally. This response was uniformly observed in 8 patients. Stimulation of the main trunk of the HG nerve caused slight ipsilateral deviation and retrusion of the

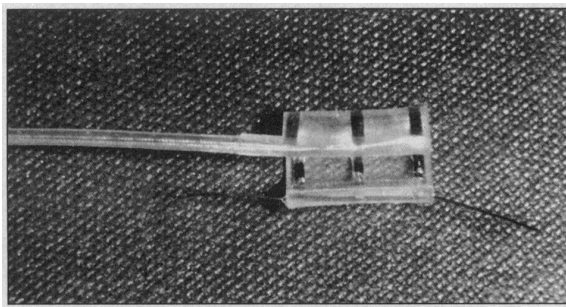


Figure 1. Medtronic 3990 (Medtronic, Inc, Minneapolis, Minn) electrode.

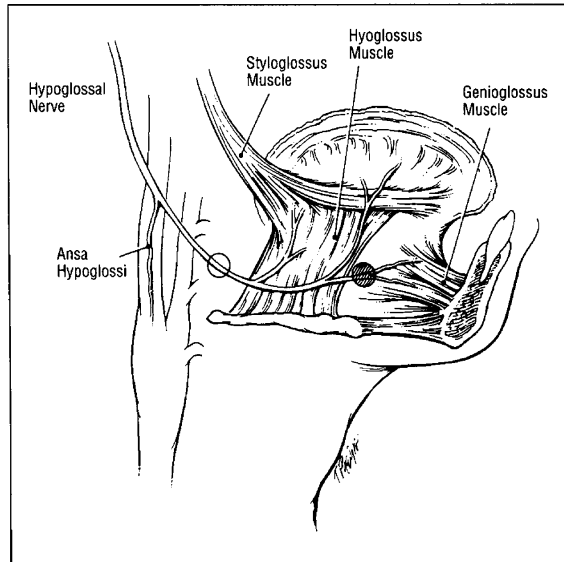


Figure 2. Electrode placement on hypoglossal nerve. Open circle indicates placement on the main trunk of the hypoglossal nerve; shaded circle, placement on the branch of the hypoglossal nerve that supplies the genioglossus muscle.

tongue in the 7 patients studied. This motor response was due to activation of the intrinsic and extrinsic tongue muscles, including the tongue retrusor muscles.

SLEEP LABORATORY PROTOCOL: EFFECT ON AIRWAY PATENCY IN OSA

Characteristics of the 5 patients with OSA assessed with temporary implantable HG electrodes are listed in the **Table**. The mean ($\pm$ SD) age of these patients was 42.0 ± 6.7 years. The patients had a mean ($\pm$ SD) non-REM apnea-hypopnea index of 108.0 ± 43.1 events per hour during non-REM sleep. Stimulation of the branch of the HG nerve that supplies the genioglossus muscle caused contralateral protrusion of the tongue identical to that seen in the patients studied intraoperatively. Stimulation of the main trunk of the HG nerve also produced tongue retrusion with ipsilateral deviation, the same motion observed in the intraoperative stimulation trials.

The effects of HG nerve stimulation on sleep in the patients with OSA are shown in representative polysom-

Characteristics of Patients With Obstructive Sleep Apnea*

Patient No./ Age, y	Weight, kg	BMI, kg/m ²	CPAP, cm H ₂ O	AHI in NREM, Episodes/h	AT/ DBT
1/51	104.5	34	18	88.2	0.38
2/39	136.8	43.3	8	77.3	0.16
3/33	143.6	46.1	16	106.7	0.98
4/43	83.2	27.9	8	84.4	0.73
5/45	127.2	43.9	14	122.5	0.76

*BMI indicates body mass index; CPAP, continuous positive airway pressure; AHI NREM, apnea-hypopnea index during non-rapid eye movement sleep; and AT/DBT, apnea time/disordered breathing time (the relative proportion of apnea present in disordered breathing episodes).

nographic recordings in **Figure 3** and **Figure 4**. The polysomnographic tracings reveal clear increases in inspiratory airflow without any arousals or changes in sleep stage during stimulation. Figure 3 displays a representative example of HG stimulation during a single breath. The stimulated breath shows an increase in $\dot{V}_I$ max of 270 mL/s, as well as elimination of the inspiratory flow limitation that was present in the unstimulated breaths. Stimulation of the distal HG nerve in this patient also eliminated the snoring artifact seen in the P_N tracing. Figure 4 shows that repeated stimulation during consecutive inspirations produced consistent increases in $\dot{V}_I$ max. When stimulation was turned off for a single breath, airflow decreased.

