

The Effects of Transcutaneous Electrical Stimulation during Wakefulness and Sleep in Patients with Obstructive Sleep Apnea¹⁻³

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Introduction

Collapse of the upper airway (UA) in obstructive sleep apnea (OSA) results from an imbalance of the forces promoting patency and closure of the airway. During wakefulness, patency of the UA is maintained by an effective level of tonic and phasic UA dilator muscle activity (1-5). During sleep, this activity diminishes, allowing the forces favoring closure such as negative intraluminal pressure, surface tension, and gravity to overcome the forces of patency (6). Nasal continuous positive airway pressure (CPAP) effectively prevents UA collapse in patients with OSA by quantitatively increasing intraluminal pressure to a level that exceeds the forces favoring collapse. Unfortunately, not all patients are tolerant of the level of CPAP required to maintain UA patency (7, 8).

Because dilator muscle tone is sufficient to prevent UA collapse during wakefulness in patients with OSA, an alternative neurophysiologic approach to treatment would focus on the maintenance of adequate levels of UA dilator muscle activity during sleep. In anesthetized dogs, Miki and coworkers (9) demonstrated that direct electrical stimulation of the genioglossus resulted in significant reductions in UA resistance. This concept of augmenting UA dilator muscle function was also tested in humans with the application of transcutaneous electrical stimulation (TES) in the submental region. In a limited number of patients with OSA, Miki and coworkers demonstrated that TES decreased the obstructive apnea index without any detrimental effect on sleep architecture (10).

This work in humans with OSA raised several important issues that we elected to evaluate further. The first issue was related to whether or not submental TES actually increased the size of the UA by producing anterior movement of the

SUMMARY Upper airway (UA) collapse in obstructive sleep apnea (OSA) is considered in part to result from the decrease in UA dilator muscle tone that occurs during sleep. We hypothesized that augmentation of UA muscle function by transcutaneous electrical stimulation (TES) might function to enlarge UA size during wakefulness and/or prevent UA collapse during sleep in patients with OSA. Eight male patients with OSA were studied both awake and asleep, with TES administered to the submental region in two patients and to both the submental and subhyoid regions in six patients. Fast-CT scans obtained at FRC and end-inspiration (V_Tel) demonstrated increased UA size with tidal breathing, $p \leq 0.05$. The active generation of -10 cm H₂O pressure at FRC substantially decreased UA size, $p \leq 0.001$. However, no changes in UA size were detected at either FRC or V_Tel with TES applied at 50 and 100% of the maximal tolerated intensity. The collapsibility of the UA in response to the generation of -10 cm H₂O pressure was also unchanged by TES. In contrast to the lack of effect of TES on UA size, voluntary protrusion of the tongue increased cross-sectional area (CSA) of the oropharyngeal (OHP) segment of the UA, $p < 0.05$, and to a lesser extent the CSA of the distal velopharyngeal segment, $p = 0.06$. When applied during sleep, TES failed to prevent or improve either sleep-disordered breathing or sleep architecture. These results documented that TES applied in the submental and subhyoid regions was ineffective in enlarging the UA during wakefulness as well as in preventing UA collapse during sleep in patients with OSA. More direct and/or selective stimulation of UA muscles will likely be required if neuromuscular stimulation is to become an effective treatment for OSA.

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tongue or, alternatively, if UA dimensions were not increased, did it work by stiffening (i.e., decreasing the compliance) the UA to prevent its collapse under the influence of negative intraluminal pressures.

The second major issue we explored was related to the mechanism of apnea termination. In the unstimulated condition, UA obstruction normally terminates coincident with evidence of arousal in the cortical EEG. Because these arousals, which fragment nocturnal sleep, are considered to be responsible for the excessive daytime sleepiness that develops in these patients, it is of paramount importance to determine whether TES terminates obstructive events by direct recruitment of UA dilator muscle function without inducing arousal, or actually promotes arousal with the subsequent return of UA dilator muscle activity to waking levels.

Additionally, we evaluated the effectiveness of TES in both the supine and lateral decubitus positions in patients

with positional as well as nonpositional OSA. These studies were conducted because we hypothesized that TES might be more effective in reopening the UA in the lateral decubitus than supine sleep position or in patients with less severe (i.e., sleep-position-dependent) OSA.

Finally, in the event that submental TES was confirmed not to be effective in reestablishing UA patency, we evaluated the effect of simultaneous stimulation in both the submental and subhyoid regions (i.e., transhyoid stimulation) to ascertain whether the concomitant

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recruitment of strap muscles would improve the effectiveness of TES. This approach was based on the work in dogs by Van de Graaff and coworkers (11), which demonstrated that contraction of the strap muscles contributed to the maintenance of UA patency.

