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Effect of genioglossus contraction on pharyngeal lumen and airflow in sleep apnea patients.

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ABSTRACT.

The purpose of this study was to quantify the mechanical effect of genioglossus stimulation on flow-mechanics and pharyngeal cross-sectional area in patients with obstructive sleep apnea, and to identify variables that determine the magnitude of the respiratory effect of tongue protrusion.

Pressure:flow and Pressure:cross-sectional area relationships of the velo- and oropharynx were assessed in spontaneously breathing Propofol-anesthetized subjects, before and during genioglossus stimulation.

Genioglossus contraction decreased the critical pressure significantly from 1.2 ± 3.3 to –0.7 ± 3.8 cmH_2O ($p<0.01$), with the individual decreases ranging from –0.6 to 5.9 cmH_2O. Pharyngeal compliance was not affected by genioglossus contraction. The pharyngeal response to genioglossus stimulation was related to the magnitude of advancement of the posterior side of the tongue, but not to the severity of sleep apnea, critical pressure, compliance or the shape and other characteristics of the velopharynx.

Genioglossus contraction enlarges both the velo- and the oropharynx, and lowers the critical pressure without affecting pharyngeal stiffness. The response to genioglossus stimulation depends on the magnitude of tongue protrusion achieved, rather than on inherent characteristics of the patients and their airway.

INTRODUCTION.

Upper airway dilator muscle activity is crucial for counteracting the negative intraluminal pressure generated in the pharynx during inspiration. Diminution of this activity during sleep is thought to lead to pharyngeal collapse and obstruction in patients with obstructive sleep apnea (OSA)(1-3). Activation of the genioglossus (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 (4,5). As electrically induced (6) and volitional (7) tongue protrusion enlarges the pharynx and prevents pharyngeal obstruction during wakefulness, it appears conceivable that this muscle is the main pharyngeal dilator. Prevention of pharyngeal obstruction in patients with OSA by electrical stimulation (ES) of the GG during sleep may both prove the dominant respiratory role of this muscle, as well as provide a potential treatment modality.

Unfortunately, multiple trials attempting to relieve OSA by stimulating upper airway dilators during sleep resulted in modest and/or inconsistent results (7-13). To better understand the physiological effects of GG-ES on pharyngeal flow-dynamics in OSA patients during sleep, we conducted recently a study (14) based on concepts of flow through a collapsible tube (15,16). In this work we found that GG-ES resulted in a moderate decrease in the critical (closing) pressure (Pcrit), with similar results obtained with intramuscular and unilateral hypoglossal electrodes (14). Insufficient intensity of stimulation possible during sleep, failure to stimulate the relevant muscle(s), or hypotony of the non-stimulated upper airway muscles, could all be part of the explanation for the lower response in humans, as compared to animals used in upper airway research.

The present study was designed to further evaluate the mechanical effects of electrically induced tongue protrusion on the pharynx. We hypothesized that if the GG is the main pharyngeal dilator, i.e., pharyngeal patency during wakefulness depends largely on GG activity, GG contraction should prevent pharyngeal obstruction despite profound sleep- or anesthesia-related hypotony of pharyngeal dilators. Therefore, studies were performed under Propofol anesthesia, to establish stable muscle relaxation, ascertain adequate GG-ES without arousal, and enable undisturbed instrumentation and visualization of the pharynx.

Methods.

Subjects. We sent letters to all patients who undertook a full sleep study in the Technion Sleep Laboratory during the last year prior to the present study, requesting them to participate in our research, and recruited all volunteers. 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 (BMI) > 35 kg/m^2, 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. The instrumentation used in the present study is shown in Figure 1. Standard polysomnographic techniques, including right and left electrooculogram (EOG), submental surface EMG, C3-O1 and C3-A2 EEG, ECG and oxygen saturation, were employed to monitor anesthesia and exclude arousal. Subjects breathed through a tight-fitting nasal mask and a pneumotachometer, connected to a Validyne ± 2 cmH_2O pressure transducer, 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 cm H_2O. 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 1000 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 nose 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 drip of 6-12 mg/kg/hour. Using 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 oxymetry.

Electrical stimulation: ES of the GG (GG-ES) was applied via Teflon coated, 0.007 in. diameter hook-wire electrodes with bared ends, inserted sublingually, bilaterally, 10-15 mm deep into the anterior, retro-mandibular body of the GG, as previously described (13,14). Four-6 electrodes were inserted in each subject. Forty Hz bursts of 2-6 sec, with biphasic pulses of 100 μs width, were applied using a neuromuscular stimulator (Dynex III, Medtronic Inc, Minneapolis, MN). Pharyngoscopic observation enabled 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.

Experimental procedure. Patients were prepared with EEG, EOG, submental EMG, 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 oro-pharyngeal (OP) collapse were determined visually by lowering Pn, enabling also determination of the primary site of pharyngeal collapse (17). Thereafter, the endoscope was placed first above the area of VP collapse. Flow:Pn and CSA:Pn relationships before and during GG-ES were determined quasi simultaneously: With the patient maintained on holding pressure, Pn was lowered randomly for few breaths, encompassing 4-6 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 2-3 consecutive breaths, and after additional 2-3 unstimulated breaths, Pn was raised back to the holding pressure, until stable baseline ventilation was observed. The same protocol was repeated after the endoscope was lowered below the VP site of collapse, to determine the OP CSA:Pn relationships.

To assess the effect of GG-ES on the OP flow:Pn and CSA:Pn relationships independently of the occlusion at the level of the VP, naso-pharyngeal intubation was performed in 6 subjects. A no. 6.5 tube was inserted through the nose, and placed under endoscopic guidance at the level of the lower rim of the soft palate, thereby preventing VP collapse. The outer end of the tube was cut and secured under the nasal mask.

Data analysis. The flow:Pn relationships data were analyzed using digital software. 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. The flow:Pn relationships was determined with least square linear regression. This relationship was used to calculate Pcrit as the level of Pn below which airflow became zero, as well as the flow:Pn slope. ΔPcrit (baseline Pcrit minus Pcrit during GG-ES) was used to quantify the mechanical effect of GG-ES. The lowest Pn at which no flow limitation occurred was derived from the flow:Pn curve.

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. Due to the state of anesthesia and high Pn levels that prevented flow limitation, the breathing rate of all patients was relatively slow (always <20/min), resulting in sufficiently long end-expiratory pause (always >0.5sec). Our computerized system extracted 10 pictures/sec, and several equal-size pre-inspiratory pharyngeal CSAs were always available, indicating that this time was sufficient for pressure and CSA equilibration, and that pharyngeal intraluminal pressure, after this period without flow, was stable, i.e., equal to Pn. The pharyngeal CSA in each digitized frame was outlined manually, and calculated digitally using computer software. 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, at the same distance from the endoscope before and during ES, 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 square 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 Pcrit (that was often below VP Pcrit, i.e., at Pn levels without airflow), we calculated Pcrit from the CSA:Pn relationships,

In addition to the CSA:Pn relationships of the VP and OP, visualization of the pharynx enabled determination of several other parameters considered potentially relevant to understand the effect of GG-ES on pharyngeal patency: The primary site of collapse (VP

or OP, before and during GG-ES), effect of GG-ES on the posterior side of the tongue, presence of visible oscillations of the pharyngeal walls, and changes in the shape of the VP during both lowering of Pn and GG-ES. In patients in whom the OP was studied, we measured the retro-epiglottal CSA, and the magnitude of forward movement of the posterior side of the tongue during GG-ES, by measuring the anterior-posterior diameter of the OP at the level of the epiglottis crest.

