Upper airway response to electrical stimulation of the genioglossus in obstructive sleep apnea

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OBSTRUCTIVE SLEEP APNEA (OSA) is a common disorder characterized by recurrent episodes of upper airway obstruction during sleep. It is well recognized that increasing degrees of airflow obstruction during sleep are related to elevations in pharyngeal collapsibility across a spectrum from health to disease (30). Despite considerable research efforts over the last three decades, the pathophysiological mechanisms leading to increases in pharyngeal collapsibility are not well understood.

The importance of upper airway dilator muscles in maintaining pharyngeal stability has been long recognized, and of those the genioglossus muscle (GG), which is the main tongue protrusor muscle, has been thought to play an important role (22). On the basis of both anatomic considerations and physiological findings in animal studies, investigators have emphasized the relative importance of this muscle in maintaining upper airway patency (8, 13, 17–19, 20, 32). Additional evidence from human studies also indicates that GG stimulation increases airflow substantially (21, 32) and improves OSA when this muscle is activated electrically (7, 25). Although these responses suggest an alteration in upper airway function, the mechanism for this change, and specifically the precise effect of the GG on upper airway collapsibility in sleeping humans, has not been evaluated.

In previous studies (33), investigators have demonstrated that the upper airway functions as a simple collapsible tube during sleep. Such tubes collapse and limit flow to a maximal level whenever the intraluminal pressure falls below a critical pressure (Pcrit). The Pcrit, a measure of upper airway collapsibility, depends on the stability of its walls and the surrounding pressure (23), and it can be determined empirically by analyzing upper airway pressure-flow relationships during sleep. In previous studies, our laboratory found that the magnitude of the fall in Pcrit to intervention can predict the response in apnea severity to therapy (27, 29). In a recent study (25), our laboratory demonstrated improvements in sleep apnea to nightly hypoglossal stimulation, although the effect of stimulation on upper airway pressure-flow relationships and Pcrit had not been evaluated.

The goal of the present work was to study the effects of GG contraction on upper airway pressure-flow relationships during sleep in OSA patients and to quantify its effects on upper airway collapsibility. We hypothesized that GG contraction in the sleeping human will...
affect upper airway mechanics similarly to its effects in our feline model (32), i.e., decreasing Perit without changing upstream resistance. In addition, based on our laboratory’s previous observations, we expected GG contraction to result in only a modest reduction in Perit and partial resolution of flow limitation (21, 25, 26). To test these hypotheses, novel methods were employed to selectively stimulate this muscle in five OSA patients previously implanted with a hypoglossal (HG) nerve-stimulating system and in nine OSA patients stimulated acutely with fine-wire electrodes inserted into the GG. The upper airway pressure-flow relationships were determined both on and off electrical stimulation (ES) to define the role of the GG in modulating upper airway collapsibility during sleep. In addition, we compared the two modes of ES, and changes in Perit were also related to responses in apnea severity, to elucidate the potential role of ES in treating OSA patients.

METHODS

Subjects and ES. Patients with moderate to severe OSA (>20 obstructive or mixed apneic and hypopneic episodes per hour sleep), previously documented on a conventional overnight polysomnographic sleep study, were recruited for these studies. The studies were approved by the competent authorities (Human Investigations Review Boards) of the respective institutions, and written, informed consent was obtained from each patient.

Two groups of patients were studied. The first group (HG-ES group) consisted of five patients chronically implanted with a unilateral HG nerve stimulator for therapeutic purposes, as previously described (25). Three of the patients were implanted and studied in the Johns Hopkins Sleep Disorder Center, and the other two in the Antwerp University Hospital. The HG nerve-stimulating device (Inspire 1, Medtronic, Minneapolis, MN) consisted of an intrathoracic pressure sensor, an externally programmable pulse-generating unit, and a half-cuff, silicone-insulated, bipolar platinum electrode. GG was activated selectively via a large distal HG branch, and only unilateral ES was used for reasons of safety. At the time of the study, the stimulators were programmed to deliver pulses of 91- (3 patients) or 117-μs duration (2 patients) at 40 Hz in bursts of 1- to 1.5-s duration, triggered by the negative intrathoracic pressure produced during inspirations.

