The Effect of Electrical Stimulation on Obstructive Sleep Apnea Syndrome*

Christian Guilleminault, MD; Nelson Powell, MD; Bruce Bowman, PhD; and Riccardo Stoohs, MD

Patients with severe obstructive sleep apnea polygraphically documented underwent electrical stimulation treatment trials. Submental and intraoral stimulations were applied during waking and during nocturnal sleep. The stimulation was applied using a custom-designed neuromuscular electrical stimulator (EdenTec Corp) providing symmetric biphasic constant voltage pulses. Pulse duration of each phase was set to 80 μs based on a subjective evaluation of pulse durations from 80 to 300 μs to minimize sensation while generating equivalent motor responses. Pulse repetition rate was set to 50 pulses per second. Cephalometric radiographs and endoscopies were obtained with and without stimulations during waking. Most commonly, stimulations induced alpha EEG arousals. Submental subcutaneous stimulation induced good contractions of platysmal muscles but had no impact on the upper airway. Intraoral stimulation induced clear tongue muscle movements but with change of shape of the upper airway and posterior movements of the tongue. Each time a breakage of apnea was noted, it was associated with a time-linked alpha EEG arousal. The results obtained by us and others do not, at this time, give convincing support for the use of electrical stimulation using submental surface or intraoral electrodes as a viable approach for effective control of obstructive sleep apnea syndrome symptoms. (Chest 1995; 107:67-73)

CPAP=continuous positive airway pressure; OSAS=obstructive sleep apnea syndrome

Key words: airway patency; electrical stimulation; obstructive sleep apnea

tispecialty expertise. Dental appliances have also not been tested systematically; most reports have essentially been testimonials unsupported by appropriate experimental protocols providing objective data. Interestingly, the generic label “dental appliances” is commonly used in the literature without discrimination between the many different models found from region to region throughout North America (it should be noted that the effectiveness of these models and their complications have yet to be investigated in parallel studies).

With such dismal results obtained from the most recommended treatments, it is evident that further research toward new and better therapeutic approaches should be undertaken. In 1989, Miki et al.,2 after experimentation on dogs, reported positive results with submental electrical stimulation during sleep on upper airway patency in patients with OSAS. Our report is the second in a series of experiments we have performed on patients with OSAS and controls, using electrical stimulation during sleep, as previously tried in Japan.

METHODS

Stimulator

A custom-designed neuromuscular electrical stimulator (EdenTec Corporation, Eden Prairie, Minn), providing biphasic constant voltage pulses, was used in the study. Biphasic pulses were chosen to obtain active stimulations under both electrodes and thus maximize motor responses. The pulse duration was set to 80 μs based on subjective evaluations of pulse durations from 80 to

*From the Stanford University Sleep Disorders Center, Palo Alto, Calif (Drs Guilleminault, Powell, and Stoohs), and EdenTec Corporation, Eden Prairie, Minn (Dr. Bowman). Supported by National Institute of Aging Grant RR-07772 and by the General Clinical Research Center Grant RR-00070 from the National Institutes of Health.

Manuscript received November 24, 1993; revision accepted June 15, 1994.
Table 1—Thresholds and Tolerable Amplitude With Electrical Stimulation*

<table>
<thead>
<tr>
<th></th>
<th>Current, mA</th>
<th>Voltage, V</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Submental stimulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory threshold</td>
<td>1-3</td>
<td>4-10</td>
</tr>
<tr>
<td>Motor threshold</td>
<td>5-6</td>
<td>10-20</td>
</tr>
<tr>
<td>Maximum tolerable</td>
<td>6-12</td>
<td>20-40</td>
</tr>
<tr>
<td><strong>Sublingual stimulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory threshold</td>
<td>1-1.5</td>
<td>7-10</td>
</tr>
<tr>
<td>Motor threshold</td>
<td>1.5-3</td>
<td>9-15</td>
</tr>
<tr>
<td>Maximum tolerable</td>
<td>2.5-4</td>
<td>12.5-17.5</td>
</tr>
</tbody>
</table>

*Stimulus voltages and currents were recorded respectively for sensory threshold (Vst, Ist), motor threshold (Vmt, Imt), operational levels (Vop, Iop), and maximum tolerable (Vmax, Imax). Thresholds and tolerable amplitudes are summarized in the table for both surface submental stimulation and intraoral sublingual stimulation.