Paired and unpaired t-test were used to assess the effect of GG-ES and to compare groups, respectively. ANOVA was used for comparison of results over the range of OSA severity groups. Correlations were assessed by the least square methods. Chi-square logistic regression was used to compare the categorical variables.

RESULTS.

Thirty two subjects, all males, were studied, and their anthropometric and polysomnographic characteristics are given in Table 1. Patients were predominantly middle-aged men, and only 10 of them had a BMI>30. Five patients were hypertensive, one had mild diabetes, and none had any other significant disease. The subjects had a wide range of apnea-hypopnea index (AHI), and could be divided into 4 groups of OSA severity: 5 subjects had AHI of 4-5/h, and could be defined as having a borderline disorder; 11 subjects with mild OSA (AHI 6-20); 8 subjects with moderate OSA (AHI 21-40); and 8 subjects with severe OSA (AHI > 41). The mean age of the four groups was not significantly different. The AHI tended to increase with increasing BMI ($R = 0.44$, $p< 0.05$). Non of the patients had REM-only OSA, and with increasing OSA

severity, the percentage of apneas and hypopneas observed during REM sleep declined significantly ($R = -0.61$, $p<0.001$). The percentage of complete apneas, the sleep time with O_2 saturation below 90%, as well as the lowest O_2 saturation recorded during sleep, increased with increasing OSA severity ($R = 0.72$, 0.56 and –0.48, respectively, $p<0.01$).

Flow: Baseline findings. 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 6 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 in patients who occluded at about the same Pn at both levels. Therefore, the magnitude of flow limitation was always determined by the VP. Data derived from the flow:Pn relationships measurements of the upper airway, over the range of flow limitation, are given in table 2. In the baseline condition, without GG-ES, mean Pcrit values increased significantly with increasing OSA severity. As shown in figure 2, Pcrit correlated significantly with the AHI ($R = 0.45$, $p<0.01$). With the exception of one patient, only subjects without or with mild OSA had Pcrit values below atmospheric pressure, and all patients with severe OSA had Pcrit of 0 or higher. No correlation was found between the slope of the flow:Pn relationships and Pcrit or AHI. At atmospheric pressure (i.e., without CPAP, Pn=0), airflow was present, per definition, only in subjects with Pcrit below 0.

Flow: Effect of ES on the VP. GG-ES lowered Pcrit and the Pn under which flow limitation occurred significantly (table 2). ΔPcrit was positive in all but one subject, ranged between –0.6 to 5.9 (2.0±1.8 cm H_2O), and was similar in all sub-groups. It was

independent of baseline Pcrit (figure 2), and did not correlate with any of the anthropometric, polysomnographic, or flow-mechanic parameters evaluated in this study. Increases in airflow at atmospheric pressure (without CPAP) during GG-ES, occurred in 5 of the patients with mild OSA, but only in two patients in each of the other OSA subgroups, resulting in small mean flow values in the OSA subgroups as compared to the healthy subjects (Table 2). The GG-ES-induced increase in airflow at atmospheric pressure correlated significantly with baseline Pcrit and ΔPcrit (R= -0.66 and 0.55, respectively, $p<0.01$). The flow:Pn slope was not affected by GG-ES, i.e., GG-ES shifted the flow:Pn relationships to the left similarly in all subgroups (Table 2).

Flow: Effect of ES on the OP. The effects of GG-ES on the flow:Pn relationships of the OP was evaluated in the 6 patients with nasopharyngeal intubation. In these patients, GG-ES lowered Pcrit from BL of –5.7±3.2 to –9.9±3.9 cmH_2O ($p<0.01$). Their mean ΔPcrit (3.9±1.1 cmH_2O) was significantly higher than their ΔPcrit assessed without nasopharyngeal tube (i.e., determined by the VP, 1.9±1.3 cmH_2O, $p<0.05$). The flow:Pn slope of the OP was not affected by GG-ES. The OP ΔPcrit of these subjects was similar to the ΔPcrit of the subjects whose OP was studied without nasopharyngeal intubation, and their Pcrit was determined from the CSA:Pn relationships (4.2±2.9 cmH_2O, $p>0.7$).

Flow: Effect of the endoscope on upper airway assessment. To evaluate the possible effect the endoscope could exert on our results, we compared the flow:Pn relationships obtained while the endoscope was positioned above the VP, to that obtained while the endoscope was positioned below the VP, to observe the OP. No significant difference

was observed between the two sets of measurements: Baseline Pcrit was 0.2±3.3 and 0.6±3.3 cmH_2O with the endoscope above and below the area of VP collapse, respectively, and decreased to –1.7±3.9 and –1.3±3.2 cmH_2O during ES ($p>0.2$ for the comparisons of measurement performed with the endoscope above and below the VP). Similarly, the position of the endoscope did not affect the flow:Pn slope ($p>0.7$ for the comparisons of the two measurement sets). In 3 other patients, the flow:Pn relationships was evaluated also before insertion of the endoscope. In these patients too the endoscope had only negligible effects on Pcrit and the flow:Pn slope. Baseline Pcrit was 2.9±1.7 and 3.3±0.8 cmH_2O without and with the endoscope, respectively, and GG-ES decreased Pcrit to 0.5±1.0 and 0.4±0.9 cmH_2O.

Pharyngoscopy: VP compliance. VP compliance (CSA:Pn) varied considerably between patients. It correlated significantly with the patients' BMI ($R = 0.45$, $p<0.05$), but not with their Pcrit, flow:Pn relationships, or their AHI. Endoscopic pictures depicting the effect of GG-ES on the VP at 3 different Pn levels in one of the patients are shown in figure 4. GG-ES enlarged the VP at all Pn levels above Pcrit, but had, in the mean, no effect on VP compliance (16.4±11.2 and 14.9±10.0 mm^2/cmH_2O, before and during GG-ES, respectively, $p>0.6$). As pharyngeal occlusion is recognized by both CSA and flow = 0, Pcrit levels derived from the flow:Pn and CSA:Pn were very close (BL: 1.2±3.3 vs.1.4±2.8; GG-ES: –0.7±3.8 vs. –0.5±2.9 cmH_2O, respectively). Therefore, GG-ES shifted the CSA:Pn relationships to the left, toward lower Pn levels (Figure 5). Also, VP compliance did not affect the Pcrit response to GG-ES ($R=-0.09$ for the correlation

between VP compliance and ΔPcrit), neither did changes in compliance correlate with changes in Pcrit (R=-0.29, p>0.2).

Pharyngoscopy: Determinants of the response to GG-ES. As the primary goal of pharyngoscopy was to assess parameters that may affect the response to GG-ES, we divided our patients into two equal groups of patients with ΔPcrit lower and higher than 1.5 cmH_2O ('non-responders', n=16, ΔPcrit = 0.7±0.6, and 'responders', n=16, ΔPcrit= 3.3±1.5 cmH_2O, respectively). The two groups were compared for the incidence of non-parametric pharyngoscopic data expected to affect the response to GG-ES (Figure 6).

The primary site of occlusion was similar in the two groups of patients, i.e., the 6 patients with simultaneous VP and OP occlusion responded to GG-ES similar to the others. GG-ES had no effect on the site of occlusion in most subjects, changing it variably in 5 of the patients (3 from simultaneous VP and OP to primary VP occlusion, and 2 from VP to simultaneous VP and OP occlusion).

