Interacting effects of genioglossus stimulation and mandibular advancement in sleep apnea

Ron Oliven,1 Naveh Tov,1 Majed Odeh,1 Luis Gaitini,1 Uri Steinfeld,1 Alan R. Schwartz,2 and Arie Oliven1

1Bnai Zion Medical Center, Technion, Haifa, Israel; and 2the Johns Hopkins Sleep Disorders Center, Baltimore, Maryland

Submitted 8 November 2008; accepted in final form 11 February 2009

Although many anatomic abnormalities have been implicated in the pathogenesis of obstructive sleep apnea (OSA), the role of neuromuscular mechanisms is obvious, since apneas occur only during sleep, when muscle tone diminishes. The importance of upper airway dilator muscles for pharyngeal stability has long been recognized (2, 22, 29), and of those, the role of the genioglossus (GG) has been studied most extensively. Activation of the GG, the main tongue protrusor, has been shown in animal studies to reduce pharyngeal resistance and collapsibility by far more than all other upper airway dilators (15, 16). Electrically induced tongue protrusion has been shown to reduce pharyngeal resistance during wakefulness (24), lower the critical pressure (Pcrit) during sleep and anesthesia (18, 19), and enlarge the pharynx (19). However, despite its central role, electrically induced GG contraction resulted in rather modest effects on upper airway mechanics (i.e., collapsibility), with wide variations in response between subjects (18, 19). Failure to stimulate adequate areas of the GG and hypotonia of the nonstimulated upper airway muscles were considered as possible explanations for the lack of response in some of the patients.

Forward displacement of the mandible is known to improve upper airway patency in unanesthetized humans, as described over four decades ago (14). More recently, the concept was extended to the treatment of OSA using appliances designed to displace the mandible anteriorly during sleep (2, 5). MA has been shown to decrease Pcrit during sleep (9) and muscle paralysis (11) and to enlarge both the oro- and velopharynx (11). However, MA produces only a partial clinical effect in OSA, even when custom-made devices are used (28).

We hypothesized that combining two moderately effective methods known to lower Pcrit may improve the results by shifting Pcrit well below atmospheric pressure. The combined effect of MA and GG electrical stimulation (GG-ES) is difficult to predict: both MA and GG contraction are thought to ameliorate pharyngeal patency by displacing the tongue anteriorly, thereby preventing its collapse into the pharynx, reducing external pressure at the level of the velopharynx, and possibly stretching the soft palate indirectly by pulling lateral pharyngeal structures (11, 19). Due to the similar mode of action, their combination may be less than additive. On the other hand, if MA improves the operating length of the GG (20), they may act synergistically. The present study was undertaken, therefore, to evaluate the interacting mechanical effects of MA and electrically induced tongue protrusion on the pharynx in patients with OSA. Studies were performed under propofol anesthesia, to enable instrumentation and visualization of the pharynx, adequate GG-ES and optimal MA, without arousal.

METHODS

Subjects. Patients with OSA (defined as symptomatic patients with more than 5 episodes of obstructive apneas and/or hypopneas per hour sleep), previously documented on a conventional overnight polysomnographic sleep study, were recruited for this study. Patients with any disease that could pose a risk for anesthesia, including ischemic heart disease, any lung disease, severe or uncontrolled hypertension, and body mass index > 39 kg/m², as well as subjects with known side effects to any previous anesthesia, were excluded. All studies were performed in the respiratory research laboratory of Bnai-Zion Medical Center. The aims and potential risks of the study were explained, and informed consent was obtained from all subjects. The study was approved by the Institutional Human Investigations Review Board.