300 ms at amplitudes generating equivalent motor responses and minimal sensation. The pulse repetition rate was set to 50 pulses tetanization per second based on the minimum rate to produce a contraction. The stimulus amplitude was “rammed” up on each period over a 1-s period from sensory threshold to operation level, and held for an additional 1 to 2 s in order to minimize potentials for causing arousals related to sudden onset of sensation or motor contraction. Stimulus voltages and currents were recorded for sensory threshold and maximal tolerable threshold, respectively. Stimulations were gated to respiratory movements (end expiration and end inspiration being determined from airflow or from thoracoabdominal movements). Bilateral stimulations were also tried in a systematic fashion during the same sleep states. The stimulations were then applied using two stimulators with amplitudes set independently. Threshold and tolerable amplitudes for both surface submental stimulations and intraoral submental stimulations are summarized in Table 1.

Subjects

All subjects were patients with documented OSAS (two of them despite previously performed uvulopalatopharyngoplasty) who signed informed consent forms approved by the institutional review board. All subjects had undergone nocturnal clinical investigation, polysomnography, imaging testing, and otolaryngologic evaluations with endoscopy, to confirm the severity of the syndrome and the predominant locations of the upper airway collapse. The upper airway collapse involved the base of the tongue. This was based on findings obtained with endoscopy and cephalemeters during wake examination and obtained with endoscopy performed during NREM sleep. All subjects had also been titrated previously for appropriate relief of their syndrome with nasal CPAP and had demonstrated a positive response to this treatment, with significant abatement of subjective symptoms and clear improvement at follow-up polysomnography. They had discontinued their nasal CPAP for a minimum of 48 h (and usually longer) before the experimental trial. Seven men, with a mean age of 61 ± 8 years, a mean body mass index of 27.2 ± 3 kg/m², a mean respiratory disturbance index of 55 ± 6 per hour of sleep, and a mean lowest SaO₂ during the night of 80.2 ± 4% signed informed consent forms.

Experimental Design

Overall Plan: Subjects were requested to stop nasal CPAP treatment for a minimum of 3 days before the experimental protocol. Reappearance of the abnormal nocturnal features was checked by nocturnal ambulatory recordings (MESAM-4 equipment [Madaus Co]® or Edentrace equipment [EdenTec Corp]®) and by reports from patients and spouses on the recurrence of symptoms. Prior to the beginning of the experimental manipulations, oral dental impressions were obtained. These impressions were used to build individual oral appliances with embedding of stimulation electrodes that could sit at different levels on specific muscles (specifically tongue muscles) or in close proximity to the hypoglossal nerve, bilaterally. Thus, during the experimental sessions, two methods of stimulation were used: (1) submental stimulation and (2) intraoral stimulation with direct application of stimulii on muscles and on nerves. A selector allowed easy selection of the electrodes used for stimulation, as there were several (up to eight) electrodes on both sides that could be used as stimulating electrodes (Fig 1 and 2). The beginning of stimulation was planned to occur at different time points during the night—at the beginning of inspiration, at the end of expiration, and at midinspiratory cycle and midexpiratory cycle. With each stimulation, the stimulating electrode selected and the timing of the stimulation within the respiratory cycle were continuously recorded, as were the timing of apneas and hypopneas within the respiratory cycle. Stimulations were planned to occur (1) during apneic events, to try to break the upper airway occlusions or (2) before any apneas occurred during sleep. These two experimental conditions were set up (1) to note whether electrical stimulations of the upper airway dilator muscles could reopen a closed airway and (2) to observe whether early stimulation (ie, before appearance of apneas and hypopneas) could avoid upper airway collapse, with maintenance of a sufficiently large upper airway patency. Patients were continuously kept in the supine position during baseline and experimental nights so that sleeping position would not influence the data.

Patient Schedule: Each subject underwent a midafternoon awake study and a nocturnal sleep study. In the afternoon, subjects were fitted with submental and intraoral electrodes, and sensory threshold, motor threshold, and maximum tolerance were determined. Endoscopies were performed to verify electrode placements and responses to stimulations. These responses were also photographed through the endoscope to measure them. Cephalometric radiographs were also taken before and during stimulations to evaluate the effects of stimulations on the upper airway patency.