The shape of the VP orifice was variable (mainly elliptic, rectangular or crescent-like), but, at Pn levels above flow limitation, the transverse diameter always exceeded the sagittal diameter. With decreasing Pn levels, two pattern of narrowing could be distinguished, with the shape of the orifice just before occlusion becoming either a transverse slit (i.e., predominant sagittal narrowing of the VP), suggesting that the main occluding force was the weight of the tongue, or a round orifice (i.e., transverse>sagittal narrowing), suggesting larger forces from the lateral walls. The two pattern of occlusion

were present similarly in patients with low and higher ΔPcrit (Figure 6), indicating that this parameter did not affect ΔPcrit, and suggesting that GG contraction may exert a mechanical effect on the lateral walls of the pharynx.

Oscillation or vibration of the VP walls was observed in 14 of the subjects, almost exclusively at lower levels of Pn during inspiratory flow limitation. In all other subjects, flow limitation occurred without visible vibrations. Although visible vibrations may be a marker of increased wall pliability, we found no significant relationships between their presence and ΔPcrit.

Placing the endoscope above the area of VP collapse enabled sufficient overview over the OP to recognize the direction of tongue movement during GG-ES in all patients, including those in whom no separate OP studies were performed. Two patterns of movements of the posterior side of the tongue during GG-ES could be distinguished: A descent or depression of the tongue, occasionally associated with mild posterior bulging, and forward displacement of the tongue. Descent of the tongue could be expected to unload the VP anterior wall (soft palate), but this pattern of tongue movement was not more common in subjects with high ΔPcrit. Similarly, the combination of forward displacement and descent of the tongue during GG-ES was not associated with higher ΔPcrit, and was observed in 3 and 2 patients in the high and low ΔPcrit groups, respectively. However, visible forward displacement of the posterior part of the tongue during GG-ES was more common in the high ΔPcrit group (Figure 6). When the effect of each of the 5 parameters evaluated in this section was assessed using a forward stepwise

regression model for categorical variables (SPSS), only visible forward displacement of the tongue was found to be significant ($p<0.04$).

Pharyngoscopy: The OP. Endoscopic pictures depicting the effect of GG-ES on the OP at 3 different Pn levels in one of the patients are shown in figure 7. OP studies (without nasopharyngeal intubation) were performed in 14 subjects, and their data are shown in table 3, compared to the VP data of the same patients. Although baseline OP Pcrit tended to be higher in patients with moderate and severe OSA (as compared to those with no- and mild OSA), the difference was not significant ($p>0.5$). Baseline OP Pcrit was significantly lower than that of the VP (-2.6 ± 3.9 and 0.3 ± 3.4 respectively, $p<0.03$). Patients with higher OP Pcrit tended to have also higher VP Pcrit, but this correlation was not significant ($R=0.34$, $p>0.3$). GG-ES had a larger effect on OP than on VP (ΔPcrit 4.2 ± 2.9 and 2.3 ± 1.9, respectively, $p<0.03$). There was a significant correlation between OP and VP ΔPcrit ($R=0.55$, $p<0.05$). OP compliance was significantly larger than VP compliance ($p<0.03$), and there was no correlation between OP and VP compliance ($R=0.09$). GG-ES did not affect OP compliance.

The significant relationships between GG-ES-induced advancement of the tongue and ΔPcrit presented qualitatively for the whole group in figure 6, could be assessed more accurately in this subgroup of patients with OP studies, by measuring their OP sagittal diameter and its change during GG-ES. A significant correlation was found between the GG-ES-induced increase in the OP sagittal diameter and the increase in CSA of both OP

and VP (R=0.60 and 0.62, respectively, assessed at atmospheric pressure, $p<0.01$, figure 8).

The position of the epiglottis, assessed by separate measurements of the retroglottal CSA, varied substantially between subjects, as the epiglottis sometimes leaned on the posterior OP wall even at high Pn with the OP widely open. This position did not cause flow limitation. Similarly, the response of the epiglottis to GG-ES was variable, and did not correlate with the change in OP CSA.

DISCUSSION:

The present paper evaluated the effect of electrically induced GG contraction on pharyngeal lumen, mechanics and flow-dynamics, in anesthetized subjects with a wide range of AHI. The main findings are as follows: 1. In the mean, GG-ES had a moderate effect on pharyngeal airflow, but the range of mechanical response was wide, and substantial improvement in pharyngeal patency was observed in half of the patients. 2. Improved response to GG-ES was related primarily to the magnitude of forward displacement of the tongue, rather than to the inherent characteristics of the patients and their airway evaluated in this study. 3. GG-ES decreased collapsibility primarily by enlarging the pharynx rather than changing its compliance.

ES of striated muscles provide an important tool to assess their mechanical effect and has been largely employed for the study of upper airway dilator muscles. Understanding the

response to isolated contraction of these muscles provides insight to their effect when activated physiologically in conjunction with other muscles. In the case of GG-ES, evaluation of its mechanical effects on the pharynx may reveal also physiological findings of direct clinical relevance, enabling the development of new treatment modalities for OSA, based on electrical activation of the GG during sleep. In the present study we choose to use anesthesia to assess the mechanical effect of GG-ES in OSA patients, to enable endoscopic evaluation of the effect of contraction of this muscle over a wide range of Pn levels, a task that could not be performed during normal sleep. It is important to note that the use of anesthesia poses substantial limitations to extrapolation of our findings to conditions occurring during sleep. Anesthesia may produce more muscle relaxation than sleep, rendering the upper airway more passive and more collapsible (18). Drug-induced depression of neural output to the GG could affect its response to ES, although Propofol does not influence involuntary isometric skeletal muscle strength (19). In addition, changes in lung volume are known to affect pharyngeal stability, lung volume may change differently during anesthesia and sleep, and we did not measure changes in lung volume in this study. However, we found in the present study a similar baseline Pcrit and decrease in Pcrit during GG-ES as in our previous work, performed with very similar stimulation and flow:Pn evaluation techniques, during sleep (14). This finding indicates that the magnitude of response in the previous study was not due to the limited intensity of stimulation feasible during sleep (to prevent arousal), but that the intensity of stimulation, required to obtain adequate GG contraction with optimal mechanical effect, is rather low. In addition, this finding also suggests that the effect of anesthesia on the response to GG-ES was not substantial. This was probably due to the technique used to assess Pcrit during sleep

(repetitive Pn drops from a high Pn), designed to assess pharyngeal collapsibility in the presence of maximal upper airway dilator muscle relaxation (16, 20). Moreover, 19 OSA patients of the current study underwent independently clinical sleep studies for the titration and adjustment of CPAP. In these patients, the mean recommended CPAP was very close to the mean pressure under which flow limitation was observed during anesthesia (7.89±2.40 and 7.97±2.92 cmH_2O, respectively). These findings support previous observations suggesting that mechanical properties of the pharynx during Propofol anesthesia correlate to those observed during sleep (21). Another concern related to the use of anesthesia was that although we attempted to obtain stable anesthesia by administering propofol by continuous infusion, using in each subject a dose sufficient to abolish responses to pain and prevent arousal while maintaining stable breathing, we did not monitor the depth of anesthesia. Therefore, depth of anesthesia varied between subjects, and could change slightly during the few minutes needed to evaluate the pharynx at several levels of Pn. However, Pn drops were performed in random order, and at each Pn level stimulated breath followed the unstimulated one. Therefore, we believe that instability of anesthesia is unlikely to have affected systematically the response to GG-ES. For the same reasons, we believe that subtle, unintended changes in neck position, that could have occurred during the study because the heads of the patients were not fixed firmly to the bed, were unlikely to cause systematic errors. Interestingly, the presence and position of the endoscope had a negligible effect on our results. All this suggests, therefore, that the experimental conditions did not cause an important distortion of the results, and that our findings are likely to be relevant also during sleep. On the other hand, more caution is warranted in predicting the potential therapeutic effect of GG-ES during sleep from

mechanical findings. The severity of AHI is only partially explained by mechanical properties (22). Sleep is characterized by oscillations in the control of pharyngeal patency, a phenomenon suggested being most important for the occurrence and severity of OSA, and such oscillations did not occur under the conditions of the present study.