Recording procedures. Standard polysomnographic techniques, including right and left electrocereogram (EOG), submental surface EMG, C3-O1 and C3-A2 EEG, ECG, and oxygen saturation, were employed for monitoring during anesthesia. Subjects breathed through a tight-fitting nasal mask and a pneumotachometer, connected to a Validyne ±2 cmH2O pressure transducer (Validyne Engineering, Northridge, CA), with the mouth carefully and tightly sealed. The pneumotachometer was connected to a digitized variable-pressure

source at the inflow port, enabling variation of nasal pressure (Pn) between 20 to −10 cmH2O (MAP-Med, Marburg, Germany). Pn was monitored with a catheter connected to a side port of the mask. Intrathoracic pressure was measured with an esophageal balloon catheter (Ackrad Laboratories, Cranford NJ), used to recognize upper airway airflow limitation, as well as to distinguish between inspiration and expiration during complete apneas. Analog-to-digital acquisition of all parameters was performed at 1,000 Hz for monitoring and data storage on a digital polygraphic data acquisition system (LabVIEW, National Instruments, Austin, TX).

Pharyngoscopy. A flexible fiber-optic endoscope (Olympus BF-3C40, 3.3 mm OD) was inserted through an adequately sealed port in the nasal mask and positioned in the pharynx. The image was recorded on videotape, accompanied by audio explanations.

Anesthesia. Propofol anesthesia was delivered by an anesthesiologist, using a loading dose of 2.5 mg/kg and continuous infusion of 6–12 mg·kg⁻¹·h⁻¹. Using continuous positive airway pressure (CPAP) levels that enabled breathing without flow limitation, we aimed to maintain the patient under stable anesthesia that eliminated any reaction to pain, ES, and other manipulations, while maintaining adequate ventilation, as monitored by the pneumotachometer and pulse oximetry.

Electrical stimulation. Electrical stimulation (ES) of the GG (GG-ES) was applied via Teflon-coated, 0.018-cm-diameter hook-wire electrodes with bare ends, inserted sublingually, bilaterally, 10–15 mm deep into the anterior, retromandibular body of the GG, as previously described (17). Four to six electrodes were inserted in each subject. Forty-herz bursts of 2–6 s, with biphasic pulses of 100-μs width, were applied using a neuromuscular stimulator (Dynex III, Medtronic, Minneapolis, MN). Pharyngoscopic observation enabled us to choose the electrodes and stimulation intensity that provided the best pharyngeal dilatory response. The intensity of stimulation was limited to levels that were well tolerated during wakefulness in previous and preliminary experiments.

Mandibular advancement. MA was performed bimanually by one of the researchers who, while facing the patient, placed his thumbs on the maxilla to fix the head firmly and prevent its movement, positioned his fingers behind and around the mandibular angles bilaterally, and pulled the whole mandible forward. The mandible was advanced to obtain maximal velopharyngeal dilatation, as verified by pharyngoscopy. This position was maintained stable to record ~10 breaths without and with GG-ES.

Experimental procedure. Patients were prepared with EEG, EOG, submental EMG, ECG, venous access, and esophageal balloon and placed in the supine position. Following induction of anesthesia, Pn was raised to the level that abolished flow limitation (holding pressure), the endoscope and GG electrodes were positioned, optimal ES characteristics were determined, and the mouth was sealed. The sites of velo (VP)– and oropharyngeal (OP) collapse were determined visually by lowering Pn, enabling also determination of the primary site of pharyngeal collapse. Thereafter, the endoscope was placed first above the area of VP collapse. Flow:Pn and cross-sectional area (CSA):Pn relationships before and during GG-ES were determined simultaneously. With the patient maintained on holding pressure, Pn was lowered randomly for 8–10 breaths, encompassing four to six levels associated with inspiratory flow limitation and the level below which airflow ceased and the VP occluded. At each Pn level, after the fourth breath, GG-ES was performed for two to three consecutive breaths, and after additional two to three unstimulated breaths, Pn was raised back to the holding pressure for 2–3 min until stable baseline ventilation was observed. The same protocol was repeated after mandibular advancement. In a subgroup of patients, the endoscope was lowered below the VP site of collapse, to determine the OP CSA:Pn relationships, and the same protocol, before and during mandibular advancement, was repeated.

Data analysis. The flow:Pn relationship data were analyzed using digital software (Matlab). Maximal inspiratory flow was measured at the level when inspiratory flow reached a maximal level and plateaued while esophageal pressure fell progressively, indicating the presence of flow limitation. Values obtained before and after GG-ES (which were, by definition, almost identical) were averaged. The flow:Pn relationships was determined with least-squares linear regression. This relationship was used to calculate Perit as the level of Pn below which airflow became zero, as well as the flow:Pn slope. ΔPcrit (baseline Perit minus Perit during GG-ES) was used to quantify the mechanical effect of the manipulations evaluated.