In the evening, equipment was set up to perform complete polysomnography on all patients. This involved measurements of EEG, electro-oculogram, chin electromyogram, ECG, nasal airflow, thoracic and abdominal movement by noncalibrated inductive respiratory plethysmography, respiratory efforts with measurement of esophageal pressure, and pulse oximetry. Every attempt was made to reduce monitoring artifact and to obtain the clearest EEG recording possible. Stimulations were performed in specific sequences: isolated, in successive volleys, and during NREM or REM sleep. In four subjects, endoscopy was performed for a fixed period during sleep at the time of stimulation during NREM sleep.

Submental Stimulation: Patients were left to fall asleep. All of them presented normal NREM-REM sleep succession, but in the baseline condition, none of them presented slow-wave sleep. The protocol called for the beginning of stimulation with the onset of stage 2 NREM sleep. The investigation was performed in stages. Initially, stimulations were started within 5 s of appearance of an abnormal breathing event. The stimulation continued through the apnea or the hypopnea (50 pulses tetanization per second with repetition every second). Stimulations were stopped with resumption of breathing and started again with a new event. A mean of 15 events were explored in succession. Then a break occurred. Four different electrode combinations were tried with unilateral stimulation. Next, bilateral stimulations using the different electrode combinations were tried. After these initial trials, stimulations before onset of any events were performed. Once clear stage
1 or stage 2 NREM sleep was observed, a series of stimulations was initiated. This repetitive stimulation was independent of the respiratory cycle and was terminated when 15 abnormal breathing events had been seen.

During REM sleep, the two types of stimulation timing were also applied. There was a mean of 15 breathing events investigated within 5 s of onset with unilateral and with bilateral stimulations, and groups of stimulations were also performed starting prior to onset of apnea or hypopnea and stopped after occurrence of a mean of 15 breathing events despite unilateral or bilateral stimulations.

**Intraoral Stimulation:** The device with stimulating electrodes was tightly fitted in the mouth, using support from frontal and lateral teeth. This precision was possible as each device was custom made from dental impressions. The tight fitting avoided movements of stimulating electrodes. Here also, stimulations were applied unilaterally and bilaterally. As with submental stimulations, two different approaches were used: (1) stimulations within 5 s of onset of a breathing event and (2) stimulations before onset of any event.

Finally, we also timed the onset of stimulations with regard to the respiratory cycle. The esophageal pressure recording was the triggering index: bilateral stimulations were started at the beginning of inspiration, at the end of inspiration, and during the last third of expiration. Recordings were performed during NREM and REM sleep. A block of 15 events was studied. At the end of a block of events, the stimulation paradigm was interrupted; patients were left to develop their usual sleep and breathing pattern for a period of time that was within the same time range as the prior stimulation period. Finally, once these different avenues had been explored, bilateral stimulations were performed repetitively for 20 min without interruption, independent of the sleep state or stage.

**Analysis**

Recordings were analyzed for presence/absence of apneas and hypopneas, relationship between stimulations and upper airway occlusion, and relationship between stimulation and presence/absence of EEG arousals. The frequency of apneas-hypopneas during baseline and stimulation nights was compared with subdivision by sleep state and circadian time during the night. We also compared duration and frequency of apneas and hypopneas

**Figure 1.** Example of submental electrodes used for transcutaneous stimulations during sleep. A selector allowed us to choose the set of stimulating electrodes.

**Figure 2.** Example of intraoral electrodes inserted in an individual oral appliance.
and associated oxygen desaturation seen during intervals without stimulations with intervals with stimulations on the experimental night. Apnea and hypopnea were defined based on analysis of airflow, thoracic and abdominal movements, esophageal pressure, and oxygen saturation monitorings. We used the internationally used definitions of apnea and hypopnea for duration and type (i.e., obstructive, mixed, and central). For this study, an apnea was defined as decrease of airflow by 90% compared with best airflow seen in the prior 60 s. Hypopnea was defined as a 30% decrease of airflow compared with best airflow also measured during the past 60 s.