For the second group, in nine patients (8 men), all studied in the Johns Hopkins Sleep Disorder Center laboratory, GG-ES was applied via Teflon-coated, 0.007-in.-diameter hook-wire electrodes with bared ends inserted sublingually, bilaterally, for the study night, as previously described (26). Bursts (40 Hz) of 1–2 s, with biphasic pulses of 100-μs width, were applied by using a neuromuscular stimulator (Dynex III, Medtronic). Clearly visible ES-induced protrusion of the tongue during wakefulness was used to indicate that the electrode had been optimally placed.

Instrumentation. Standard polysomnographic techniques, including right and left electroencephalogram, submental surface electromyogram, C3-O1 and C3-A2 EEG, ECG, and oxygen saturation, were employed to monitor sleep and arousal. Subjects breathed through a tight-fitting nasal mask and a pneumotachometer (Fleisch 2 and Validyne MP-45; ±2 cmH₂O). The mask was connected to a variable pressure source at the inflow port, enabling variation of nasal pressure between 20 and −10 cmH₂O. Nasal pressure was monitored with a catheter connected to a side port of the mask. Infrathoracic pressure was measured with a water-filled catheter positioned in the esophagus and was used to recognize upper airway airflow limitation (2), as well as to distinguish between inspiration and expiration during the stimulation protocol. The site of pharyngeal airflow obstruction (velo- vs. oropharynx) was determined by positioning a pharyngeal catheter with a side hole at the rim of the soft palate in seven of the patients studied with GG-ES, as previously described (3), and relating the pressure measured at this site to the mask and esophageal pressure. Pressures were monitored with Gould-Statham transducers (P23ID). All parameters were recorded continuously on a polygraph recorder (no. 780, Grass Instruments, Quincy, MA). In parallel, analog-to-digital acquisition of all parameters was performed at 128 Hz for monitoring and data storage.

Pressure-flow relationships. The upper airway pressure-flow relationships during sleep was delineated as previously described (2, 26). Patients were studied in the supine position, and nasal pressure was maintained at 10–12 cmH₂O during stable sleep to maintain the pharyngeal mucosa in a relatively hypotonic state (28). The nasal pressure was lowered to several levels in duplicate, encompassing levels associated with and without inspiratory flow limitation and the level below which airflow ceased (the upper airflow occluded completely). ES was applied just before inspiratory onset of the third breath after reduction of nasal pressure during stable stage 2 non-rapid eye movement sleep. For the five patients with HG stimulators, baseline pressure-flow relationships and the pressure-flow relationships during HG-ES (applied during each inspiration) were determined in random order, and the maximal inspiratory flow was determined on the third breath after reduction of nasal pressure. The pressure-flow relationships of the nine patients studied with GG-ES (applied only once during each drop in nasal pressure) was determined concomitantly with the baseline pressure-flow relationships (Fig. 1).

Arousal exclusion during ES. To minimize disruption of sleep, an oral dose of triazolam (0.25 mg) was given to all patients before the studies. To avoid arousing patients from sleep during GG-ES, the stimulus intensity was initially titrated and adjusted in each subject during wakefulness to determine sensory and pain thresholds. During sleep, the arousal threshold was defined, and later ES trials were performed by using slightly lower ES intensities. GG-ES was applied manually during stable non-rapid eye movement sleep periods and was limited to single inspirations, which started shortly before the inspiratory negative deflection in esophageal pressure. Both EEG and airflow responses were assessed to exclude arousal during stimulation. In addition to conventional polysomnographic criteria (absence of EEG (alpha rhythm > 3 s) and/or electromyogram (increased amplitude) signs of arousal (1) during or immediately after ES), strict temporal linkage between increases in airflow and ES, with an immediate return of flow and pressure signals to prestimulation levels on the first breath after ES, were required (21, 26).