The video movies of the pharyngeal lumen, taken during the evaluation of the flow:Pn relationships, before and during GG-ES, were digitized and viewed, and single pictures from the end-expiratory pause were captured and stored. The pharyngeal CSA in each digitized frame was outlined manually and calculated digitally using a locally developed pixel-counting program. The esophageal pressure tube, marked at regular levels, was used as a landmark, in addition to pharyngeal structures, to help measuring the CSA perpendicular to the pharyngeal axis, and as a reference for calculating the CSA in absolute units. The CSA:Pn relationships (i.e., pharyngeal compliance) was determined for the close-to-linear portion of this relationships only, with least-squares linear regression, as the Pn range over which flow limitation occurs is always within this range (see DISCUSSION). To assess the effect of GG-ES on the OP closing pressure (Pclose), which was usually below VP Perit, i.e., at Pn levels without airflow, we calculated Pclose from the CSA:Pn relationships.

Statistical analysis. SPSS was used for statistical analysis. Quantitative variables were expressed as means ± SD. Normality of distribution was assessed using Kolmogorov-Smirnov. All data were found to be normally distributed. The effects of manipulations were compared by ANOVA for repeated measures. A statistically significant difference was defined by a value of P < 0.05.

RESULTS

Fourteen subjects, all men, were studied, and their anthropometric and polysomnographic characteristics are given in Table 1. The patients’ age range was 27–70 yr, their apnea-hypopnea index (AHI) ranged between 9 and 79 per hour, and their BMI was between 26 and 38 kg/m², with five having a BMI > 30 kg/m².

Flow. The VP was the primary site of collapse in all of our subjects, based on the simultaneously observed occlusion of the VP and cessation of airflow, but in four of them an almost simultaneous occlusion at the OP level could be noted. At all Pn levels above Pcrit, OP CSA was larger than VP CSA, including those patients who occluded at about the same Pn at both levels. Therefore, the magnitude of flow limitation was always determined by the VP. The pressure:flow relationships of one of the patients, obtained during baseline conditions, during GG-ES, during MA, and during MA and GG-ES, are shown in Fig. 1. GG-ES, MA, and the combination of both

<table>
<thead>
<tr>
<th>Table 1. Anthropomorphic and sleep study data of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
</tr>
<tr>
<td>AHI, events/h</td>
</tr>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Apneas, events/h</td>
</tr>
<tr>
<td>SaO₂ &lt; 90%, % of sleep time</td>
</tr>
<tr>
<td>Lowest SaO₂, %</td>
</tr>
</tbody>
</table>

Values are means ± SD. AHI: apnea-hypopnea index; BMI: body mass index; SaO₂: % of sleep time spent with arterial oxygen saturation below 90%. Lowest SaO₂: lowest arterial oxygen saturation recorded during the sleep study.
shifted the pressure:flow relationships to the left, resulting in progressively lower Pcrit. Data derived from the pressure:flow relationship for the whole group are shown in Fig. 2. Pcrit decreased significantly during GG-ES, the decrease observed during MA was significantly larger, and GG-ES and MA had a significantly larger effect (ΔPcrit) on OP Pclose than on VP Pclose. Also, the effect of GG-ES at the OP was close to that of MA, and there was no significant difference between the effects of the two procedures. Probably due to the smaller number of subjects, ΔPclose during GG-ES before and during MA was not significantly different both at the VP and the OP level. OP compliance (CSA:Pn) was significantly larger than VP compliance both at BL and during GG-ES and MA. In contrast to the VP, MA increased OP compliance significantly, but the change in com-

The pharynx of 12 of the patients was completely obstructed at atmospheric pressure at baseline (Pcrit = 0 cmH2O), but MA + GG-ES lowered Pcrit below 0 in all. As shown in Fig. 4, the mean flow observed at atmospheric pressure increased progressively with GG-ES during MA and the combination of both. The mean flow observed with GG-ES during MA was close to the level observed at baseline with the lowest CPAP that prevented flow limitation (P = 0.054 for the comparison of these two values).