The effects of direct stimulation of the HG nerve on $\dot{V}_I$ max are displayed for all OSA patients in **Figure 5**. The $\dot{V}_I$ max increased by a mean ($\pm$ SD) of 176.1 ± 32.6 mL/s with stimulation of the main trunk of the HG nerve and by 197.2 ± 112.0 with stimulation of the branch supplying the genioglossus muscle. Thus, stimulation of the main trunk of the HG nerve and the branch that supplies the genioglossus muscle improved inspiratory airflow. In all 5 patients, the airflow increased by a mean ($\pm$ SD) of 184.5 ± 61.7 mL/s ($P=.02$).

Stimulation of the HG nerve resulting in beneficial effects on the airway was achievable at voltage levels below the arousal threshold in all patients studied. The mean ($\pm$ SD) motor recruitment threshold for tongue movements in these patients was observed at 1.1 ± 0.2 V. The arousal threshold, however, exceeded that of motor recruitment by 0.8 ± 0.4 V.

One patient studied intraoperatively experienced transient bradycardia during stimulation. No other complications occurred in either study group. No temporary or permanent sensory deficits or paralysis of the tongue occurred in any patient.

COMMENT

We studied the motor effects of direct electrical stimulation of the HG nerve at 2 locations, the main trunk of the nerve and the distal nerve branch to the genioglossus muscle. In addition, the effect of HG nerve stimulation at these sites on upper airway patency in patients with OSA was evaluated. Our findings indicate that the motor responses observed during electrical stimulation

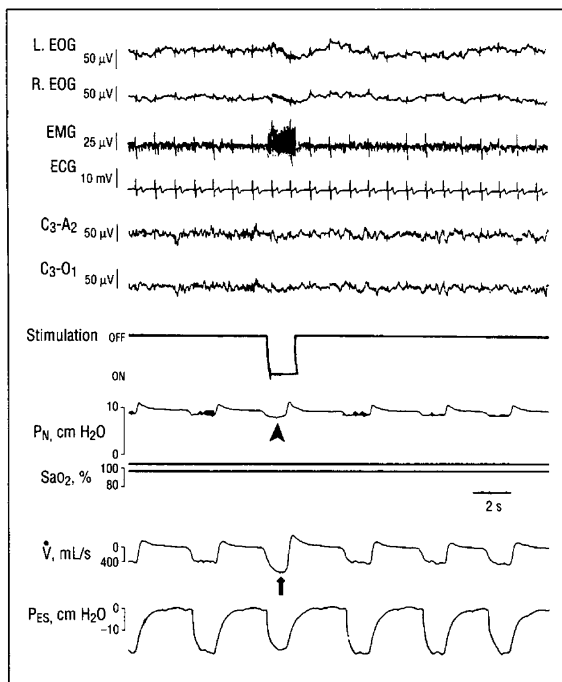


Figure 3. Polysomnographic tracings showing the effect of hypoglossal nerve stimulation during a single inspiration. Note the increase in maximal inspiratory airflow ($\dot{V}_I$) with stimulation (solid arrow) and elimination of the snoring artifact in the P_n tracing (arrowhead). L. EOG indicates left electro-oculogram; R. EOG, right electro-oculogram; EMG, submental electromyogram; ECG, electrocardiogram; C_3-A_2 , surface electroencephalogram; C_3-O_1 , surface electroencephalogram; P_n , nasal mask pressure; SaO_2 , oxygen saturation; and P_{es} , esophageal pressure.

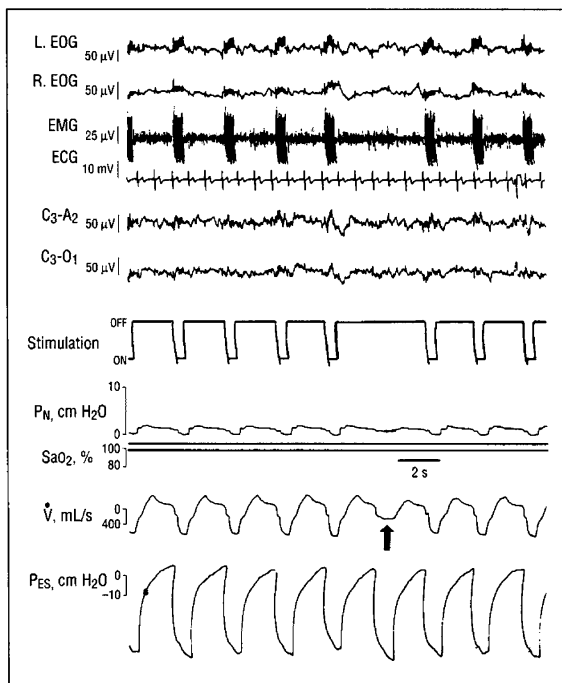


Figure 4. Polysomnographic tracings show the effect of repeated stimulation of the hypoglossal nerve. Note the decrease in inspiratory airflow ($\dot{V}_I$) for the single nonstimulated breath (arrow). See Figure 3 for an explanation of the abbreviations.

