

# Effect of coactivation of tongue protruder and retractor muscles on pharyngeal lumen and airflow in sleep apnea patients

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**Oliven A, Odeh M, Geitini L, Oliven R, Steinfeld U, Schwartz AR, Tov N.** Effect of coactivation of tongue protruder and retractor muscles on pharyngeal lumen and airflow in sleep apnea patients. *J Appl Physiol* 103: 1662–1668, 2007. First published August 2, 2007; doi:10.1152/jappphysiol.00620.2007.—The present study evaluated the effect of coactivation of tongue protruders and retractors on pharyngeal patency in patients with obstructive sleep apnea. The effect of genioglossus (GG), hyoglossus (HG), and coactivation of both on nasal pressure (Pn):flow relationships was evaluated in a sleep study (SIS,  $n = 7$ ) and during a propofol anesthesia study (AnS,  $n = 7$ ). GG was stimulated with sublingual surface electrodes in SIS and with intramuscular electrodes in AnS, while HG was stimulated with surface electrodes in both groups. In the AnS, the cross-sectional area (CSA):Pn relationships was measured with a pharyngoscope to estimate velopharyngeal compliance. In the SIS, surface stimulation of GG had no effect on the critical pressure (Pcrit), HG increased Pcrit from  $2.8 \pm 1.7$  to  $3.7 \pm 1.6$  cmH<sub>2</sub>O, but coactivation lowered Pcrit to  $0.2 \pm 1.9$  cmH<sub>2</sub>O ( $P < 0.01$  for both). In the AnS, intramuscular stimulation of GG lowered Pcrit from  $2.6 \pm 1.3$  to  $1.0 \pm 2.8$  cmH<sub>2</sub>O, HG increased Pcrit to  $6.2 \pm 2.5$  cmH<sub>2</sub>O ( $P < 0.01$ ), and coactivation had a similar effect to that of GG (Pcrit =  $1.2 \pm 2.4$  cmH<sub>2</sub>O,  $P < 0.05$ ). None of the interventions affected significantly velopharyngeal compliance. We conclude that the beneficial effect of coactivation depends on the pattern of GG fiber recruitment: although surface stimulation of GG failed to protrude the tongue, it prevented the occlusive effect of the retractor, thereby improving pharyngeal patency during coactivation. Stimulation of deeper GG fibers with intramuscular electrodes enlarged the pharynx, and coactivation had no additive effect.

tongue muscles; sleep apnea; pharynx; genioglossus; hyoglossus

THE PHARYNGEAL REGION has been shown to function as a self-supporting, soft-walled collapsible tube, whose patency depends on wall characteristics and the balance between intraluminal pressure and extraluminal forces. Although many anatomical abnormalities have been implicated in the pathogenesis of obstructive sleep apnea (OSA), the role of functional mechanisms is obvious, since apneas occur only during sleep. It has been postulated that upper airway dilator muscle activity is crucial for counteracting the negative intraluminal pharyngeal pressure, and diminution of this activity during sleep is the major reason for pharyngeal collapse and obstruction in patients with obstructive sleep apnea (2, 25, 31). However, the mode by which peripharyngeal muscles act in concert to maintain pharyngeal patency and the cause for their failure to prevent pharyngeal collapse during sleep in patients with OSA, are poorly understood. Activation of the genioglossus (GG), the main tongue protruder, has been shown to reduce pharyngeal resistance and collapsibility by far more than all other

upper airway dilators (20, 21, 26). However, multiple trials attempting to relieve OSA by stimulating the GG during sleep or anesthesia resulted in modest and/or inconsistent results (4, 7, 8, 13, 19, 22–24, 28, 29). The inability of this muscle, acting alone rather than in conjunction with other muscles, to sufficiently prevent pharyngeal collapse suggests that coactivation of other peripharyngeal muscles is necessary to enable effective pharyngeal enlargement.

While evaluating the electromyographic and mechanical activity of the muscles that retract the tongue, Fregosi, Fuller and coworkers (9, 10) reported that these retractors were always activated in parallel with the GG. This coactivation of tongue retractors and protruders was thought to improve the mechanical stability and, therefore, the functional efficacy of these muscles. In a later study the same researchers reported that electrical coactivation of these muscles in the rat improved pharyngeal stability compared with isolated protruder stimulation (11).