CSA. Endoscopic pictures depicting the effect of GG-ES, MA, and MA + GG-ES on the VP and OP in one of the patients are shown in Fig. 5. Both GG-ES and MA enlarged the pharynx at all Pn levels. VP compliance (CSA:Pn) varied considerably between patients but was not affected significantly by our manipulations (16.5 ± 16.0, 13.7 ± 8.5, 14.5 ± 8.5, and 12.5 ± 6.7 mmH2O for BL, ES, MA, and MA + GG-ES, respectively). Therefore, the enlarging effects of both GG-ES and MA were, in the mean, similar at low and high CPAP levels and shifted the CSA:Pn relationships to the left without changing the slope (compliance) of the CSA:Pn relationship. No correlation was found between baseline VP compliance and the response to GG-ES or MA.

OP studies were performed in six subjects, and their data are shown in Table 2 compared with the VP data of the same patients. As pharyngeal occlusion occurred at the VP at higher CPAP levels, the Pclose of the OP could only be derived from the endoscopic data. For equal comparison, we calculated also the Pclose of the VP for the same patients. OP Pclose was significantly lower than that of the VP, both before and during ES and MA. GG-ES and MA had a significantly larger effect (ΔPclose) on OP Pclose than on VP Pclose. Also, the effect of GG-ES at the OP was close to that of MA, and there was no significant difference between the effects of the two procedures. Probably due to the smaller number of subjects, ΔPclose during GG-ES before and during MA was not significantly different both at the VP and the OP level. OP compliance (CSA:Pn) was significantly larger than VP compliance both at BL and during GG-ES and MA. In contrast to the VP, MA increased OP compliance significantly, but the change in com-

Fig. 1. Pressure:flow relationships over the range of flow limitation in one of the patients at baseline (BL), electrical stimulation of the genioglossus (ES), mandibular advancement (MA), and combination of the two (MA + ES). MA lowered critical closing pressure (Pcrit) more than ES. The decrease in Pcrit during MA + ES is slightly more than additive. The slope of the pressure:flow relationships remained nearly unchanged, although it is slightly steeper [i.e., lower upstream resistance (Rus)] during MA + ES. Pn, nasal pressure.

Fig. 2. Effect of genioglossus contraction and mandibular advancement on Pcrit (top) and Rus (bottom). BL, baseline; ES, electrical stimulation of the genioglossus; MA, mandibular advancement; MA + ES, combination of MA and ES. Values are means ± SD. *P < 0.001 compared with BL. **P < 0.001 compared with ES. ***P < 0.001 compared with MA.
main findings are as follows. The mandible, on pharyngeal lumen and flow dynamics. The protrudes the tongue, and MA, which produces a similar effect significantly larger reduction in Pcrit than (negative synergy) or equal to the sum of both. Our combined effect of GG-ES and MA may be expected to be less "CPAP CPAP CPAP" or equal to the sum of both. Our combined effect of GG-ES and MA may be expected to be less "CPAP CPAP CPAP" or equal to the sum of both. Our combined effect of GG-ES and MA may be expected to be less than (negative synergy) or equal to the sum of both. Our finding that MA enhanced the effect of GG-ES, and, therefore, the combined effect of these two manipulations was larger than their sum, suggests that MA improved the mechanical properties of the GG, most likely by elongating its fibers closer to their optimal mechanical length. Although the magnitude of ∆Pcrit achieved with GG-ES during MA was not large, it was 38% greater than the baseline ∆Pcrit. The present findings bear some similarity to previous observations in the feline isolated upper airway model, which have shown an interaction between tongue advancement and caudal tracheal displacement (23). In addition, in the same study, increasing anterior displacement of the tongue lowered eventually Pcrit similarly to the response observed during tracheal displacement. This response suggested that marked tongue protrusion may decrease the Pcrit by lengthening the airway. Applied to the present study, stretching and stiffening of pharyngeal walls and peripharyngeal soft tissue by MA could have improved the mechanical response to GG-ES. However, such stiffening would have been expected to reduce pharyngeal compliance, which was not observed. Therefore, we favor the possibility that MA elongates the GG, thereby increasing its response to ES. We have previously shown that physiological positional changes of the head and trachea shorten the GG sufficiently to substantially reduce its mechanical effect (20). One may speculate that sleep and anesthesia induce a similar shortening of the GG, rendering this muscle less effective, and MA can restore its mechanical efficacy. However, this explanation needs to be validated since the length of the GG was not measured.