Methods

Subjects

Eight male patients with a polysomnographically confirmed diagnosis of OSA were recruited from the population undergoing clinical evaluation at the Mayo Sleep Disorder Center. Four patients with nonpositional and four with positional sleep apnea were recruited. Nonpositional sleep apnea was defined as an apnea plus hypopnea index (AHI) ≥ 40 per hour in both the supine and lateral decubitus positions. Positional sleep apnea was defined as an AHI ≥ 40 per hour in the supine position and AHI ≤ 10 per hour in the lateral decubitus position. Criteria for exclusion were (1) major illness: chronic obstructive pulmonary disease (FEV₁ < 65% predicted), pneumonia, congestive heart failure, psychiatric disease, neurologic impairment, hepatic or renal failure; (2) drugs: narcotics, sedatives, or stimulants in the past 24 h; (3) focal upper airway disease: tumors, cysts, tonsillar hypertrophy or prior uvulopalatopharyngoplasty or tracheostomy.

All eight subjects underwent a fast-computed tomographic (fast-CT) study of the UA to evaluate the effects of submental and transhyoid electrical stimulation on UA size during wakefulness. A second overnight polysomnogram (PSG) was performed to evaluate the effects of transcutaneous electrical stimulation (TES) on sleep architecture and sleep-disordered breathing.

Polysomnography

Overnight PSG was performed using a multichannel polygraph (Model 78-D; Grass Instruments, Quincy, MA) to record electroencephalographic (EEG) activity from three lead locations (C3-A2 or C4-A1, Fz-Cz, Oz-Cz), submental and anterior tibialis electromyographic (EMG) activity, as well as electrooculographic (EOG) activity. Oxyhemoglobin saturation was monitored by ear oximetry (Biox 3700; Ohmeda, Louisville, CO). Oral and nasal airflow were monitored with thermocouples, thoracoabdominal movement by inductive plethysmography (Respirace®; Ambulatory Monitoring, Ardsley, NY) and electrocardiographic (ECG) activity by bipolar chest leads.

An apnea was defined as a cessation in airflow for ≥ 10 s. Hypopnea was defined as a fall in oxyhemoglobin saturation of $\geq 2\%$, associated with a qualitative reduction in airflow. The apnea plus hypopnea index (AHI) was calculated using the following formula: total number of apnea plus hypopneas observed/total sleep time.

Each submental stimulation PSG record was scored in 30-s epochs according to the

standard sleep stage scoring criteria (12). Scoring was separated into two sleep position categories, supine and nonsupine. The percentage of sleep observed in each sleep stage was computed as a proportion of total sleep time.

Submental Stimulation

Submental electrical stimulation was delivered using a transcutaneous electrical neuromuscular stimulation (TENS) system (Respond II, Model 3108; Medtronic, Inc., Minneapolis, MN). The stimulation intensity was titrated to the minimum perceptible (Vmin) and the maximum tolerable (Vmax) in the awake state for each patient. For any given dial setting this system delivers constant current over a 100 to 1,000 ohm load. The current delivered at Vmax ranged from 15 to 39.6 mamps. In order to maximize comfort and muscle activity, pulse characteristics were fixed at a duration of 0.3 ms and a frequency of 50 pulses/s (9, 13, 14). The stimulation was delivered to the submental region using 2.125-inch $\times$ 4.25-inch self-adhering TENS electrodes (Uni-Patch, Wabasha, MN) trimmed to fit the defined regions of stimulation. Patients 1 and 2 underwent selective submental stimulation. The electrodes were placed on each side of the midline, beginning anteriorly at the posterior edge of the mandible and extending laterally to the inferior ramus of the mandible and caudally to the region of the hyoid bone. Patients 3 to 8 underwent transhyoid stimulation. One electrode was placed anterior to the hyoid bone in the submental region, and the second was placed inferior to the hyoid bone extending caudally to the level of the thyroid cartilage.

Stimulation was applied in a continuous fashion for a minimum of two breaths preceding the acquisition of fast-CT scans. During the overnight stimulation studies, the stimulus was applied continuously in an intermittent mode (1 to 6 s of stimulation followed by 1 to 8 s without stimulation) for periods ranging from 5 to 45 min followed by periods of no stimulation. Stimulation periods varied to allow for observation of all sleep stages with and without stimulation. Patient 1 was studied using event-associated stimulation, but it was found that continuous intermittent mode stimulation allowed for greater habituation to the stimulus. During the overnight study, stimulation intensity was increased progressively up to Vmax in an attempt to abolish disordered breathing events while not inducing transient arousals or actual wakefulness.