The use of pharyngoscopy enabled us to asses several parameters that could help understand the mechanical action of GG contraction, as well as evaluate their effect on the response to GG-ES. This includes the end-expiratory CSA:Pn relationships at the level of the VP- and OP, used, as in previous studies (23,24), as a measure of wall compliance at the area where collapse occurs at low Pn levels. Several limitations of this method of assessing compliance, as well as the specific methodology used in the present study, need to be addressed. We used anatomic structures and markings on the esophageal tube, but no specific methodology, to ensure that the CSA plane measured was and remained perpendicular to the axis of the pharynx, and the distance from the endoscope remained unchanged during ES. However, as stimulated breaths followed non-stimulated ones, and ES-induced changes were rather modest, we believe that possible inaccuracies were small and did not introduce a systematic error. An unavoidable confounder is the unknown change in lung volume caused by changes in Pn, causing CSA:Pn relationships to include the mechanical effects of changing lung volume (23). Also, changes in CSA over the range of Pn levels evaluated may also change the resting length of the GG, and, therefore, its shortening during ES (25), and could affect the CSA:Pn slope during ES. In addition, the complete CSA:Pn relationships of the pharynx is typically exponential, rising initially steep and almost linearly from Pcrit with increasing Pn levels, up to near-maximal distension,

after which increasing Pn produces only minor dilation (23). In our patients, as in previous studies (26), flow limitation occurred only at the lower Pn range of the steep part of the CSA:Pn curve. As only this Pn range was considered relevant for flow-mechanics, we limited our CSA:Pn measurements in most patients to the steeper quasi-linear portion, as previously suggested (27). This caused a loss of additional information relevant for the complete pharyngeal "tube law". Therefore, this study provides information regarding the interaction between the CSA:Pn slope and GG-ES over the range of flow limitation only, while the complete curve, that could provide the effect of GG-ES on the maximal segmental CSA and the estimated external pressure, remains to be evaluated. Although pharyngeal compliance is expected to have a major impact on pharyngeal collapsibility, we did not find a significant correlation between baseline CSA:Pn slope and AHI or Pcrit. Similarly, although we expected that low compliance (i.e., stiffer pharynx) would enhance the flow-mechanical effect of tongue protrusion, we found no correlation between VP compliance and ΔPcrit. These findings suggest that other baseline parameters and forces acting on the pharynx mask the mechanical effects of pharyngeal compliance. For example, VP compliance was much lower than OP compliance, but its Pcrit was usually higher, due to the smaller maximal distension size of the VP. Interestingly, while the lack of GG-ES effect on VP compliance may have been expected (27), as forward displacement of the tongue mainly unloads the soft palate, GG-ES also failed to change OP compliance, differently from previous findings by Isono et al.(27). However, in the latter study, the whole tongue (i.e., including retractors) was stimulated, and in 4 out of the 5 patients in which compliance decreased, this decrease was associated partially or totally with reduction in maximal CSA, as observed in our study that evaluated the effects of tongue

retractors ES (28). Our current findings suggest that GG-ES applied near the mandible fails to stiffen the posterior side of the tongue, or that stiffening of the GG without a similar change in other parts of the tongue and/or the lateral OP walls has no effect on overall OP compliance. Either way, GG-ES-induced forward displacement of the tongue, under the experimental conditions, enlarged the pharynx and lowered Pcrit primarily by mechanisms not related to changes in CSA:Pn. With compliance remaining unchanged, GG-ES seems to lower Pcrit primarily by unloading (i.e., reducing external pressure) of the collapsible segment, a parameter known to be a most prominent mechanism determining pharyngeal patency (29). The finding that GG-ES-induced forward displacement of the tongue enlarged the VP both in the sagittal and the lateral direction, suggests that GG contraction affects also the lateral pharyngeal walls, as described during medial hypoglossus branch stimulation in rats (30), probably involving mechanical coupling of base of tongue and soft palate via the fauces (31).

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, but preliminary attempts were unsuccessful (11). Miki et al. reported later on successful amelioration of OSA with submental ES (8), thought to activate the GG, but these results could not be reproduced by other investigators (7,9,11). Attempt to use CT guidance to implant fine-wire electrodes in close proximity to anterior branches of the hypoglossus nerves in OSA patients resulted in partial responses that were not reproducible in a systematic fashion (9). Similarly, flow increased when ES was applied with fine-wire electrodes implanted into the GG in OSA patients (13), but apneas could not be prevented

without the use of CPAP. Sublingual ES with surface electrodes produced mechanical improvements (6), but insufficient to be clinically useful (12). More recently, hypoglossus nerve stimulation with cuff-electrodes has been shown to be effective (10), and a multi-center study, evaluating the effect of cuff electrodes implanted unilaterally on the anterior branch of the hypoglossus nerve, demonstrated a significant, but only partial, improvement in OSA (32).

In continuation to previous work, the present study was undertaken to further evaluate the respiratory action of the GG and the magnitude of improvement in pharyngeal patency expected to be achieved by this muscle, considered to be the main pharyngeal dilator. We evaluated parameters associated both with the pattern of response to GG-ES, and others related to the patients and the mechanical characteristics of their pharynx. Not surprising, we found that GG-ES-induced pharyngeal enlargement and decrease in Pcrit correlated with the magnitude of forward displacement of the tongue, assessed either by observation (figure 6) or by measurement (increase in OP sagittal diameter, figure 8). GG-ES successfully advanced the posterior wall of the tongue in this study in only part of the subjects, and these subjects benefited most from this intervention. As seen in figure 1, the unique fiber orientation of the GG implies that contraction of the GG as a whole may not be adequate, as only horizontally and diagonally oriented fibers can advance the posterior part of the tongue and are expected to be responsible for the respiratory function of this muscle. Actually, with the mouth closed, contraction of vertically oriented fibers, that depress the tongue, may cause posterior bulging and obstruction. On the other hand, responses to GG-ES were not related to the severity of OSA (either AHI or baseline

Pcrit), site of collapse and pattern of VP closure, or compliance of the pharynx. Hence, our findings suggest that improving stimulation methods to focus on relevant GG fibers (33), rather than patient selection, is the most promising step expected to improve the results of GG-ES. However, we did not study patients with oropharyngeal primary site of occlusion. One may speculate that in patients in whom OP Pcrit is substantially higher than VP Pcrit, GG-ES may be more effective, as the OP response to GG-ES was significantly larger than that of the VP. Also, considering the large number of parameters that could affect the response to GG-ES, it is possible that parameters not evaluated in this study may have affected our results. For example, specific facial/skeletal morphometry and inherent physiological characteristics may affect the GG response to ES, and therefore the magnitude of forward displacement of the tongue. In addition, based on the maximal levels of ΔPcrit observed in our patients, GG contraction, as produced in the present study, is unlikely to stabilize the pharynx to the level present during wakefulness, and completely prevent OSA in patients who have a Pcrit>4-5 cmH_2O. The fact that the pharynx is maintained patent during wakefulness although the GG is only partially active (34), indicates that physiological activation of the GG differs from that produced by ES, and/or that forces other than those produced by GG contraction play a dominant role in the maintenance of pharyngeal patency, and also affect the response to GG contraction (25).