Because the mean slope of the pressure:flow relationships of the pharynx remained unchanged during GG-ES and MA, ∆Pcrit during these manipulations was similar to the change in effective CPAP, i.e., the decrease in the level of CPAP needed to prevent flow limitation during GG stimulation or MA. ∆Pcrit can be considered, therefore, as an estimate of a “CPAP equivalent”: in the present study we found that GG-ES, MA, and the combination of both were equivalent to the application of CPAP of about 2, 4, and 7 cmH2O, respectively. It should be noted that the larger effect observed with MA compared with GG-ES in this study was the result of the specific methodology of the GG, most likely by elongating its fibers closer to their optimal mechanical length. Although the magnitude of ∆Pcrit achieved with GG-ES during MA was not large, it was 38% greater than the baseline ∆Pcrit. The present findings bear some similarity to previous observations in the feline isolated upper airway model, which have shown an interaction between tongue advancement and caudal tracheal displacement (23). In addition, in the same study, increasing anterior displacement of the tongue lowered eventually Pcrit similarly to the response observed during tracheal displacement. This response suggested that marked tongue protrusion may decrease the Pcrit by lengthening the airway. Applied to the present study, stretching and stiffening of pharyngeal walls and peripharyngeal soft tissue by MA could have improved the mechanical response to GG-ES. However, such stiffening would have been expected to reduce pharyngeal compliance, which was not observed. Therefore, we favor the possibility that MA elongates the GG, thereby increasing its response to ES. We have previously shown that physiological positional changes of the head and trachea shorten the GG sufficiently to substantially reduce its mechanical effect (20). One may speculate that sleep and anesthesia induce a similar shortening of the GG, rendering this muscle less effective, and MA can restore its mechanical efficacy. However, this explanation needs to be validated since the length of the GG was not measured.

Because the mean slope of the pressure:flow relationships of the pharynx remained unchanged during GG-ES and MA, ∆Pcrit during these manipulations was similar to the change in effective CPAP, i.e., the decrease in the level of CPAP needed to prevent flow limitation during GG stimulation or MA. ∆Pcrit can be considered, therefore, as an estimate of a “CPAP equivalent”: in the present study we found that GG-ES, MA, and the combination of both were equivalent to the application of CPAP of about 2, 4, and 7 cmH2O, respectively. It should be noted that the larger effect observed with MA compared with GG-ES in this study was the result of the specific methodology.
used and may not reflect a physiological or practical superiority of MA. We advanced the mandible manually, aiming to achieve an optimal effect under pharyngoscopic guidance. This technique was chosen after failure of a thermoplastic oral appliance to produce adequate tongue advancement in preliminary trials, in accordance with a recent publication (28). Although the manual technique could be unstable, we found no evidence for consistent instability, and considered the necessity to obtain optimal MA to evaluate the effect of GG-ES at this condition more important. GG-ES, on the other hand, was produced by stimulating the GG near its mandibular insertion. The lack of substantial tongue advancement in some of the patients (19) suggests that direct GG-ES may result in suboptimal recruitment of the GG fibers that advance the tongue. The magnitude of reduction of apnea hypopnea index in OSA patients with neural stimulation of the hypoglossus nerve was larger than reported for MA devices (26). An additional limitation of this study was the use of anesthesia, required to enable the procedures performed in this study without arousal. Although propofol anesthesia was often referred to as “drug-induced sleep” (2, 5), it may produce more muscle relaxation than sleep, rendering the upper airway more passive and more collapsible (7, 21) and lowering neural output to the GG (7), thereby limiting extrapolation of our findings to conditions occurring during sleep. However, propofol does not influence involuntary isometric skeletal muscle strength (8), and the mechanical properties of the pharynx during anesthesia have been shown to be relevant to OSA (6). Also, we found a similar decrease in Pcrit during GG-ES performed with equal stimulation techniques during sleep and propofol anesthesia (18, 19). Comparison of baseline Pcrit and the response to GG-ES of the patients of the present study to those of the patients of Ref. 18 (who were studied during sleep with essentially the same methodology and had similar anthropomorphic and sleep study data) has shown no significant difference. This indicates that whatever the differences between sleep and anesthesia may be, they do not seem to affect significantly the response to GG-ES. On the other hand, more caution is warranted in predicting the potential therapeutic effect of GG-ES and MA during sleep from our mechanical findings. The severity of OSA is only partially explained by mechanical properties (30). Sleep is characterized by periodic changes in pharyngeal patency, and such fluctuating instability was not observed during anesthesia.