Fast-computed Tomography

All eight patients underwent imaging of their upper airways using fast-CT (C-100; Imatron, San Francisco, CA). Scanning was performed in the awake, supine, and head neutral positions. Axial scan slices were 8 mm thick and arranged in contiguous pairs with each pair separated by 4 mm. The scanning sequence included the entire upper airway from the hard palate to the hyoid bone. The time to obtain eight axial slices was 224 ms.

During the scanning acquisition, the patients' respiratory movements were monitored using inductive plethysmography (Respirace®; Ambulatory Monitoring). Scans were obtained under three conditions: FRC, end-tidal inspiration (VT_{ei}), and FRC with upper airway pressure of -10 cm H₂O. During the negative pressure maneuvers, the patients' nares were obstructed with small plugs. One plug was connected to a pressure transducer (P23XL; Spectramed, Oxnard, CA). The negative pressure was generated by inspiratory effort initiated at FRC against the occluded nares. The subject generated the target pressure with the use of a handheld pressure gauge. The investigator monitored the pressure via a multichannel polygraph (Model 8-20D; Grass Instruments, Quincy, MA). Each UA condition (FRC, VT_{ei}, -10 cm H₂O) was scanned with 0, 50, and 100% of Vmax stimulation. All scans were obtained with the subject's mouth closed.

One additional scan was obtained in Patients 2 to 8. This scan was performed at FRC during voluntary protrusion of the tongue with the lips closed around it. No stimulation was applied during the tongue protrusion scan.

Cross-sectional area (CSA) was determined for each axial slice using a computerized program with CT window level of -300 Hounsfield Units (HU) used to define the air-tissue interface of the UA. The retropalatal segment of the UA from the hard palate to the inferior margin of the soft palate was designated as the velopharynx (VP). The retroglottal segment extending from the inferior margin of the soft palate to the level of the hyoid bone was defined as the oropharynx (OHP).

Data Analysis

The sample size was calculated to detect a 50% reduction in the AHI with submental stimulation. The calculation assumed (1) an 85% response rate, which would be similar to the response obtained using nasal continuous positive airway pressure (15); (2) a 5% control response rate; (3) an alpha error of 0.05; and (4) a beta error of 0.2.

The values for AHI and sleep stages were compared between nonstimulation and stimulation using Wilcoxon's signed-rank test. The simultaneous effect of stimulation (0, 50, and 100%) and condition (FRC, VT_{ei}, -10 cm H₂O) on CSA of the UA at each scan level was analyzed using a two-way analysis of variance (ANOVA). A paired two-tailed *t* test was performed on the CSA data for the specific factors identified as significant by ANOVA. In comparing the extent of oxyhemoglobin desaturation between the groups, nonstimulated and stimulated, a paired two-tailed *t* test was performed. All data are presented as mean $\pm$ SEM.