Data analysis. The pressure-flow relationship data were analyzed as previously described (2). The maximal inspiratory flow was measured at each level of nasal pressure. The maximal inspiratory flow obtained in duplicate trials, as well as values obtained before and after GG-ES (which were, by definition, almost identical) were averaged. Only values measured during flow-limited breaths (recognized by the deviation of flow and esophageal pressure tracings) were used to delineate the pressure-flow relationships with least squares
linear regression \((2)\). This relationship was then used to calculate \(P_{\text{crit}}\) as the level of nasal pressure below which airflow became zero, as well as the “effective pressure” as the nasal pressure below which flow limitation was observed, and upstream resistance as the reciprocal of the pressure-flow relationships slope. Values obtained without and with ES were compared with paired two-tailed \(t\)-test.

RESULTS

Anthropometric and polysomnographic characteristics of all study patients are given in Table 1. Both HG-ES and GG-ES patients were predominantly middle-aged men, and the two groups were of similar body mass index. The patients implanted with HG-ES had, on average, higher apnea-hypopnea index than the patients studied with GG-ES, but this difference was not significant.

The baseline pressure-flow relationships and the pressure-flow relationships obtained during HG-ES and GG-ES in representative patients are illustrated in Fig. 2. A similar increase in airflow was obtained during ES over the entire pressure range, resulting in a nearly parallel leftward shift of the regression line toward lower nasal pressure (and higher maximal inspiratory flow) values. Of note, the slope of the regression line changed only slightly during HG-ES and remained nearly unchanged during GG-ES in the presented patients, indicating that the upstream resistance did not change substantially. The leftward shift in the pressure-flow relationships reflected the fact that both the \(P_{\text{crit}}\) and the effective pressure (the pressure below which flow limitation was observed)
decreased during ES. It can also be seen that at the nasal pressure that equaled the baseline Pcrit (4.5 and 0.4 cmH2O for GG-ES and HG-ES, respectively), the maximal inspiratory airflow reached >300 and 100 ml/s during ES. In contrast, despite the substantial decrease in Pcrit during ES, airflow remained zero at atmospheric pressure (nasal pressure = 0) during GG-ES, since ES failed to decrease Pcrit below zero in this patient.

The effect of HG-ES and GG-ES on Pcrit is shown in Fig. 3 for the two patient groups. ES reduced Pcrit in all patients from −1.32 ± 1.97 (SD) to −5.30 ± 3.30 cmH2O (P < 0.05) and from 1.63 ± 2.02 to −1.56 ± 2.53 cmH2O (P < 0.01) for HG-ES and GG-ES, respectively (ΔPcrit = 3.98 ± 2.31 and 3.18 ± 1.70 cmH2O, respectively; P = not significant). In contrast, ES did not influence upstream resistance (19.80 ± 7.93 vs. 20.04 ± 6.27 cmH2O·l−1·s and 18.12 ± 7.92 vs. 17.57 ± 9.81 cmH2O·l−1·s, HG- and GG-ES off vs. on, respectively). The parallel leftward shift in the pressure-flow relationships led to a concomitant decrease in the effective pressure of similar magnitude to the decrease of Pcrit (Table 2) in both groups.

The site of pharyngeal obstruction, evaluated in seven of the subjects studied with GG-ES to determine whether the response to GG-ES varied with the site of collapse, revealed that pharyngeal collapse occurred in the velopharyngeal area in four patients and in the oropharyngeal area in the remaining three patients. The site of collapse did not influence the response to GG-ES since the ΔPcrit for the patients with velopharyngeal and oropharyngeal obstruction was 3.6 ± 1.9 and 3.8 ± 1.8 cmH2O, respectively.