Endoscopic investigations during day and night time were compared, and confrontation of daytime endoscopic and cephalometric evaluations was performed. Subanalysis for stimulation-related breakage of apnea and determination of EEG arousal were performed. When the mean duration of apnea was shortened or if an apneic event seemed to be interrupted by stimulation, subanalysis was performed to look specifically at the breakage of apnea as related to the stimulation. Due to the risks of misinterpreting the data, we did not consider the EEG during the stimulation period, and we also did not consider the first 3 s immediately following the end of the stimulation. These EEG sequences were eliminated in determining stimulus-induced arousals, as we could not rule out the presence of stimulus-induced EEG artifacts. We considered, however, that the apnea breakage was related to a bona fide EEG arousal and not to a direct effect on the upper airway muscles, if the EEG arousal was seen in association with the breakage of the apnea for a longer duration and persisted with return of normal breath for at least 3 s after our EEG measurement onset.

**Results**

The results of the investigation can be summarized very briefly: independently of the paradigm selected, we were unable to improve the condition of our seven patients using the above stimulation protocol compared with baseline results.

**Stimulation With Submental Electrodes**

**Endoscopic Results:** Similar findings were noted during waking and sleep. Submental electrodes induced good contraction of the platysma. There was an easy visualization of the subcutaneous muscular response. However, no effect on the posterior airway space could be noted at maximum tolerance.

**Polygraphic Analysis:** A mean total of 60 apneas and hypopneas were investigated per subject during NREM sleep and a mean of 30 during REM sleep, with unilateral and with bilateral stimulations started just after onset of events. A similar mean total of apneas and hypopneas seen during NREM and REM sleep were investigated with unilateral and with bilateral stimulations triggered before any event. Data obtained during stimulations were compared with the apneas and hypopneas observed during the interval between stimulation periods and compared with baseline recordings.

No change in the number of apneas and hypopneas, amount of oxygen desaturation, and mean duration of respiratory events was observed when no arousals were noted in association with stimulation compared with mean duration of events monitored on baseline and compared with events monitored during the interval without stimulation on the experimental night. We were unable to terminate apneas after their onset or to prevent their occurrence. Above a threshold, which varied with each individual, arousals would occur. The duration of apneas may be reduced by the arousals. If an apnea or a hypopnea was not interrupted by an arousal, oxygen desaturation and mean duration of events were similar to those seen just prior to the start of the stimulation in NREM sleep (Table 2).

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>Mean Lowest SaO2</th>
<th>Mean Duration of Events, s</th>
<th>Mean No. of Apnea/Hypopnea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NREM</td>
<td>REM</td>
<td>NREM</td>
</tr>
<tr>
<td>Baseline</td>
<td>7</td>
<td>83.7 ± 1.8</td>
<td>83.6 ± 3.2</td>
</tr>
<tr>
<td>Submental bilateral stimulation</td>
<td>7</td>
<td>83.1 ± 2.6</td>
<td>83.1 ± 3.6</td>
</tr>
<tr>
<td>Before any event</td>
<td>7</td>
<td>83.9 ± 1.8</td>
<td>83.3 ± 2.4</td>
</tr>
<tr>
<td>After onset of event (90)</td>
<td>7</td>
<td>83.1 ± 2.4</td>
<td>83.9 ± 3.7</td>
</tr>
<tr>
<td>Submental unilaterial stimulation</td>
<td>7</td>
<td>83.7 ± 2.8</td>
<td>83.4 ± 2.4</td>
</tr>
<tr>
<td>Before onset of event</td>
<td>7</td>
<td>83.3 ± 2.5</td>
<td>83.3 ± 2.8</td>
</tr>
<tr>
<td>After</td>
<td>7</td>
<td>83.6 ± 1.7</td>
<td>83.3 ± 2.5</td>
</tr>
<tr>
<td>Intraoral bilateral stimulation</td>
<td>7</td>
<td>83.9 ± 2.8</td>
<td>83.3 ± 2.7</td>
</tr>
<tr>
<td>Before</td>
<td>7</td>
<td>83.8 ± 1.6</td>
<td>83.2 ± 4</td>
</tr>
</tbody>
</table>

*The results presented in the table were collected on breathing events uninterrupted by arousals related to stimulation. None of the differences were statistically significant (Wilcoxon rank test).
Sublingual Stimulation