The mechanical effects of GG stimulation in laboratory animals seem to exceed substantially the results obtained in OSA patients, suggesting that the upper airway of the latter and/or its dilator muscles act differently from those of healthy mammals. Nevertheless, we hypothesized that coactivation of tongue protruders and retractors can improve upper airway patency also in OSA patients. To evaluate the effect of coactivation on pharyngeal mechanics, two studies were performed and are presented herewith. In the first, patients were studied during sleep, and a surface electrode was used to stimulate both the GG and/or tongue retractors. In the second study, propofol anesthesia was used to enable the use of pharyngoscopes, the same surface electrode was used to stimulate the retractors, but GG stimulation was performed with intramuscular electrodes. Accordingly, the response to coactivation was assessed with two different modes of GG fiber recruitment, coupled with the same mode of retractor stimulation.

## METHODS

**Subjects.** Patients with OSA (more than 5 episodes of obstructive or mixed apneas or hypopneas per hour of sleep), previously documented on a conventional overnight polysomnographic sleep study, were recruited for these studies. The studies were approved by the Human Investigations Review Boards of the respective institutions, and written informed consent was obtained from each patient.

Two studies were performed in two groups of patients, all men. 1) The first study (sleep study, SIS) was performed in seven OSA patients during sleep in the Johns Hopkins Sleep Disorder Center Laboratory, Baltimore, MD. 2) The second study (anesthesia study, AnS) was performed in the Respiratory Research Laboratory of

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Bnai-Zion Medical Center, Haifa, Israel, on seven patients anesthetized with propofol. 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<sup>2</sup>, as well as subjects with known side effects to any previous anesthesia, were excluded from the AnS. In both studies, patients were studied in the supine position. In the SIS study, the patients were video-observed and returned to the supine position whenever they changed position.

**Recording procedures.** The same instrumentation was used in the two studies, but in the AnS, pharyngoscopy and intramuscular GG electrodes were added (Fig. 1). Standard polysomnographic techniques, including submental surface EMG, C3-O1 and C3-A2 EEG, right and left electrooculogram (EOG), ECG, and oxygen saturation, were employed to monitor sleep or anesthesia and exclude arousal. Subjects breathed through a tight-fitting nasal mask and a pneumotachometer, connected to a Validyne  $\pm 2$  cmH<sub>2</sub>O 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 (P<sub>n</sub>) between 20 and -10 cmH<sub>2</sub>O. P<sub>n</sub> 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. In the SIS, all parameters were both recorded continuously on a polygraph recorder (no. 780; Grass Instruments, Quincy, MA) and digitized for monitoring and data storage. In the AnS, analog-to-digital acquisition of all parameters was performed on a digital polygraphic data acquisition system (LabVIEW, National Instruments, Austin TX).

**Electrical stimulation.** Electrical stimulation (ES) of the retractor muscles was performed as previously described (22). A U-shaped electrode, made of conductive rubber, was attached to an individually fitted dental mandibular prosthesis to keep it positioned in place under the tongue and served for transmucosal surface stimulation of tongue muscles. The electrode was partially insulated, enabling stimulation

through free, noninsulated surfaces only. It was divided into anterior and posterior parts and was shaped in a way that its posterior free surfaces overlaid the sides of the tongue, adjacent to the hyoglossus muscle (HG), while the anterior free surface overlaid the upper surface of the GG muscle, close to its insertion into the mandible. In addition, in the AnS patients, two to four Teflon-coated, 0.007-in.-diameter hook-wire electrodes with bared ends were inserted transmucosally, bilaterally, 10–15 mm deep into the anterior, retromandibular body of the GG, as previously described (23, 28). The electrode pair that provided clear advancement of the posterior wall of the tongue was used. HG stimulation was performed in both studies with the posterior part of the sublingual surface electrode. GG stimulation was performed with the anterior part of the surface electrode in the SIS, while in the AnS the intramuscular electrodes were used. Bursts (40 Hz) of 2–6 s, with biphasic pulses of 100- $\mu$ s width, were applied using a neuromuscular stimulator (Dynex III, Medtronic, Minneapolis, MN). The intensity of stimulation was limited to levels that were well tolerated during wakefulness in preliminary experiments and did not cause arousal during the studies performed during sleep.