Results

Sleep Architecture

The sleep architecture data for both nonstimulated and stimulated sleep are

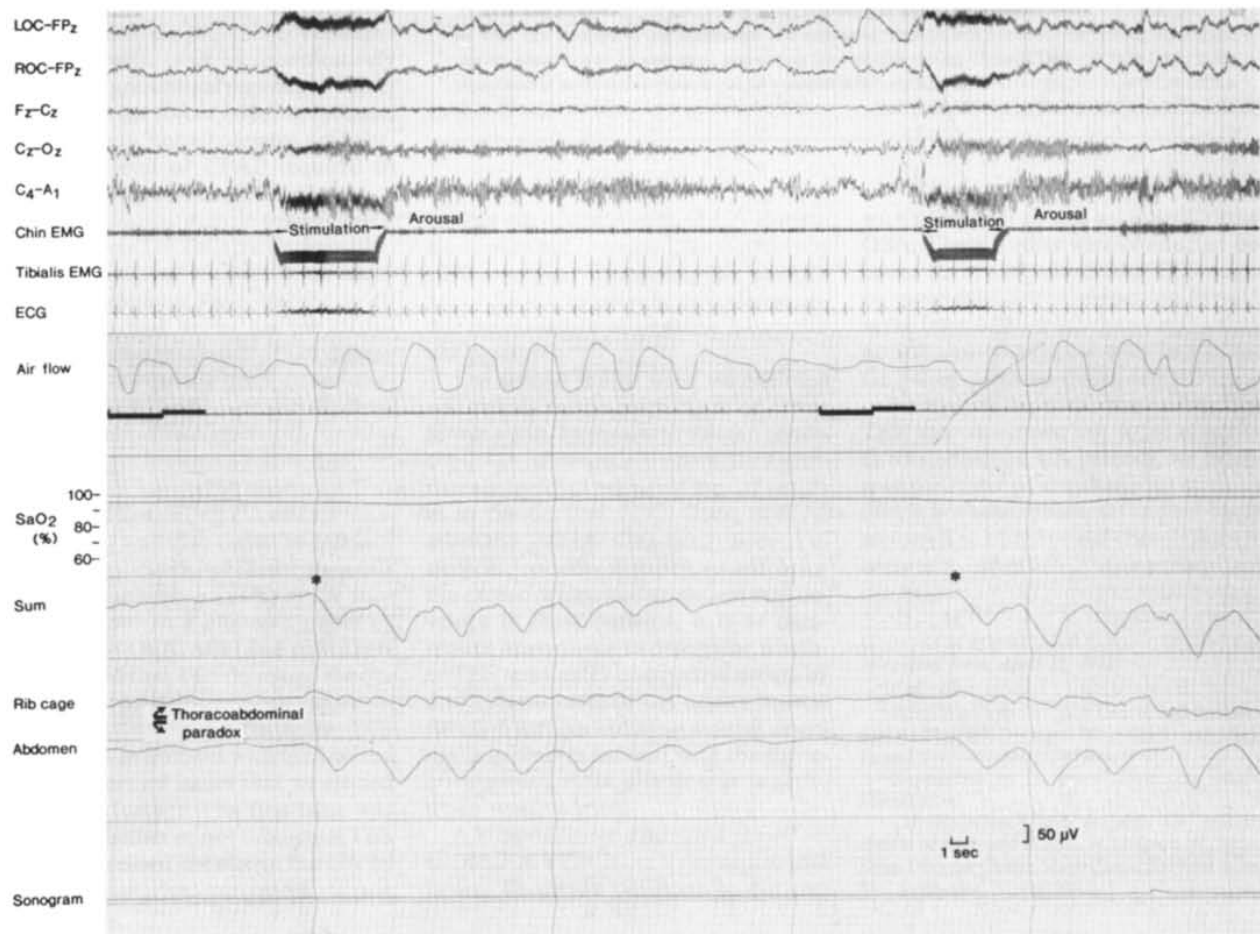
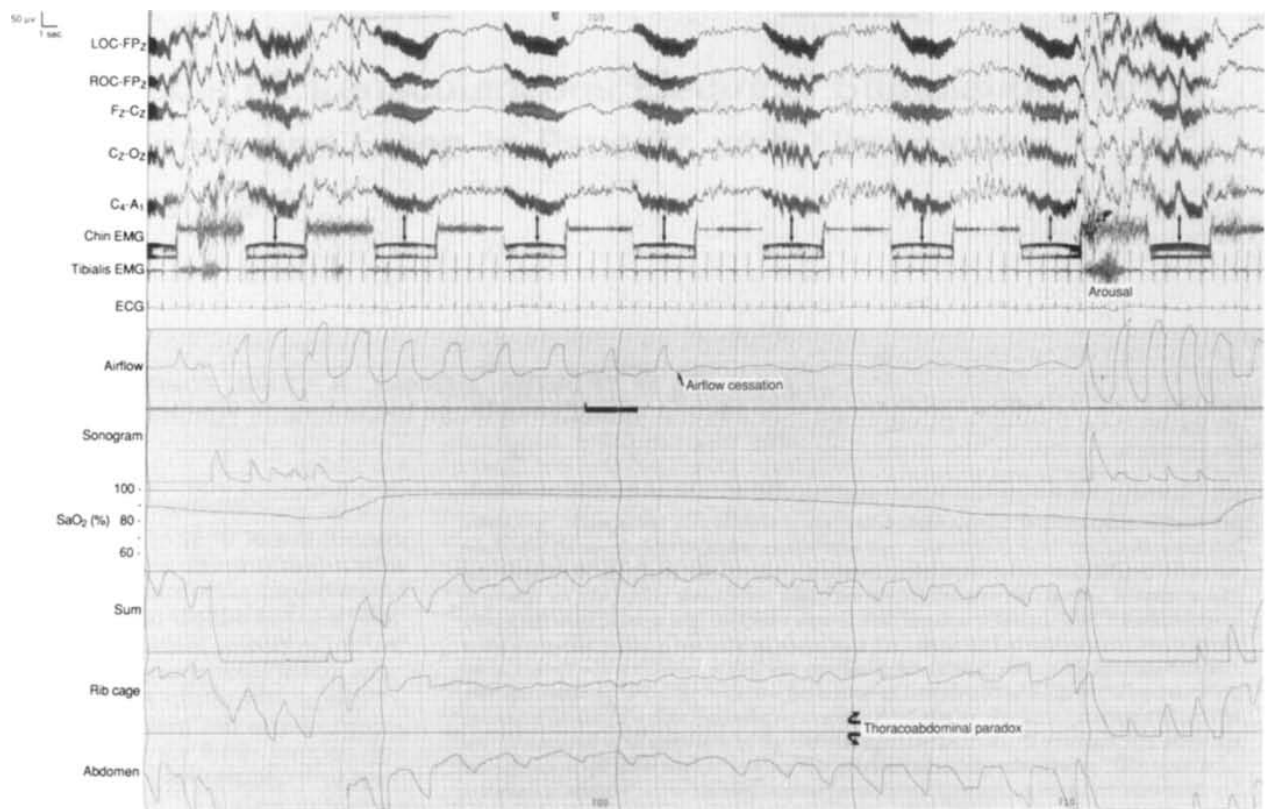