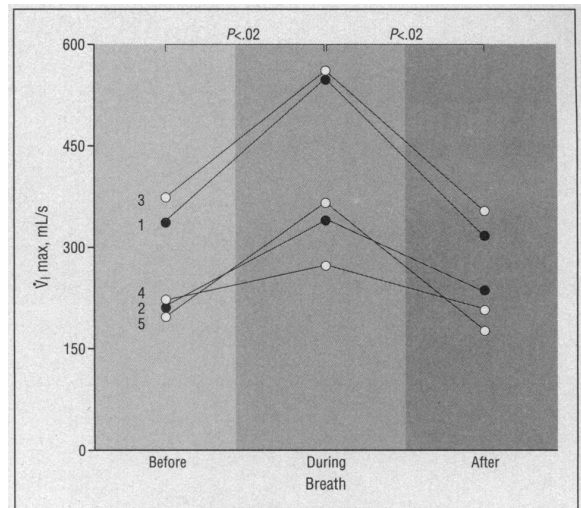


Figure 5. Mean maximal inspiratory airflow ($\dot{V}_I$ max) levels for each of 5 patients before, during, and after hypoglossal nerve stimulation. Open circles indicate electrode placement on the main trunk of the hypoglossal nerve; closed circles, placement of electrodes on the branch of the hypoglossal nerve that supplies the genioglossus muscle. Patients are indicated by numbers 1 through 5.

of the HG nerve are site specific. Stimulation of the main trunk of the HG nerve caused slight ipsilateral deviation and retrusion of the tongue. Stimulation of the distal HG nerve to the genioglossus muscle caused protrusion and contralateral deviation of the tongue. Despite these differences in motor effects, however, HG nerve stimulation at both loci during sleep consistently resulted in increased $\dot{V}_I$ max without arousal from sleep. Considering the motor effects and airflow responses, we conclude that activation of the genioglossus muscle by HG nerve stimulation opened the airway, whether or not the tongue retrusor muscles were also recruited.

Previous studies showed the mechanism for improvement in pharyngeal airflow dynamics was due to a decrease in pharyngeal collapsibility.¹⁰⁻¹⁴ The decrease in pharyngeal collapsibility has been attributed to the dilating effect of the genioglossus muscle on the airway. Our results indicate that the same airway opening effect may be derived with stimulation of the main trunk of the HG nerve and the branch that supplies the genioglossus muscle. This suggests that genioglossus contraction opens the airway even with simultaneous contraction of the tongue retrusor muscles (hyoglossus and styloglossus).

Our main objective was to study the effect of direct HG nerve stimulation on airflow dynamics in patients with OSA. We recognize, however, that the patients studied required analgesics and sedation immediately after surgery to allow for examination of responses to stimulation during sleep. Although these medications may have affected sleep arousal thresholds, the observed responses to direct nerve stimulation did not differ from responses observed in a previous study during genioglossus muscle stimulation without sedation.⁹ We, therefore, conclude that the analgesics and sedatives did not influence the response in airflow to stimulation.

Despite clear differences in motor responses, we found no differences in the airflow response to stimula-

tion of the main trunk of the HG nerve or the branch that supplies the genioglossus muscle. Nevertheless, we favor stimulating the branch of the HG nerve that supplies the genioglossus muscle in future studies examining the feasibility of HG nerve stimulation for treatment of OSA. One reason for our preference is that the tongue retrusor muscles were recruited when the main trunk of the HG nerve was stimulated. Although these muscles did not diminish the effect of stimulation on airflow, greater numbers of patients must be studied before a firm conclusion can be drawn about the role these muscles play in the control of airflow dynamics. In addition, selective stimulation of the genioglossus muscle seemed to achieve a comparable response, although fewer muscles were activated. Another reason for stimulating the HG nerve branch that supplies the genioglossus muscle is that stimulation of the main trunk of the HG nerve resulted in profound bradycardia in 1 patient studied intraoperatively. This was believed to be related to vagus nerve stimulation.¹⁵ Therefore, more distal placement of the electrode may avoid unwanted vagal nerve reflex effects and muscle activation. Thus, we believe that future studies of HG nerve stimulation for the treatment of OSA should focus on this approach.

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