**Pharyngoscopy.** In the AnS, a flexible fiber-optic endoscope (Olympus BF-3C40, 3.3 mm OD) was inserted through an adequately sealed port in the nose mask. The pharynx was photographed and video-recorded continuously on videotape throughout the evaluation of the pressure:flow relationships. The endoscope was positioned above the velopharyngeal site of collapse, as this was the primary site of collapse in all AnS patients.

**Anesthesia.** Propofol anesthesia was delivered in the AnS by an anesthesiologist, with a loading dose of 2.5 mg/kg, and continuous drip of 6–12 mg·kg<sup>-1</sup>·h<sup>-1</sup>. Using P<sub>n</sub> levels that prevented flow limitation, we aimed to maintain the patient under stable anesthesia, that eliminated any reaction to pain, ES, and other manipulations, while maintaining adequate spontaneous ventilation, as monitored by the pneumotachometer and pulse oxymetry.

**Site of collapse.** To determine the site of pharyngeal collapse (velo- or oropharynx) in the SIS, we measured the pharyngeal pressure at P<sub>n</sub> < P<sub>crit</sub> with an occluded tube whose sidehole was positioned before sleep at the lower rim of the soft palate. In the AnS, the site of collapse was determined visually, lowering P<sub>n</sub> until occlusion was observed with the endoscope positioned first above and then below the velopharynx.

**Experimental procedure.** Patients were prepared with EEG, EOG, submental EMG, and esophageal balloon and placed in the supine position, and the primary site of collapse was determined. The upper airway pressure:flow relationships was delineated as previously described (30). P<sub>n</sub> was maintained at high levels that prevented flow limitation (holding pressure) and, during stable phase 2 sleep or anesthesia, was lowered intermittently to encompass pressure levels associated with flow limitation and the level below which airflow ceased as the upper airway occluded completely (P<sub>crit</sub>). ES was applied just before inspiratory onset of the 3rd or 4th breath after lowering P<sub>n</sub>, for one inspiration. P<sub>n</sub> was lowered to each level repeatedly to evaluate separately the effect of ES of the GG, the HG, and combined stimulation of both muscles.

**Data analysis.** In both studies, 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 P<sub>n</sub>:flow relationships was determined with least-squares linear regression. This relationship was used to calculate P<sub>crit</sub> as the level of P<sub>n</sub> below which airflow became zero, as well as the P<sub>n</sub>:flow slope, as previously described (20).  $\Delta$ P<sub>crit</sub> (P<sub>crit</sub> during ES minus baseline P<sub>crit</sub>) was used to quantify the mechanical effect of ES.

In the AnS, video movies of the pharyngeal lumen, taken during the evaluation of the flow:P<sub>n</sub> relationships, before and during ES, were digitized and viewed, and single pictures from the end-expiratory pause (i.e., no flow condition, P<sub>n</sub> = intraluminal pressure) were captured and stored. The pharyngeal cross-sectional area (CSA) in