The present study was undertaken to quantify the mechanical, respiratory function of the GG and factors that affect pharyngeal response to GG-ES, rather than to assess the clinical usefulness of GG-ES. Nevertheless, several conclusions may be relevant and

important for further pursuit of a treatment modality based on upper airway muscle stimulation during sleep: First, the field of GG-ES should be narrowed and focus on specific fiber bundles of the GG, acting to advance the posterior part of the tongue; Second, although the magnitude of response to GG-ES seems to be independent of the inherent characteristics of the patients evaluated in this study, the responses obtained suggest that this treatment modality by itself is unlikely to be sufficient for patients with very high Pcrit, even if an adequate mode of stimulation can be found; In addition, pharyngeal compliance is not affected by GG-ES, and other means should be pursuit to lower (mainly VP) compliance during sleep; Nevertheless, although the GG is only one of many muscles that act in concert to prevent flow limitation in the pharynx, it may substantially improve pharyngeal patency when activated adequately to obtain optimal anterior displacement of the tongue.

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TABLES

Table 1. Anthropomorphic and sleep-study data of all subjects.

	(AHI<6) n=5	mild OSA (AHI 6-20) n=11	moderate OSA (AHI 21-40) n=8	severe OSA (AHI >40) n=8	all n=32
AHI (events/hour)	4.6 ± 0.5	17.0 ± 2.4	29.5 ± 8.6	61.9 ± 17.9	29.7 ± 22.8
age (years)	44.0 ± 10.7	51.6 ± 9.2	45.5 ± 13.6	46.3 ± 6.3	47.5 ± 9.7
BMI (kg/m^2)	27.8 ± 0.9	28.1 ± 3.1	29.3 ± 2.9	33.9 ± 6.6	29.9 ± 22.8
apnea/tot (%)	4.3 ± 7.2	21.4 ± 17.9	44.1 ± 30.7	62.3 ± 30.8	36.4 ± 31.5
AH REM/tot (%)	49.0 ± 26.5	44.2 ± 21.3	24.3 ± 7.8	10.4 ± 5.5	30.3 ± 21.8
SO_2<90% (% time)	0.5 ± 0.6	6.5 ± 10.7	5.0 ± 10.3	20.2 ± 22.5	9.3 ± 15.6
lowest SO_2 (%)	88.5 ± 2.9	86.3 ± 6.1	84.4 ± 8.5	79.7 ± 7.2	84.2 ± 7.2

AHI: apnea hypopnea index. BMI: body mass index. Apnea/tot: % apneas/ total number of apneas+hypopneas. AH REM/tot: % of apneas+hypopneas observed during REM sleep/ total number of apneas+hypopneas. SO_2<90%: % of sleep time spent with oxygen saturation below 90%. Lowest SO_2: lowest SO_2 recorded during the sleep study.

Table 2. Effect of genioglossus stimulation on upper airway flow:pressure relationships parameters.

		(AHI<6) n=5	mild OSA (AHI 6-20) n=11	moderate OSA (AHI 21-40) n=8	severe OSA (AHI >40) n=8	all n=32
Pcrit (cmH_2O)	BL	-1.7 ± 2.1	0.8 ± 3.6	1.7 ± 3.0	3.1 ± 2.1¶	1.2 ± 3.3
	ES	-4.3 ± 4.5*	-1.2 ± 4.3*	0.6 ± 2.6*	0.5 ± 3.0*	-0.7 ± 3.8^{+}
Pflim (cmH_2O)	BL	5.4 ± 3.0	6.3 ± 3.6	6.3 ± 3.2	9.7 ± 1.8¶	7.0 ± 3.4
	ES	2.3 ± 1.7*	4.9 ± 3.7*	6.1 ± 4.9	6.9 ± 2.6*	5.3 ± 3.8^{+}
Vat (l/min)	BL	4.0 ± 5.5	2.5 ± 4.6	1.3 ± 3.6	0 ± 0¶	1.9 ± 4.0
	ES	11.8 ± 12.0*	4.0 ± 6.6*	1.8 ± 4.8	1.3 ± 2.2	3.6 ± 6.8^{+}
V/P slope ($l/min/cmH_2O$)	BL	3.1 ± 0.9	3.5 ± 2.3	4.0 ± 1.3	3.9 ± 1.8	3.7 ± 1.7
	ES	2.6 ± 0.4	3.1 ± 2.0	3.9 ± 0.9	4.0 ± 2.1	3.5 ± 1.7

Pflim: Pn under which flow limitation occurred. Vat: flow at atmospheric pressure (Pn=0). V/P slope: flow to pressure relationships. BL: baseline. ES: electrical stimulation of genioglossus.

* - $p<0.05$, $^{+}$ - $p<0.01$ for the comparison of BL and ES (t-test).

¶ - $p<0.01$ for the trend-changes with increasing OSA severity (ANOVA).

Table 3. Comparison of the effects of genioglossus stimulation on oro- and velopharyngeal characteristics.

		Pcrit cmH_2O			compliance mm^2/cmH_2O	
		BL	ES	ΔPcrit	BL	ES
AHI<20 (n=9)	OP	-3.1 ± 3.6	-7.3 ± 5.2	4.2 ± 3.3	32.0 ± 24.4	30.2 ± 21.4
	VP	-0.9 ± 2.8	-2.9 ± 3.8	2.0 ± 1.8^{+}	16.1 ± 14.3	15.2 ± 12.4
AHI>20 (n=5)	OP	-1.6 ± 4.5	-5.7 ± 3.2	4.1 ± 2.5	31.3 ± 18.1	31.0 ± 18.1
	VP	2.5 ± 3.5*	-0.5 ± 3.1	3.0 ± 2.1	16.6 ± 9.4	18.0 ± 12.9
All (n=14)	OP	-2.6 ± 3.9	-6.7 ± 4.5	4.2 ± 2.9	31.8 ± 21.7	30.5 ± 19.5
	VP	0.3 ± 3.4^{+}	-2.1 ± 3.6^{+}	2.3 ± 1.9^{+}	16.3 ± 12.4^{+}	16.2 ± 12.2^{+}

Data of all subjects with studies in both levels (n=14). OP: oropharynx. VP: velopharynx.

* - p= 0.066 for the comparison of BL VP Pcrit of patients with low and high AHI.

$^{+}$ - p<0.03 for the comparison of OP and VP.

All Pcrit changes from BL to ES are significant (p<0.05).

LEGENDS TO FIGURES.

Figure 1. Schematic illustration of the experimental instrumentation. Patients were prepared as customary in the sleep-lab. In addition, an esophageal balloon was used (placed more distal than shown in this picture) to measure intra-thoracic pressure (Pesoph), and a pneumotachometer was connected to a digitized CPAP device.

Figure 2. Relationships between the AHI during sleep and the Pcrit obtained under anesthesia for all participants of this study.

Open symbols – single individuals. Large closed symbols – mean group data ± SD.

nl – AHI<6. mi – mild OSA (AHI 6-20). mo – moderate OSA (AHI 21-40). se – severe OSA (AHI >41).

Figure 3. Relationships between the Pcrit values obtained before and during GG-ES (±CI). Symbols as in figure 2. BL- baseline, ES – electrical stimulation of the genioglossus. The broken line is the line of abscissa and ordinate equality. The almost parallel shift of the relationships between BL- and ES-Pcrit demonstrates that the GG-ES-induced decrease in Pcrit was independent of baseline Pcrit.

Figure 4. Pictures of the velopharynx at different Pn (CPAP) levels, before (BL, baseline) and during ES (electrical stimulation of the GG). In this patient, GG-ES had a similar effect on the velopharynx as the application of CPAP of about 4 cmH_2O.