The effect of ES-induced alterations in Pcrit on the severity of airflow obstruction can also be demonstrated by changes in maximal inspiratory flow during ES at two specific levels of nasal pressure. At nasal pressure equal to the baseline Pcrit (i.e., the pressure at which airflow without ES was zero), similar increases in inspiratory airflows were observed from zero to 197.8 ± 86.0 and 220.9 ± 67.0 ml/s during HG-ES and GG-ES, respectively. At atmospheric pressure (i.e., nasal pressure = 0), airflow increased during HG-ES from 75.8 ± 98.4 ml/s at baseline to 261.4 ± 123.8 ml/s, whereas it only increased from 11.7 ± 35.0 to 86.8 ± 87.3 ml/s in the GG-ES group (Table 2). The greater airflow response during HG-ES compared with GG-ES can be attributed to a lower baseline Pcrit in this group, which was slightly below rather than above atmospheric pressure (Table 2).

The relationship between alterations in Pcrit and apnea severity is illustrated for the HG-ES group in Fig. 4. As can be seen, reductions in the non-rapid eye movement apnea-hypopnea index were associated with substantial decreases in Pcrit, which decreased, in the mean, into a range previously associated with partial reductions but not the complete resolution of sleep apnea (10, 27, 29).

Table 2. Effect of ES on pressure and flow parameters of the upper airway

<table>
<thead>
<tr>
<th></th>
<th>HG-ES (n = 5)</th>
<th>GG-ES (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BL</td>
<td>ES</td>
</tr>
<tr>
<td>Pcrit, cmH2O</td>
<td>−1.32 ± 1.97</td>
<td>−5.30 ± 3.30</td>
</tr>
<tr>
<td>Rus, cmH2O·l−1·s</td>
<td>19.80 ± 7.93</td>
<td>20.04 ± 6.27</td>
</tr>
<tr>
<td>Peff, cmH2O</td>
<td>4.08 ± 3.44</td>
<td>0.4 ± 1.77</td>
</tr>
<tr>
<td>VPat, ml/s</td>
<td>75.8 ± 98.4</td>
<td>261.4 ± 123.8</td>
</tr>
<tr>
<td>VPat, ml/s</td>
<td>0</td>
<td>197.8 ± 86.0</td>
</tr>
</tbody>
</table>

Values are means ± SD. BL, baseline, without ES; Pcrit, critical pressure; Rus, upstream resistance; Peff, the lowest nasal (mask) pressure without flow limitation; VPat, airflow observed at atmospheric pressure (nasal pressure = 0); VPet, airflow observed at baseline Pcrit.
To evaluate which baseline characteristics could predict the Perit response to ES, we correlated both the Perit measured during ES and the ΔPerit (individual change in Perit during ES) with the patients’ baseline parameters. No correlation was found between the patients’ anthropometric and polysomnographic parameters (see Table 1) and their response to ES. Similarly, the Perit response was independent of the baseline Perit. As expected, Perit during ES depended both on baseline Perit and ΔPerit (r = 0.82, P < 0.001, and r = −0.68, P < 0.005, respectively), i.e., patients with low baseline Perit (and/or large ΔPerit) had lower Perit during ES.

DISCUSSION

The present study characterizes the effects of ES on upper airway flow dynamics during sleep in patients with OSA. The pressure-flow relationships were delineated on and off stimulation of the HG nerve and the GG muscle. Our major findings were as follows. First, we found that GG contraction resulted in a parallel leftward shift in the pressure-flow relationships, consistent with a decrease in Perit, but no change in upstream resistance. Second, Perit decreased similarly during both HG- and GG-ES. Third, this reduction in Perit accounted for the increase in inspiratory flow in both groups, indicating relief of airflow obstruction by ES. However, an increase in maximal inspiratory pressure at atmospheric pressure occurred only when Perit decreased during ES below zero, and the increase was greater when the baseline Perit was below atmospheric values. Fourth, Perit responded similarly to ES (ΔPerit) in patients who obstructed in the velopharynx and oropharynx. Last, the increases in airflow and the fall in Perit during hypoglossal stimulation were associated with substantial improvements rather than the complete abolition of sleep apnea. Taken together, our findings suggest that GG contraction ameliorates upper airway obstruction and reduces apnea severity during sleep by lowering Perit. The magnitude of observed responses supports the concept that the GG must act in conjunction with additional muscles to maintain upper airway patency completely during sleep. In addition, our findings indicate that assessing baseline pressure-flow relationships and the acute responses in Perit and airflow to GG-ES may help in selecting those patients most likely to respond to HG stimulation.