Investigation During Waking: Clear movements of the tongue could be obtained, with visual observations of muscle contractions with unilateral and bilateral stimulations. The endoscopic investigation most commonly indicated a combination of effects: a shortening of the muscle mass associated with a posterior movement of the base of the tongue. Cephalometric radiographs confirmed the findings and indicated that the muscle contractions induced an elevation of the hyoid bone, compared with just prior to baseline, with a further closing of the posterior airway space (Fig 3). In the most efficient stimulations, the shortening of the base of the tongue and the upward movement of the hyoid bone was associated with changes from an elliptic airway at rest to a narrower circumferential airway during stimulation. The upward movement of the hyoid bone was a mean of 2.5 ± 1.0 mm compared with just preceding baseline.

Investigation During Sleep: Endoscopic evaluation during stage 2 NREM sleep demonstrated similar findings to those already noted. Polygraphic recordings indicated results that were similar to those observed with submental electrodes. Independent of the timing of the stimulations (before or after the onset of an event), we were unable to change the mean duration of an event without an arousal. Our patients had a large number of abnormal breathing events to start with. These events were very predictable in their recurrence and duration, particularly during NREM sleep. We performed a comparison of events obtained during baseline recordings with events seen during intervals before new series of stimulations. We also compared the duration of events and their frequency during the 20 min of uninterrupted repetitive stimulation. No significant difference could be obtained compared with non-stimulation if sleep was maintained. When repetitive stimulations that began before the appearance of any sleep-disordered breathing but after the establishment of sleep (clear stage 1 or stage 2 NREM sleep) and continued until a mean of 15 abnormal breathing events had occurred (or for 20 to 30 min independently of the number of events), we were unable to demonstrate a decrease in the number of
sleep-disordered breathing events per minute of sleep compared with baseline recording and compared with immediately prior recording without stimulation.

Table 2 presents the data obtained with introral stimulations. The 50 NREM sleep and 30 REM sleep-disordered events used as “baseline” had a mean duration of 22.7 ± 3.9 s during NREM sleep (hand-scored). In the segments without stimulation (baseline and experimental nights), the mean duration of a sleep-disordered breathing event during NREM sleep was 24 ± 3 s (computer scored). In 14 ± 8% of the stimulated segments, the mean duration of the sleep-disordered breathing events during NREM sleep was 13 ± 5 s. These shorter events were interrupted by stimulation-induced arousals. Each of the events with a clear change from the baseline mean was identified and a complete analysis of the EEG was performed.

We followed the rules indicated in the analysis section, and we always requested at least 3 s of alpha EEG seen in association with event breakage to affirm arousal (ie, stimulation time plus 3 s for artifact due to stimulation and 3 s to affirm arousal). We had difficulties in clearly identifying exactly when the arousal started in 2% of the total number of analyzed events. We were able to use our rule in all other cases. In these cases, the EEG arousals could be related to the early reopening of the airway. We could not determine why the arousal occurred earlier in association with these events, compared with other events in which the arousal was noted only at the end of events that fell in the usual distribution of sleep-disordered breathing event duration, as there was no increase in the stimulation paradigm.

We considered also the type of sleep-disordered breathing event, ie, hypopnea or apnea. Typically, particularly during NREM sleep, subjects presented a reproducible pattern of type of breathing event. We could not demonstrate that there was a significant shift in the type of sleep-disordered breathing event noted in the intervals with and without stimulation (ie, shift from “apnea” as defined to “hypopnea”). To evaluate this, we considered the type (apnea or hypopnea) seen during a similar time segment and similar sleep stage during baseline sleep study and the type of abnormal breathing event seen in the immediately preceding interval without stimulation on the experimental night. The total number of “apneas” scored when no stimulation was applied was 72 ± 9%. The total number of “apneas” scored when stimulation was applied was 73.5 ± 12% (not significant). The variability was very minimal during NREM sleep, and it was always mildly wider during REM sleep, but subjects always presented an overwhelming pattern, and no statistical difference could be shown when we compared mean number obtained on segments matched for sleep stage and 10-min circadian time during the night.