TABLE 1
SLEEP ARCHITECTURE RESULTS FOR POSITIONAL AND NONPOSITIONAL PATIENT GROUPS WITH
OBSTRUCTIVE SLEEP APNEA UNDERGOING TRANSCUTANEOUS ELECTRICAL STIMULATION*

	Nonpositional Group (n = 4)			Positional Group (n = 4)			Combined Groups (n = 8)		
	Nonstimulated	Stimulated	p Value	Nonstimulated	Stimulated	p Value	Nonstimulated	Stimulated	p Value
TST, min	116 ± 28	117 ± 17	NS	124 ± 7	78 ± 14	NS	120 ± 13	98 ± 13	NS
Efficiency	84 ± 9	77 ± 9	NS	88 ± 2	68 ± 7	NS	86 ± 4	72 ± 5	NS
Stage 1, % TST	56 ± 13	70 ± 21	NS	42 ± 10	70 ± 13	NS	49 ± 8	70 ± 11	NS
Stage 2, % TST	26 ± 11	15 ± 10	NS	33 ± 8	18 ± 9	NS	29 ± 6	17 ± 6	NS
Stage 3-4, % TST	2 ± 2	4 ± 4	NS	11 ± 5	6 ± 5	NS	6 ± 3	5 ± 3	NS
Stage REM, % TST	17 ± 5	12 ± 7	NS	14 ± 2	6 ± 4	NS	16 ± 3	9 ± 4	NS

Definition of abbreviations: TST = total sleep time; NS = not significant.

* Data are mean ± SEM.

presented in table 1. The sleep fragmentation associated with severe OSA is demonstrated by the abnormally large percentage of Stage 1 sleep. Correspondingly, the decrease in slow wave (SW) sleep, rapid-eye movement (REM) sleep, and sleep efficiency also reflect the severity of the OSA in our study population. Because recording artifact associated with stimulation made it difficult to accurately identify the occurrence of short arousals (see figure 1), an arousal index was not tabulated.

When comparing between the conditions of nonstimulation and stimulation, overall or in subgroups (nonpositional and positional), no statistical differences were found in sleep efficiency, total sleep time, or the percentage of time spent in each stage. Although not significant, stimulation was associated with a trend toward an increase in NREM Stage 1, a decrease in NREM Stage 2, and a decrease in sleep efficiency.

Several qualitative observations were made concerning the effect of stimulation on sleep. Varying intensities of stimulation within our experimental stage were capable of producing arousal in all stages of NREM sleep at any time during the night. However, as the night progressed, the intensity of stimulation required to produce arousal increased independent of sleep stage. REM sleep was often refractory to stimulation-induced arousal within the constraints of our stimulation intensities. No subject complained of discomfort associated with the use of nocturnal stimulation. When the

subjects were questioned in the morning after the study, they failed to recall any of the arousals, whether stimulation or disordered-breathing-associated.

Sleep-disordered Breathing

The clinical effect of stimulation on disordered breathing was measured by the AHI. The AHI results for the nonpositional and positional subgroups by sleep position (supine and nonsupine) are shown in figure 2. Stimulation had no significant effect on AHI in either patient group in either position. Sleep in the nonsupine position, however, did demonstrate the anticipated effect of decreasing the AHI in the positional OSA group.

A typical nonstimulated disordered-breathing event terminates with arousal. This was also our finding for stimulated events (see figure 1). Stimulation apart

from arousal appeared to have no effect on disordered breathing. Although arousals appeared to occur earlier with stimulation and therefore could have resulted in less oxygen desaturation, the difference in mean oxygen desaturation between nonstimulated ($7 \pm 2\%$) and stimulated ($6 \pm 1\%$) disordered-breathing events was not significant ($p > 0.05$).

Upper Airway Cross-sectional Area

The comparison of CSA was performed at eight UA levels. The scans were aligned using the boundary between VP and OHP. The mean CSA over the eight levels in six subjects at FRC with the tongue neutral and tongue protruded are shown in figure 3. Tongue protrusion resulted in significant increases in the CSA at OHP Levels 1 and 2, with mean increases of 273 and 183 mm², respectively. The caudalmost segment of the velopharynx

Fig. 2. Mean apnea plus hypopnea indices (AHI) in the supine and nonsupine sleep positions for patients with nonpositional (n = 4) and positional (n = 4) OSA. The solid bars represent nonstimulated sleep, and the hatched bars represent stimulated sleep. No significant difference was demonstrated for the AHI between nonstimulated and stimulated conditions. The data are mean ± SEM.