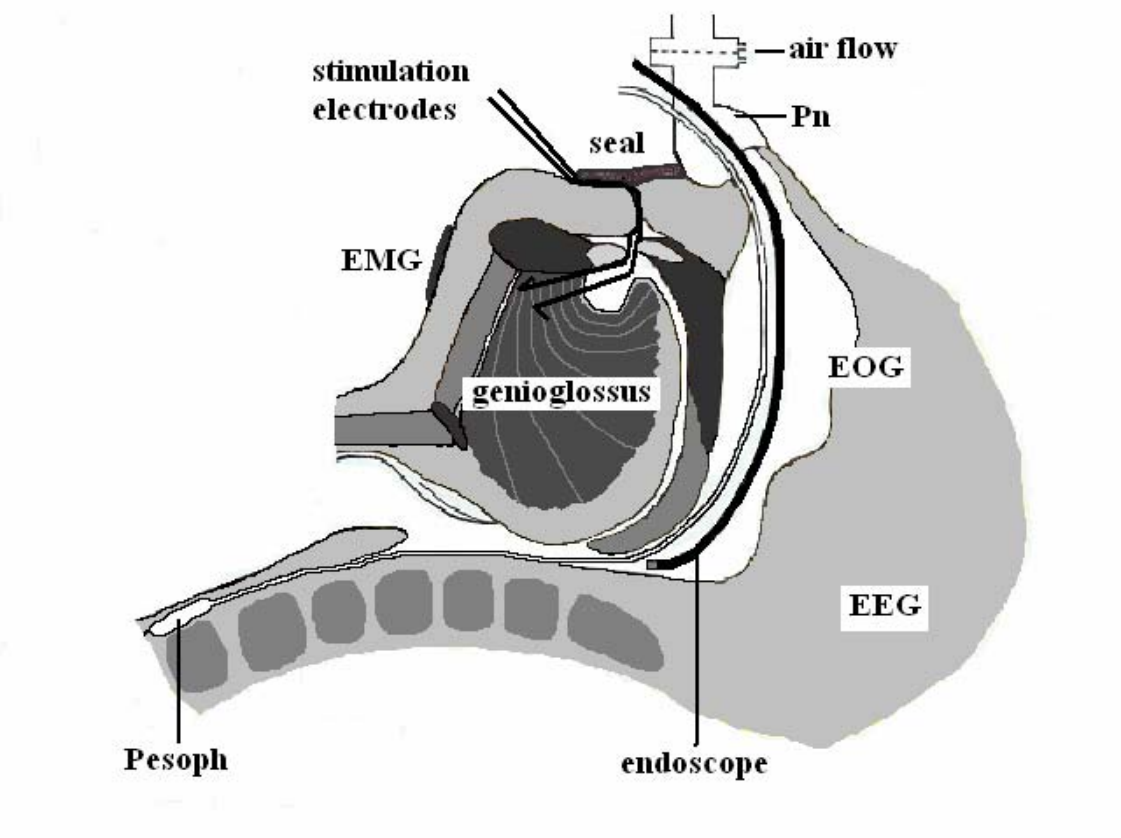
Figure 5. Relationships between the VP CSA and Pn (i.e., VP compliance), over the range of flow-limitation. Data are given for each of the AHI subgroups before (dashed lines) and during GG-ES (solid line). The arrows indicate the magnitude of GG-ES-induced shift in the CSA:Pn relationships. VP compliance (slopes) was not affected significantly by GG-ES. In the mean, GG-ES enlarged the VP CSA (up-shift at a given Pn) similarly over the whole range of Pn levels associated with flow limitation, with no significant differences between the AHI subgroups, and independently of the baseline Pcrit.

Figure 6. Comparison between subjects with larger and smaller response to GG-ES, undertaken to assess relationships between pharyngoscopic findings and the Pcrit response to GG-ES (ΔPcrit). Only anterior movement of the posterior side of the tongue was significantly related to substantial reduction in VP collapsibility, i.e., more prevalent in the group with larger ΔPcrit.

VP occl - primary site of occlusion in the velopharynx. VPa-p – decreasing Pn occluded the VP mainly in the sagittal (anterior-posterior) direction. Vibrat. – visible oscillations/vibrations of the pharyngeal walls during flow limitation. T down – downward movement (depression) of the posterior part of the tongue during GG-ES. T forw. – forward movement of the posterior part of the tongue during GG-ES. * - $p<0.04$.

Figure 7. Pictures of the oropharynx at different Pn (CPAP) levels, before and during GG-ES. In this patient, GG-ES had a larger effect on the oropharynx than the application of CPAP of 4 cmH_2O.

Figure 8. Relationships between the magnitude of GG-ES-induced advancement of the posterior side of the tongue (ΔOP_{A-P}) and the concomitant increase in CSA (ΔCSA) of the VP and OP in the subgroup of subjects in which OP_{A-P} diameter was measured (n=14). Data presented were taken at atmospheric pressure (Pn=0). The GG-ES-induced OP ΔCSA is larger than VP ΔCSA in all subjects. ΔOP_{A-P} correlates significantly with ΔCSA at both levels ($p<0.01$).



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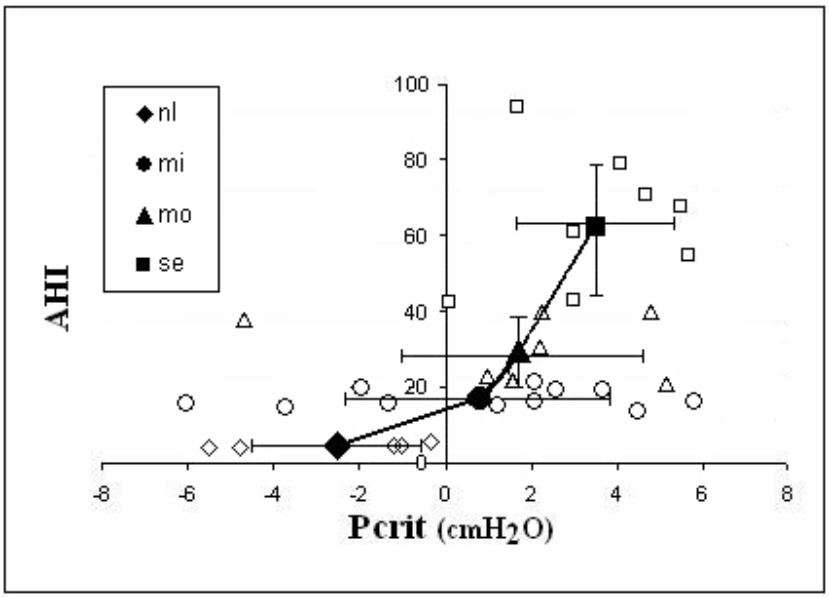