The use of pharyngoscopy enabled us to measure the CSA:Pn relationships at the level of the velo- and oropharynx, used as a surrogate of pharyngeal compliance at the area of collapse, as previously reported (10, 13). Despite unavoidable confounders of this technique (11, 19), this measure, obtained during the respiratory pause at end expiration, is likely to provide a close estimate of changes in pharyngeal stiffness. Although compliance is expected to have a major impact on pharyngeal collapsibility, both GG-ES and MA did not affect velopharyngeal compliance, and oropharyngeal compliance actually increased during MA. The lack of effect of MA or

<table>
<thead>
<tr>
<th></th>
<th>Pclose, cmH₂O</th>
<th>CSA:Pn, mm²/cmH₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BL</td>
<td>ES</td>
</tr>
<tr>
<td>VP</td>
<td>1.4±2.8</td>
<td>0.1±3.6*</td>
</tr>
<tr>
<td>OP</td>
<td>-2.8±5.5</td>
<td>-7.0±5.7</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 6 subjects. Pn, nasal pressure (at end expiration equal to intrapharyngeal pressure). *Significant difference for comparison with baseline (BL). †Significant difference for comparison with electrical stimulation of the genioglossus (ES). ‡Significant difference for comparison with mandibular advancement (MA). In addition, all closing pressure (Pclose) values at the velopharynx (VP) are significantly higher than the corresponding values at the oropharynx (OP), and all cross-sectional area (CSA):Pn values of the OP are significantly higher than the corresponding values of the VP.
GG-ES on pharyngeal compliance in this study is similar to that reported in previous animal and human studies (4, 11, 13). While advancement of the tongue is expected to enlarge the oropharynx, its effect on the velopharynx is more difficult to explain. Modeling the velopharynx as a compliant tube enables description of its mechanics by the "tube law," which relates the pressure difference across the wall (inner minus outer) to the CSA of the tube. With the CSA-to-intraluminal pressure relationships remaining unchanged, both GG-ES and MA seem to enlarge the pharynx and lower Peri primarily by unloading (i.e., reducing external pressure) of the collapsible segment. External pressure is known to be a prominent mechanism determining pharyngeal patency (27), and MA has been shown to reduce oropharyngeal pressure in animals (12).

Attempts to stimulate upper airway dilator muscles in OSA patients have been undertaken ever since the physiological importance of these muscles’ action began to be appreciated. More recently, hypoglossus nerve stimulation has been shown to induce a significant, albeit incomplete, improvement in OSA (26). Our findings suggest that repositioning the mandible improves the mechanical response to GG-ES, as even under the passive hypotonic conditions of this study, combining the effect of GG-ES with MA restored pharyngeal patency to a level that enabled flow above hypopnea level in 10/14 (71%) of the patients. We conclude that the combined effect of MA and GG stimulation is additive and may act in synergy, preventing substantial flow limitation of the relaxed pharynx in most OSA patients.

GRANTS
This study was supported by Binational USA-Israel Science Foundation (BSF) Grant 2000234.

REFERENCES