The concept that the pharynx functions as a self-supporting, soft-walled collapsible tube has provided significant insight into the pathogenesis of upper airway obstruction during sleep (10, 30). The collapsibility of such tubes depends on the stability of their walls and the surrounding pressure (23) and can be assessed by determining their Perit. In addition, once the pressure immediately below the collapsible segment (downstream pressure) falls below Perit, flow becomes limited and fails to increase as downstream pressure continues to decrease. Under these circumstances, flow depends on upstream pressure and on the tube’s upstream resistance. Perit of normal subjects is usually below −8 cmH2O (31), whereas that of OSA patients is usually above atmospheric pressure (9). Both clinical and physiological observations indicate that pharyngeal collapsibility is affected by a complex interaction of anatomic/structural and neuromuscular factors. A large number of anatomic abnormalities have been implicated in the pathogenesis of OSA, and the intrinsic collapsibility of the pharynx of OSA patients has been found to be elevated even in the presence of complete neuromuscular blockade (12, 35). In addition, abundant experimental data point to the role of dynamic neuromuscular mechanisms in maintaining upper airway patency, since upper airway obstruction develops only during sleep when neuromuscular activity wanes (22, 24, 28, 30). Therefore, evaluating both the qualitative and quantitative effects of ES on upper airway flow mechanics provides a useful tool for investigating the role specific muscles play in the modulation of upper airway patency.

Two novel techniques facilitated our evaluation of GG activation on upper airway function. First, implantation of chronic HG nerve stimulators in a small number of OSA patients (25) provided painless ES during inspiration over many hours, enabling acquisition of complete pressure-flow curves during sleep with the stimulator turned either on or off. Second, we extended these observations by further developing methods for examining the effect of direct GG-ES on the mechanical properties of the upper airway during sleep (21, 26). Several important steps were taken to avoid arousing patients from sleep and to exclude breaths associated with arousal from our analysis (see METHODS). Our protocol was designed to apply GG-ES manually during stable sleep periods and to limit the stimulation to single inspirations, which started shortly before the inspiratory negative deflection in esophageal pressure. Both EEG and airflow responses were assessed to exclude arousal during stimulation and strict temporal linkage between increases in airflow and ES, with an immediate return of flow and pressure signals to prestimulation levels on the first breath after ES (21, 26). The return of airflow to the pre-ES level in the breath after GG-ES allowed us to attribute airflow responses to the selective activation of the tongue protrusor rather than to nonspecific activation from arousal. Therefore, our methodology permitted a reliable assessment of the mechanical effects of selective ES over the entire flow-limited pressure-flow relationships during sleep and allowed us to compare responses to GG-ES and HG-ES. Measuring peak inspiratory airflow on the third breath after nasal pressure was lowered from its initial high level was based on our laboratory’s previous work (28), indicating that at this breath maximal airflow reaches its minimum, while the upper airway respiratory muscles are still almost completely relaxed, even in the presence of apnea. The effects of continuous inspiratory stimulation, applied during HG-ES, on intrinsic tongue muscle tone were not evaluated. The response to HG-ES is likely to differ from the response to GG-ES, also due to...
the higher airflow on the first and second breaths after lowering nasal pressure as well as to the initiation of HG-ES slightly after onset of inspiration.