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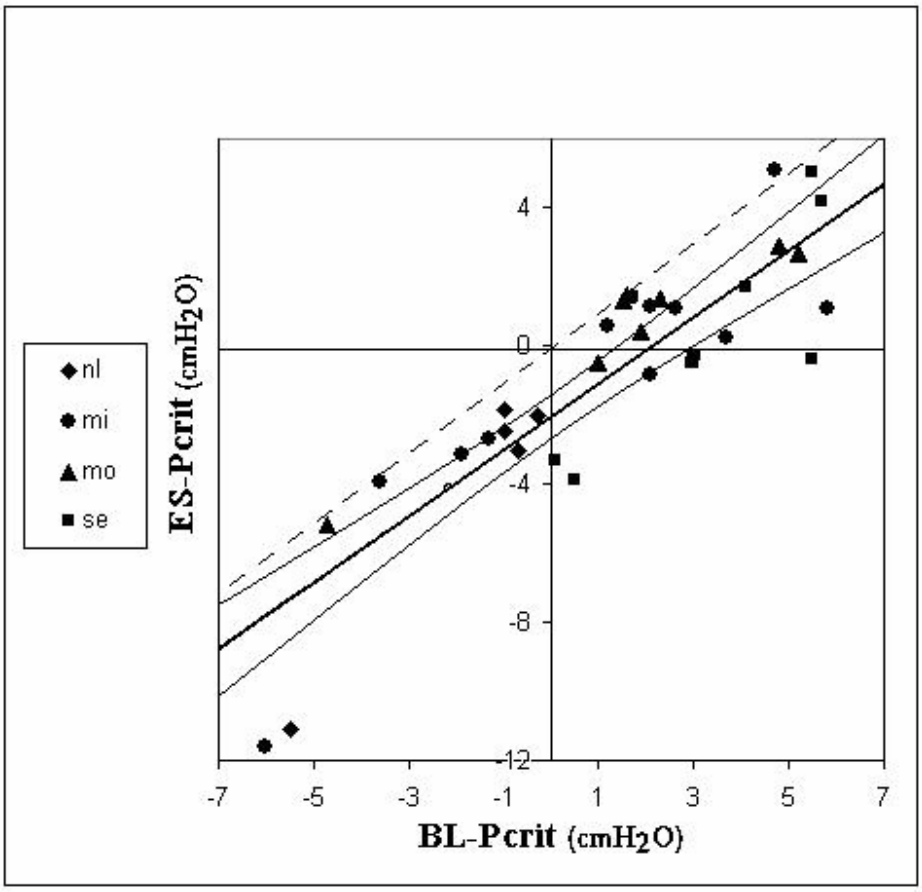

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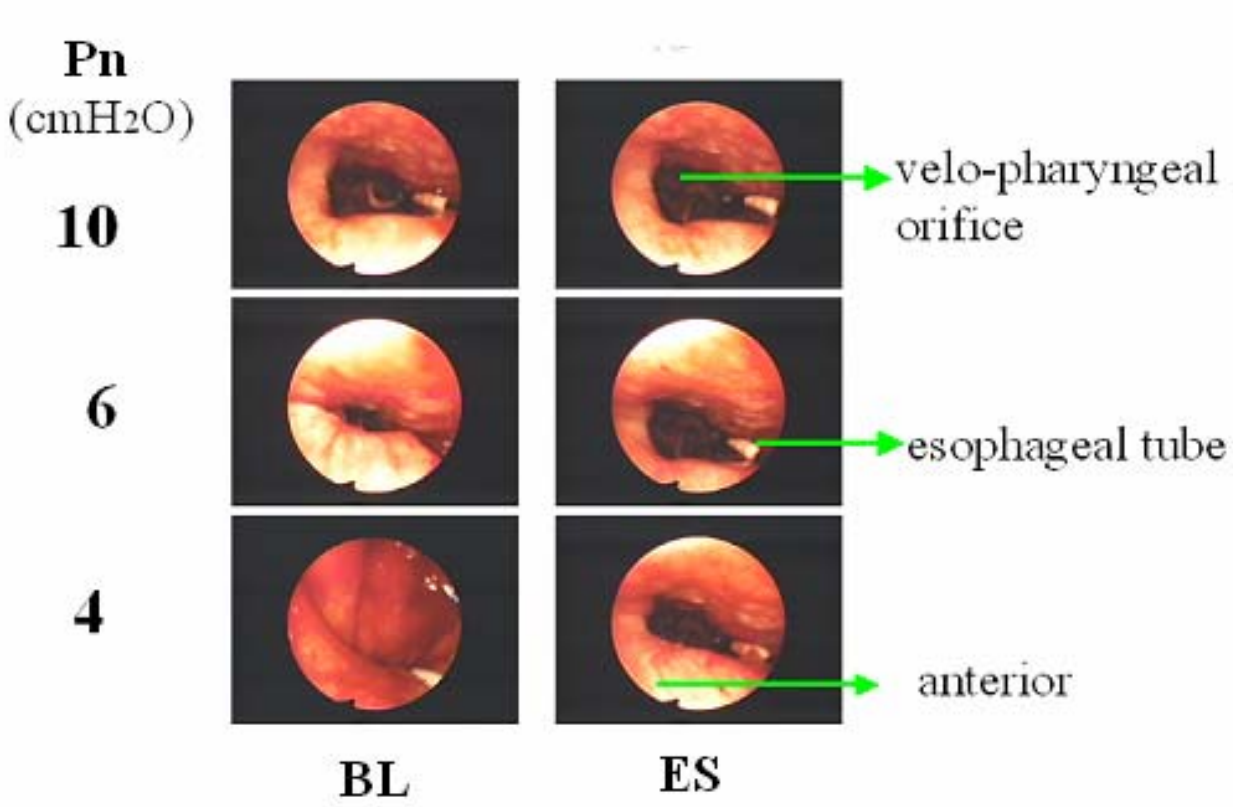

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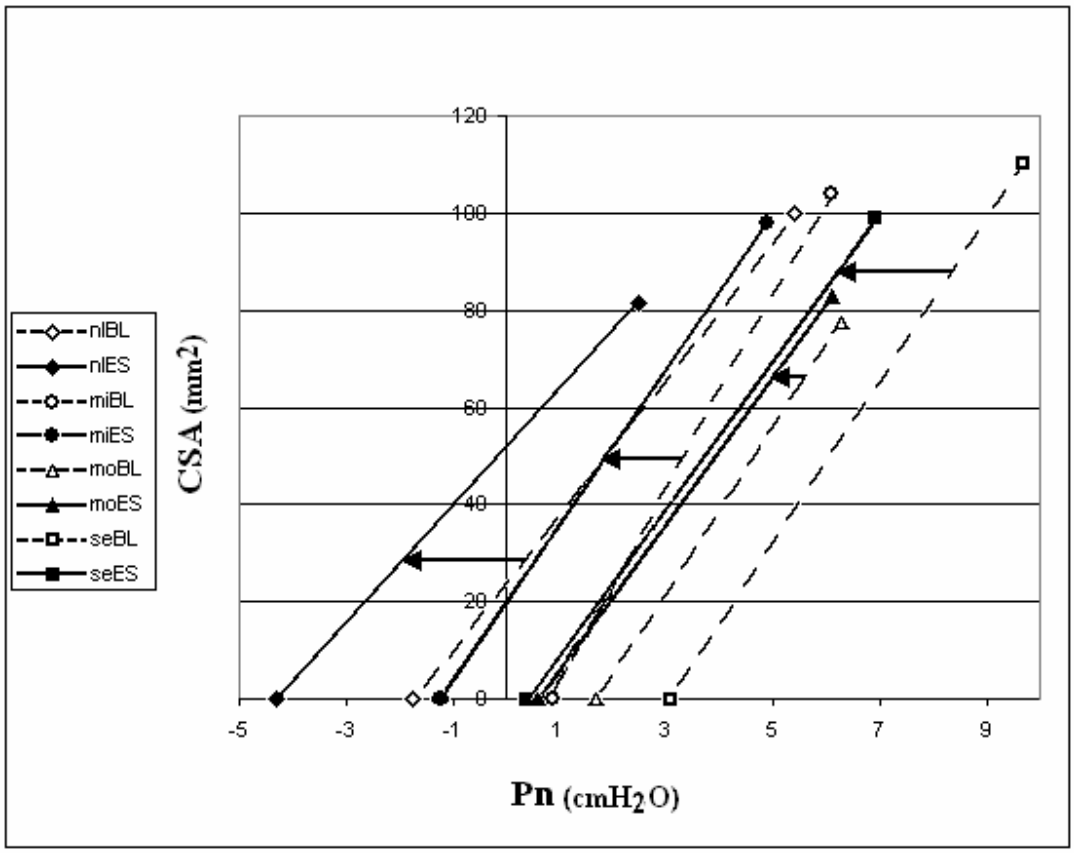