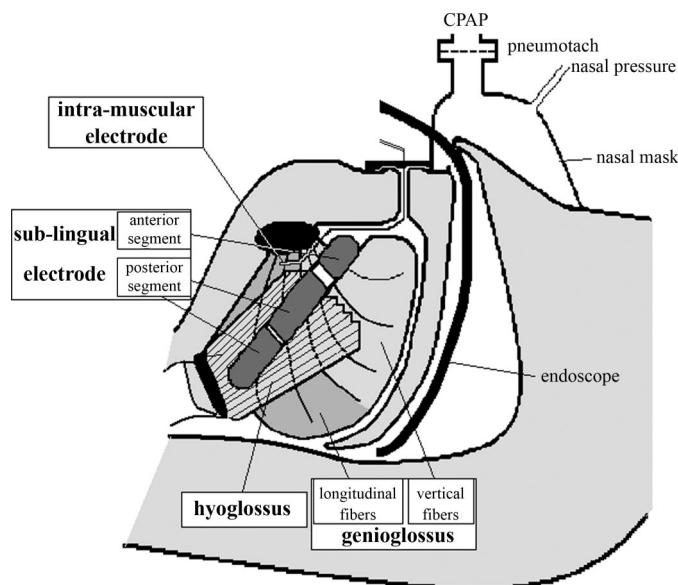


Fig. 1. Schematic illustration of the instrumentation used in the study performed under anesthesia. The same instrumentation was used in the sleep study, without the endoscope and the intramuscular electrodes. Note that the anterior part of the sublingual surface electrode is positioned above the vertically oriented genioglossus fibers, while the intramuscular electrodes are positioned in the longitudinally oriented fibers. The posterior portion of the sublingual surface electrodes is positioned over the hyoglossus muscle. CPAP, continuous positive airway pressure.

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 measure the CSA perpendicular to the pharyngeal axis and at the same distance from the endoscope, and as a reference for calculating the CSA in absolute units. The CSA:Pn relationship was determined for the quasi-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).

Data are presented as means  $\pm$  SD. Paired *t*-test was used for comparison of baseline and stimulation results. *P* values below 0.05 were considered significant.

## RESULTS

The anthropometric and polysomnographic characteristics of the two patient groups are given in Table 1. All patients were men, and eight of them had a BMI > 30. Four patients were hypertensive, and none had any other significant disease. The subjects had a wide range of apnea-hypopnea index (AHI), but both groups were similar with respect to their mean AHI, BMI, and age. The primary site of collapse was the velopharynx in five of the SIS and all the AnS patients.

The effects of ES on the Pn:flow relationships in representative patients from the two studies are shown in Fig. 2. In the SIS, surface ES of the GG (using only the anterior part of the sublingual electrode) had no effect on flow and Pcrit. ES of the HG (using only the posterior part of the sublingual electrode) obstructed the pharynx, as recognized by the shift of the Pn:flow relationships to the right and increase in Pcrit. Combined stimulation of the GG and the retractors, however, improved flow dynamics, as recognized by the left-shift of the Pn:flow relationships and decrease in Pcrit. In the AnS, ES of the GG (via the intramuscular fine-wire electrodes) shifted the Pn:flow relationships to the left and decreased Pcrit. Retractor stimulation (performed as in the SIS with the sublingual surface electrode) obstructed the pharynx as during the SIS. Coactivation (intramuscular electrodes for the GG and surface electrode for the retractors) had an effect similar to ES of the GG.

Data derived for both groups from the Pn:flow relationships measurements, over the range of flow limitation, are given in Table 2. In both studies, retractors ES increased Pcrit and upstream resistance (Rus). Stimulation of the GG with the surface electrode (SIS) had no effect on the Pn:flow. Coactivation was associated in both studies with changes similar to those obtained with the intramuscular electrodes in the AnS

Table 1. Mean BMI, age, and sleep apnea data for the two groups of OSA patients that underwent sleep studies and studies under anesthesia

	Patients Studied During Sleep ( <i>n</i> = 7)	Patients Studied During Anesthesia ( <i>n</i> = 7)
BMI, kg/m <sup>2</sup>	34.4 $\pm$ 8.0	30.4 $\pm$ 3.3
Age, yr	49.7 $\pm$ 8.8	47.9 $\pm$ 16.1
AHI, events/h	40.6 $\pm$ 21.7	37.6 $\pm$ 28.4
Lowest SO <sub>2</sub> , %	91.3 $\pm$ 3.2	87.9 $\pm$ 5.0

Values are means  $\pm$  SD. OSA, obstructive sleep apnea; BMI, body mass index; AHI, apnea-hypopnea index; Lowest SO<sub>2</sub>, lowest oxygen saturation value observed during the clinical sleep study performed before the present study.