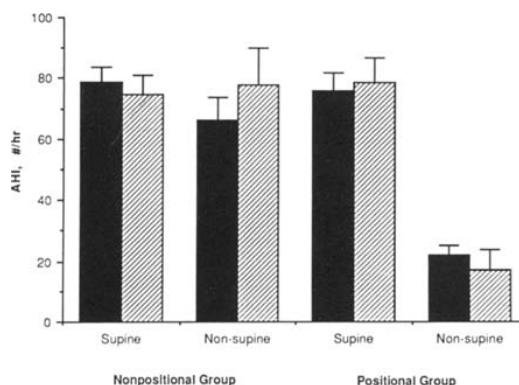


Fig. 1. *Top.* This polysomnographic tracing illustrates NREM Stage 1-2 sleep with an obstructive breathing event as demonstrated by the lack of oral and nasal airflow and presence of thoracoabdominal paradox. Four-second bursts of electrical stimulation at 80% Vmax (double-headed arrows) are shown to have no demonstrable effect on the obstructive event. Termination of the disordered-breathing event is coincident with EMG and EEG evidence of arousal. *Bottom.* This polysomnographic tracing illustrates awake and NREM Stage 1 sleep. Disordered-breathing events are present as demonstrated by reductions in airflow, oxygen desaturation, and thoracoabdominal paradox. The stimulation period is easily recognized by the high frequency artifact present in the upper eight recording channels. Although partially obscured by stimulation artifact, alpha rhythm (arousal) is present at the onset of stimulation, which is also coincident with the resolution of disordered-breathing events (asterisks).

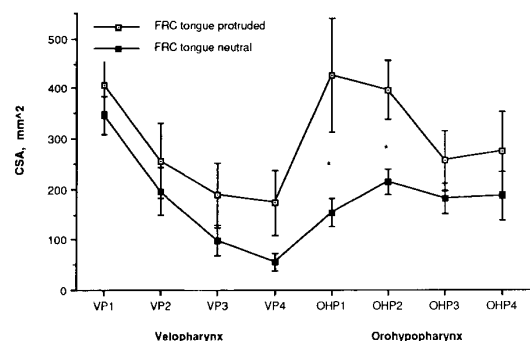


Fig. 3. Effects of tongue protrusion on upper airway (UA) mean cross-sectional areas (CSA) are represented over eight levels of the UA at FRC in six subjects with OSA. The open symbols represent the tongue protruded, and the closed symbols represent the tongue in the neutral position. Tongue protrusion resulted in a significant enlargement in the upper airway at oropharyngeal (OHP) Levels 1 and 2 (asterisks indicate $p \leq 0.05$). A trend toward enlargement was noted at velopharyngeal (VP) Level 4 ($p = 0.06$). The data are mean $\pm$ SEM.

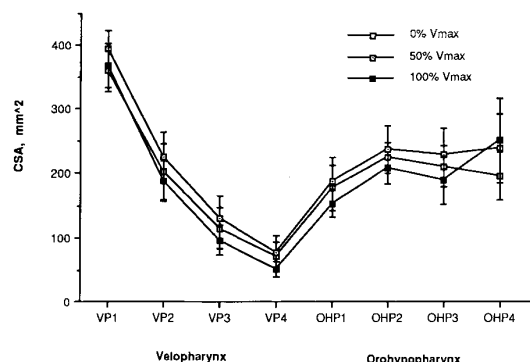


Fig. 4. Effects of transcutaneous electrical stimulation on upper airway (UA) mean cross-sectional areas (CSA) are represented over eight levels of the UA at FRC and atmospheric pressure for eight patients with OSA. Each line represents a separate intensity of submental stimulation (0, 50, and 100% Vmax). No significant differences were demonstrated between intensities of stimulation. The data are mean $\pm$ SEM.

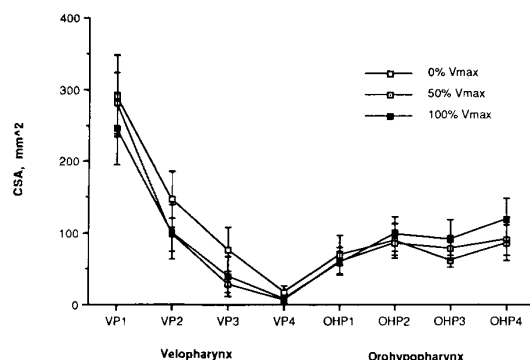


Fig. 5. Effects of transcutaneous electrical stimulation (TES) on upper airway (UA) mean cross-sectional areas (CSA) are represented over eight levels of the upper airway at FRC with -10 cm H₂O pressure for eight patients with OSA. Each line represents a separate intensity of submental stimulation (0, 50, and 100% Vmax). No significant differences were demonstrated between intensities of stimulation. The data are mean $\pm$ SEM.