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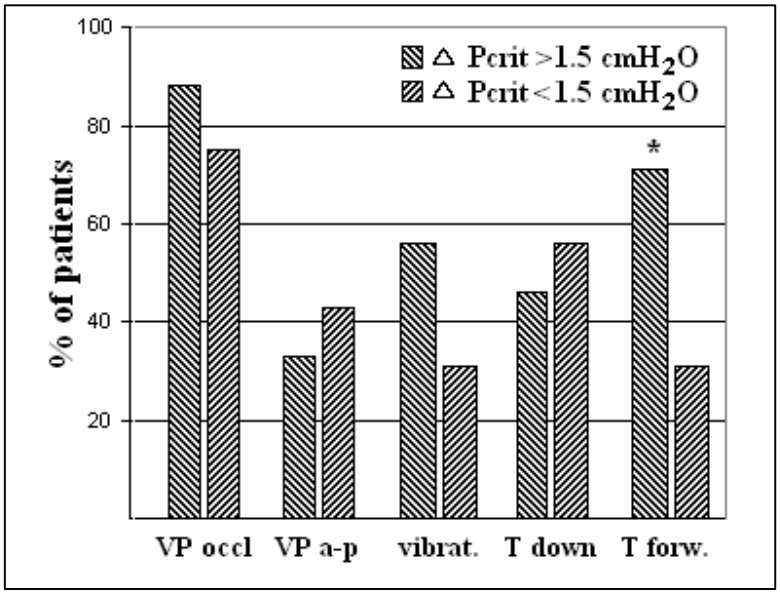
Symbols as in previous figures.



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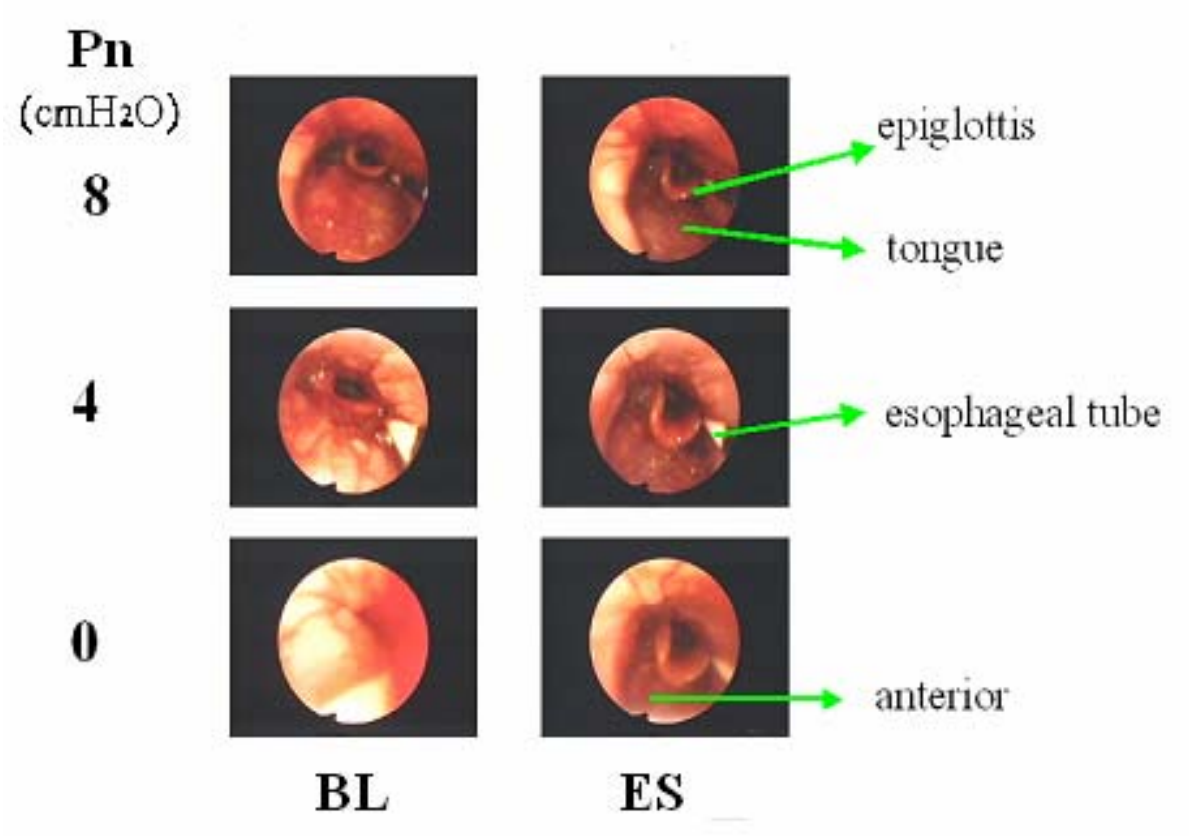

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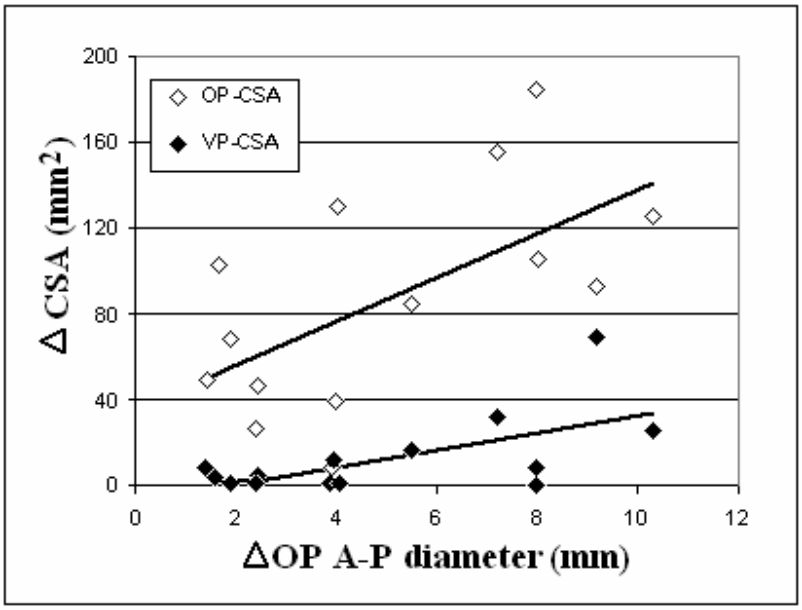

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Figure 8. Relationships between the magnitude of GG-ES-induced protrusion of the posterior side of the tongue ($\Delta OP_{A\text{-}P}$) and the concomitant increase in CSA (ΔCSA) of the VP and OP in the subgroup of patients in which $OP_{A\text{-}P}$ diameter was measured. Individual VP and OP data of each subject (n=14). Data presented were taken at atmospheric pressure (Pn=0). The GG-ES-induced OP ΔCSA is larger than VP ΔCSA in all subjects. $\Delta OP_{A\text{-}P}$ correlates significantly with ΔCSA at both levels ($p<0.01$).