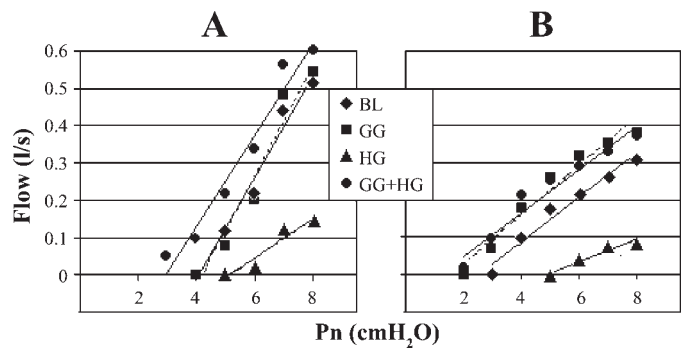


Fig. 2. Nasal pressure (Pn):flow relationships in a patient studied during sleep (A) and a patient studied under anesthesia, with genioglossus (GG) intramuscular electrodes (B). The response to retractor stimulation and coactivation is similar in both patients. Surface stimulation of the anterior part of the GG in the sleep study (A) had no effect on the Pn:flow relationships [slope during GG stimulation, represented by the dashed line, same as during baseline (BL)], while stimulation with the intramuscular electrodes (B) produced a similar effect (slope during GG stimulation represented again by the dashed line) to that of coactivation. GG, genioglossus stimulation with the surface sublingual electrode in A and with the fine-wire intramuscular electrode in B. HG, retractor (hyoglossus) stimulation with the surface sublingual electrode. GG + HG, coactivation of the 2 extrinsic muscles.

(Fig. 3), i.e., significant decrease in Pcrit, with no significant change in the slope of the Pn:flow relationships.

Endoscopy of the pharynx in the AnS revealed that ES via the posterior surfaces of the sublingual electrode caused always a visible retraction of the tongue, confirming that this site of stimulation activated retractor muscles. The CSA:Pn response to ES in one of the patients is shown in Fig. 4. GG and coactivation of the GG together with the HG enlarged the velopharynx without affecting the CSA:Pn slope. Therefore, reduction in velopharyngeal Pcrit in this patient was due primarily to enlargement of the velopharynx, without apparent change in compliance of the area of collapse. A substantial decrease in CSA:Pn slope as seen in this subject during ES of the HG was observed in three of the patients.

The individual CSA:Pn slopes of all AnS patients at the area of velopharyngeal collapse before and during tongue muscle stimulation are presented in Table 3. The mean values were similar during all modes of stimulation and did not change significantly from the mean baseline value (*P* > 0.3 for all).

## DISCUSSION

The present paper evaluated the effect of electrically induced protrusor and retractor tongue muscle contraction on pharyngeal lumen and flow dynamics. The main goal was to evaluate the additive effect of retractor muscle stimulation to that of GG stimulation. Studies were performed in sleeping and anesthetized OSA patients, using two modes of GG stimulation. The main findings are as follows. 1) Coactivation of the GG, using the surface electrode, together with the tongue retractor, enlarged the pharynx and improved airflow. 2) However, coactivation had no advantage over GG stimulation alone when the GG was activated with intramuscular electrodes.

The lack of flow response to surface stimulation of the GG occurred despite clearly visible and palpable contraction of the muscle adjacent to the anterior part of the sublingual surface electrode, associated with depression of the anterior part of the tongue. In the first three AnS patients, we tried to stimulate



Table 2. Effect of electrical stimulation on occlusion pressure ( $P_{crit}$ ) and upstream resistance in the two groups

	Patients Studied During Sleep ( $n = 7$ )		Patients Studied During Anesthesia ( $n = 7$ )	
	$P_{crit}$ , cmH <sub>2</sub> O	Rus, cmH <sub>2</sub> O $\cdot$ l <sup>-1</sup> $\cdot$ s	$P_{crit}$ , cmH <sub>2</sub> O	Rus, cmH <sub>2</sub> O $\cdot$ l <sup>-1</sup> $\cdot$ s
Baseline	2.3 $\pm$ 1.7	12.9 $\pm$ 6.9	2.6 $\pm$ 1.3	14.3 $\pm$ 3.3
Protrusor ES	2.2 $\pm$ 1.7	13.5 $\pm$ 7.1	1.0 $\pm$ 2.8‡	13.6 $\pm$ 4.8
Retractor ES	3.7 $\pm$ 1.6†	19.2 $\pm$ 6.4*	6.2 $\pm$ 2.5†	30.2 $\pm$ 22.8
Coactivation	0.2 $\pm$ 1.9†	14.3 $\pm$ 5.9	1.2 $\pm$ 2.4*	11.4 $\pm$ 4.9