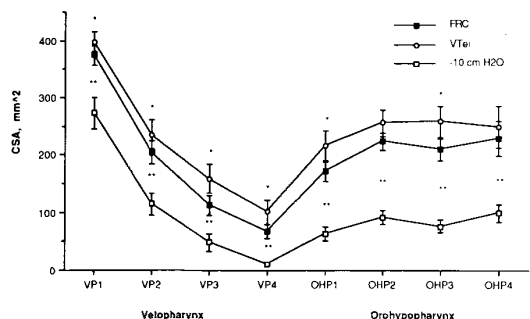


Fig. 6. Effects of tidal breathing and -10 cm H₂O pressure on upper airway (UA) cross-sectional area (CSA) over eight levels of the UA in eight patients with OSA. The effect of tidal breathing (FRC versus VTei) on CSA of the UA was significant (single asterisks indicate $p \leq 0.05$). The effect of pressure (FRC versus FRC -10 cm H₂O) on CSA was highly significant (double asterisks indicate $p \leq 0.001$).

(VP4) also demonstrated a trend toward increased CSA ($p = 0.06$), with a mean increase of 116 mm².

The effects of stimulation intensity and UA condition on CSA of the UA

were assessed using ANOVA. Under all three conditions (FRC, VTei, and -10 cm H₂O pressure) none of the stimulation intensities were observed to have any effect on CSA at any UA level. The lack

of effect of the various intensities of stimulation on the CSA of the UA at FRC and -10 cm H₂O, respectively, are shown in figures 4 and 5. Note that in the awake state, under conditions of negative UA pressure, even 100% Vmax stimulation did not prevent virtual collapse at VP Level 4 (mean CSA = 8 mm²).

Lung volume and UA pressure, like tongue protrusion, also had significant effects on CSA of the UA. Given that stimulation was found not to affect the CSA of the UA, the mean CSA is shown in figure 6 at each UA level for each condition (FRC, VTei, and FRC -10 cm H₂O) independent of stimulation. The difference observed between FRC at atmospheric pressure and FRC at -10 cm H₂O pressure was highly significant over all eight levels of the UA ($p \leq 0.001$). The effect of tidal breathing (lung volume) was also significant ($p \leq 0.05$) over all UA levels, with the exception of OHP Levels 2 and 4.

Discussion

The hypothesis of this study was that TES in either the submental or transhyoid regions would prevent UA collapse in patients with OSA by actively contracting the genioglossus, geniohyoid, mylohyoid, and/or strap muscles that were directly stimulated. This hypothesis was based on the previous work of Miki and coworkers (10) and the known physiology of the UA muscles (1–6, 11). Unfortunately, despite similar electrode placement and stimulation parameters, the present results do not support the previous work of Miki and coworkers. Their work suggested TES to be an effective modality to restore UA patency in patients with OSA independent of inducing arousals.

The findings of our study indicated that the sleep fragmentation associated with severe OSA is not improved with TES. The trend favoring an increase in NREM Stage 1 and decrease in NREM Stage 2 with stimulation would actually support a worsening of sleep fragmentation. Furthermore, in the absence of inducing arousal from sleep, TES failed to prevent both the onset of UA collapse, when started prior to apnea onset, as well as to reestablish UA patency when stimulation was begun after apnea onset. The stimulation intensity required to provoke arousal increased throughout the night independent of stage. Stimulation at Vmax failed to produce arousal in stage REM sleep late in the night. This finding is similar to the overnight increase in auditory arousal threshold that has been demonstrated by Bonnet (16).

The mechanism of arousal in OSA is considered to be multifactorial. Hypoxia, hypercapnia, acidosis, and mechanical loading of the respiratory system all contribute to increased ventilatory drive (effort) that results in arousal when a critical threshold is reached (17–21). In this context, TES is an external nonphysiologic stimulus that appears additive to the already operating physiologic stimuli responsible for arousals terminating disordered-breathing events. A constant intensity of stimulation, below the threshold for arousal, did not result in arousal until such time that sufficient stimulus for arousal was accrued by the disordered breathing event (see figure 1A). Disordered-breathing events appeared reduced in duration when associated with stimulation. The combined arousal effect of TES and a disordered-breathing event may be useful in protection against severe desaturation, but not in improving sleep fragmentation.