Delineating the entire pressure-flow relationships on and off ES provided insight into the mechanism by which GG activation modulates upper airway flow dynamics during sleep in apneic patients. The experimental methods were devised to stimulate this muscle after establishing a relatively stable hypotonic state for the pharyngeal musculature at an elevated nasal pressure (28). Under these conditions, we demonstrated a parallel leftward shift in the pressure-flow relationships during ES. This finding indicated that the GG increased airflow by lowering Pcrit without altering upstream resistance. In a previous animal study, such isolated reductions in Pcrit (without concomitant changes in resistance) were attributed to a decrease in the tissue pressures surrounding the pharynx rather than an increase in airway wall stiffness (23). In contrast, our laboratory previously observed reciprocal changes in Pcrit and upstream resistance with ES of tensor palatini and cervical strap muscles (6, 15), as well as during caudal tracheal traction, all of which increase tension along the pharyngeal wall (23, 94). Thus our findings may suggest that the GG exerts a pure dilating effect on the airway, reflecting its tethering action on the pharyngeal lumen. Moreover, we found that the Pcrit response was independent of the exact location of the flow-limiting site, confirming our laboratory’s previous finding (26). Our findings, derived from the pressure-flow relationships during flow limitation, may differ from the findings of Isono et al. (13), who studied the effect of bilateral ES of the tongue (which was likely to also affect tongue retractors) on the pharyngeal static pressure-area relationships in anesthetized patients. They found a change in oropharyngeal (but not velopharyngeal) compliance, compatible with stiffening of the retroglossal airway.

In addition to our physiological findings, the findings in the present study may also have therapeutic implications. Observed decreases in Pcrit of 3–4 cmH2O were associated with substantial increases in maximal inspiratory flow of ~200 ml/s when patients breathed at nasal pressure equal to the unstimulated Pcrit (Table 2). When patients breathed at atmospheric nasal pressure, however, this increase in airflow was considerably lower in those whose stimulated Pcrit remained close to atmospheric pressure. Therefore, greater improvement in airflow could be seen in those patients with a baseline (unstimulated) Pcrit below atmospheric pressure. In fact, baseline Pcrit closely predicted the final Pcrit during ES, and the final Pcrit is known to determine the response in sleep apnea severity to interventions (10, 25, 27, 29). Given the marked uniformity in Pcrit responses to ES, our findings suggest that the greatest improvements in apnea severity with chronically implanted HG-ES are expected in patients with an initially low (subatmospheric) Pcrit. Interestingly, despite marked differences in the stimulation platform (repeated unilateral HG-ES vs. single bilateral inspiratory GG-ES) the mechanical effects of both methods used to induce GG contraction were very similar. Thus our findings suggest that characterizing the patient’s baseline pressure-flow relationships and response to GG-ES may prove useful in predicting responses to a chronically implanted HG-ES device.

Various approaches have been previously taken to electrically stimulate the tongue muscles during sleep with the primary goal of ameliorating OSA (4, 5, 11, 16). Although ES-induced arousals confounded these initial studies, marked alterations in upper airway patency have been demonstrated with the more recent use of fine wire (26), surface (21), and nerve cuff stimulating electrodes (7), depending on the exact site of ES. Favorable results in the latter studies prompted a multicentered feasibility study that demonstrated significant increases in airflow and reductions in apnea severity over many months with a chronically implanted unilateral HG-stimulating device (25). The present findings suggest that therapeutic responses to chronic stimulation of the HG can be predicted by assessing a patient’s baseline Pcrit during sleep and his/her acute response to GG-ES. Recent studies in the rat indicate that coactivation of tongue muscles, as well as pharyngeal muscles, has an important effect on pharyngeal flow mechanics (8, 14). Accordingly, further work quantifying the effect of GG stimulation in combination with other muscles in OSA patients will be required to delineate the precise role of this muscle in maintaining upper airway patency during sleep.

DISCLOSURES

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