Values are means  $\pm$  SD. ES, electrical stimulation;  $P_{crit}$ , critical pressure; Rus, upstream resistance. \* $P < 0.05$ , † $P < 0.01$  for comparison with baseline values. (‡ $P = 0.060$ ).

the GG with the anterior segment of the surface electrode, using higher stimulation intensities than those possible during sleep but could not produce any movement at the posterior side of the tongue. As seen in Fig. 1, due to the fanlike orientation of the GG fibers, surface stimulation of the GG activates primarily the superior, vertically oriented fibers that are not expected to produce anterior displacement of the tongue. Only the inferior and middle fibers, reached by the intramuscular electrodes, pass backward, blend with the posterior body of the tongue, attach to the hyoid bone, and can pull the posterior part of the tongue forward. The different responses to the two modes of GG stimulation in our studies emphasize that mechanically the GG has at least two different actions, namely depression and flattening of the tongue, and tongue protrusion, and only the latter one is likely to have an independent respiratory role.

It was, therefore, rather surprising to find that combining surface GG stimulation with retractor stimulation enlarged the

pharynx, although when applied alone, the first had no effect and the latter occluded the airways. A possible explanation to this finding, which also provides a common denominator to our findings in the two studies, is modeled in Fig. 5, on the basis of the specific position and attachments of the HG and the two functional components of the GG. The vertical fibers of the GG depress the tongue, without affecting pharyngeal CSA (Fig. 5A). The longitudinal fibers of the GG protrude the posterior part of the tongue and enlarge the pharyngeal CSA (Fig. 5C). Although the HG is an extrinsic tongue muscle (with an external bony origin and insertion into the tongue base), its external insertion is to the hyoid bone, an unstable bony structure suspended between the pharyngeal and neck muscles, whose position and stability depend largely on the activity of the surrounding muscles. For the HG to act as a tongue retractor, the hyoid bone needs to be stable (Fig. 5B). However, if the other muscles inserting into the hyoid bone are relaxed, and contraction of the vertically oriented GG fibers prevents retraction of the tongue, the HG is expected to move the hyoid bone (including the structures attached to it) anteriorly, thereby advancing the posterior side of the tongue and enlarging the pharyngeal airways (Fig. 5D). Contraction of the longitudinal GG fibers has the same effect on the "free-floating" HG. However, as this part of the GG already advances the tongue, the concomitant contraction of the HG has no additive effect on

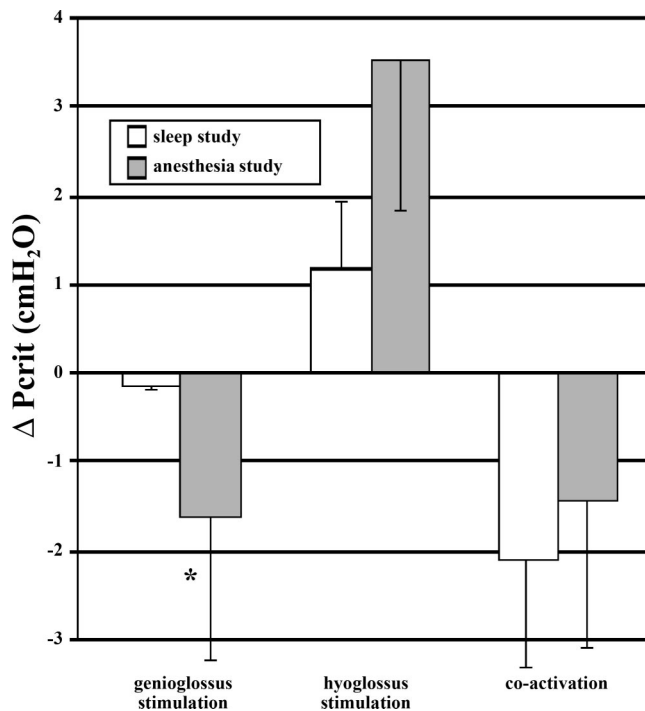


Fig. 3. Changes in the critical pressure ( $\Delta P_{crit}$ ,  $P_{crit}$  during stimulation – baseline  $P_{crit}$ ) observed during electrical stimulation of the tongue muscles. GG stimulation was performed with the sublingual surface electrode in the sleep study and with the fine-wire intramuscular electrode in the anesthesia study. \* $P < 0.05$  for the comparison between surface and intramuscular stimulation of the GG.