**Discussion**

Since the initial report by Miki et al.,1,2 several groups, working with dogs and humans, have tried to improve upper airway patency during sleep, with electrical stimulation.3,6 We tried such an approach in 1978 to 1979 with Blair Simmons who placed embedded electrodes consisting of very thin wires, in many of the upper airway muscles at the time of tracheostomy performed under general anesthesia.7 Once patients had recovered, tracheostomy openings were temporarily closed, monitoring of spontaneous EEG activities was performed,7 and secondary stimulation was applied. We always induced EEG arousals, and our first trials were considered a failure.

We recently performed two studies to reinvestigate this therapeutic possibility. One study (performed with Pierre Philip and others) investigated the impact of the stimulation procedures and device of Miki et al.5 on the sleep of normal subjects. We applied repetitive submental stimulations, as recommended for the treatment of sleep apnea, and induced a typical sleep fragmentation syndrome with appearance of repetitive bursts of alpha EEG during nocturnal sleep with each stimulus and significant impairment of alertness as indicated by the multiple sleep latency test. This report is the second phase of this investigation focusing on patients with obstructive sleep apnea. The patient population that participated had a large number of sleep-disordered breathing events (mean RDI=55), as noted in many previous reports. The pattern of repetition of abnormal events, type of events, and duration of events are very predictable, particularly during NREM sleep in these severely affected subjects. This pattern esas comparative studies, ie, with and without stimulations. However, one may argue that the reported results are valid only for the studied population and do not preclude different results with much milder sleep-disordered breathing.

We obtained negative results, close to those recently reported by Edmonds et al.5 However, in opposition to the Fairbanks and Fairbanks6 findings, we could not even induce significant changes in upper airway patency with submental stimulation without prior induction of EEG arousals. We also performed intraoral stimulations, an investigation not performed by Edmonds et al.5 and we observed clear changes in upper airway size, but despite elevation of the hyoid bone position with stimulation, a further narrowing of the upper airway with a posterior displacement of the tongue mass was noted. Once again, alpha EEG arousals were seen secondary to stimulation when
breakages of apnea were observed. Fairbanks and Fairbanks\(^6\) reported having had successful responses with stimulations of the hypoglossal nerve. Despite the poor reproduction of the polygraphic recordings in their report, it is clear, at least in Figure 4 of their published article, that an arousal response was associated with restoration of breath and lasted nearly 10 s after stimulation artifact. At the 1993 annual American Thoracic Society meeting where our results were presented, a Johns Hopkins University research team\(^8\) presented data obtained with direct stimulation of the hypoglossal nerves in patients also receiving 3 cm H\(_2\)O of positive end-expiratory pressure through nasal CPAP. Despite obtaining many negative findings similar to ours and also having alpha EEG arousals in their poststimulation recordings obviously associated with breakage of obstructive sleep apneas, these authors indicated that at times they observed a decrease in upper airway resistance with their complex apparatus using nasal CPAP as a means of investigation.

From the current studies, including ours, it appears that electrical stimulation has many pitfalls. It induces alpha EEG arousals, and submental stimulation does not seem to be effective without induction of these repetitive arousals. Intraoral stimulations may act on dilator muscles but many of the bundles included in the tongue muscles have multiple roles and contractions obtained, up to now, have modified the upper airway shape but have not opened the upper airway with maintenance of sleep.

It is possible that stimulation of specific bundles or stimulation of the hypoglossal nerves at the right place could lead to better results. This would require a very good understanding of the physiologic roles of the different bundles of specific tongue muscles and/or a good somatotopic description of the hypoglossal nerve, which is involved in so many functions (breath, swallowing, speech, etc) through movements of the tongue. Finally, it would be necessary to induce a specific protrusive movement without induction of a sleep disturbance with not only visual analysis of bursts of alpha EEG arousals, but also with maintenance of sleep continuity affirmed with more sophisticated, computer-based EEG analyses. Perhaps neuromusculature or direct stimulation of very specific muscles may be helpful when residual problems are seen in patients with OSAS already treated by other means. Currently results have been disappointing.

ACKNOWLEDGEMENT: We thank Harold Farmer for editing the manuscript.

REFERENCES

6. Fairbanks DW, Fairbanks DNF. Neuro stimulation for obstructive sleep apnea investigation. ENT J 1993; 93:52-7