In an attempt to prevent airway closure rather than recover patency, we examined continuous and repetitive intermittent stimulation. These modes of stimulation also aided in habituation to the stimulus, allowing for any nonarousal mechanism of action to be better assessed. Control over the obstructive events remained unattainable without arousal despite preobstruction stimulation (see figure 1A). Muscle fatigue, from continuous stimulation, did not appear to be a problem given the fact that the obstructive events were easily terminated when arousal occurred.

Our CSA data using fast-CT indicated that transcutaneous stimulation had no effect on the size or stability of the UA in the awake state. The lack of effect was not an insensitivity to change in CSA of the UA, as we confirmed previous findings of Burger and colleagues, that increasing lung volume and decreasing UA pressure act to increase and decrease the CSA of the UA, respectively (personal communication). The lack of change in UA size with stimulation at both FRC and VT_{ei} indicated that varying the respiratory timing of the stimulation did not alter the action.

The scans examining the act of voluntarily protruding the tongue represent an idealized version of the maximal effect attainable by stimulation of the genio-glossus. This voluntary action had the expected effect of enlarging the retroglossal OHP segment of the UA. More interesting was the borderline significant trend, $p = 0.06$, towards enlargement of the VP segment of the UA, which is usu-

ally the narrowest region, as well as the site of initial UA collapse (22, 23). This increase in CSA of the VP segment did not occur secondary to surface tension between the palate and tongue, as there was a large separating air space identified in all scans. The increase was more likely the result of anterior tension being exerted on the palatoglossal arch and, consequently, the soft palate. Such non-neuronal interactions between segments of the upper airway may account for the success of mechanical devices such as the tongue-retaining device (24).

Although our conclusions regarding electrical stimulation of the UA muscles for the treatment of OSA are contrary to those of Miki and coworkers (10), several differences are notable between the two studies. Miki and coworkers did not include hypopnea in their definition of disordered breathing, but rather they considered only apnea of greater than 10 s for inclusion. We chose not to confine our analysis to apnea alone given that significant sleep-disordered breathing also occurs secondary to hypopneas (25, 26). For the purpose of evaluating submental stimulation, the use of time criteria to score disordered-breathing events is problematic. This is because disordered-breathing events that terminate in less than 10 s are not scored, despite the possibility of arousal that may be obscured by the stimulation-induced artifact. The arousal associated with moderate levels of stimulation are shown in figure 1B. In subjects with lower amplitude alpha and more rapid return to sleep, the arousal can be difficult to detect in the presence of stimulation artifact.

Miki and colleagues did conduct sham experiments using the same stimulation conditions on an extremity. Limb stimulation did not produce arousal or improve disordered-breathing events. Unfortunately, similar stimulation conditions administered to another body location may not represent an adequate experimental control. The effects of TES, including noxious effects, are very dependent on local tissue impedance and neural innervation (13). Therefore, equal external stimulation may not produce equal neural stimulation, leading to differences in arousal threshold at different stimulation locations.

Our findings on electrical stimulation in the submental region should not be misinterpreted as evidence against previously established information on the role of UA muscles during respiration. Numerous reports exist correlating increased individual UA muscle activity

with decreased UA airflow resistance (3, 11, 27, 28). We realize that the relatively nonspecific stimulation that occurs with transcutaneous stimulation does not produce selective muscle activation and that it may in fact recruit antagonistic UA muscles. In this context, activation of the mylohyoid, which elevates the tongue and floor of mouth, may not have a beneficial effect in the prevention of sleep-disordered breathing. Similarly, nonspecific activation of the musculature of the tongue does not necessarily translate into its anterior movement. The tongue is made up of a complex set of muscles, both extrinsic and intrinsic, that permit movement in multiple directions. Therefore, the net movement resulting from submental electrical stimulation may not necessarily be in an advantageous direction. Selective stimulation of single muscles with implanted electrodes may serve to produce more specific actions, as well as to decrease the stimulus intensity, thereby avoiding the problem of stimulus-induced arousals.

In summary, submental and transhyoid TES failed to control disordered-breathing events in patients with OSA. Sufficient stimulation intensity to terminate an apneic event resulted in arousal. Submental stimulation during wakefulness also failed to enlarge the CSA of the UA at FRC or VT_{ei}, or to decrease the collapsibility of the UA in response to -10 cm H₂O pressure as measured by fast-CT. Increases in lung volume and voluntary tongue protrusion were associated with increases in UA size, whereas -10 cm H₂O pressure decreased the CSA of the UA. Further studies using more specific stimulation techniques will be required to evaluate the role of augmenting the contractile force of individual muscles in the prevention of UA collapse in patients with OSA.

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