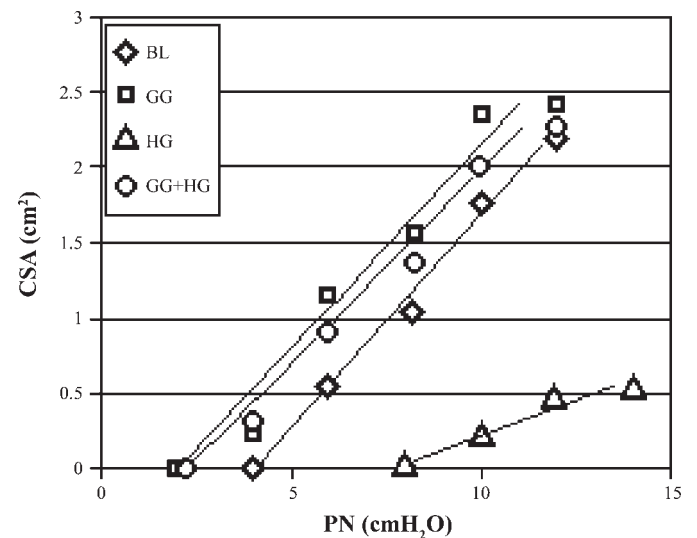


Fig. 4. Cross-sectional area (CSA):PN relationships at the level of the velopharyngeal occlusion area in one of the anesthesia study subjects. Both GG stimulation and coactivation enlarge the velopharynx and decrease  $P_{crit}$ . HG stimulation obstructs the velopharynx and increases  $P_{crit}$ .

Table 3. Effect of tongue muscle electrical stimulation on the CSA:Pn relationships in the AnS patients

Patients	Baseline	Protrusor ES	Retractor ES	Coactivation
1	0.200	0.169	0.188	0.147
2	0.288	0.300	0.112	0.302
3	0.284	0.176	0.332	0.283
4	0.255	0.275	0.338	0.173
5	0.170	0.160	0.075	0.145
6	0.046	0.050	0.022	0.058
7	0.034	0.069	0.136	0.090
Mean	0.182	0.171	0.172	0.171
SD	0.106	0.094	0.123	0.092

Values are cross-sectional area (CSA):nasal pressure (Pn) relationship in units of  $\text{cm}^2/\text{cmH}_2\text{O}$ . AnS, anesthesia study.

the pharyngeal CSA (Fig. 5E). Considering the extensive interdigitation of extrinsic and intrinsic tongue muscles, the HG may be considered, like the intrinsic longitudinal tongue fibers, to act in series with the GG, and when both contract together unopposed by other muscles (as was the case in our study during coactivation), the HG may help advancing the tongue, i.e., act as a tongue protrusor. In addition, it is possible that the posterior portion of the surface electrode activated also longitudinal intrinsic tongue fibers, and coactivation of these fibers with the GG assisted the beneficial effect observed in the SIS, by the same mechanism suggested for the HG. Interestingly, a similar phenomenon was reported by Fuller et al. (11), who observed that retractor stimulation improved pharyngeal flow and Pcrit when the tip of the tongue was anchored to a force transducer but obstructed the pharynx when the tongue was free to retract. The second tongue retractor, the styloglossus, is attached to the bony structure of the skull and is expected to be a pure tongue retractor. With the mode of stimulation used in our studies, this muscle was not activated. Our findings indicate, therefore, that coactivation may or may not enlarge the pharynx and improve patency, depending on the retractor and protrusor muscle (or muscle part) activated.

Several limitations of our studies need to be addressed. The intensity of stimulation, particularly during the SIS, was limited, as strict criteria had to be met to exclude arousal, as previously described (23). In addition, we did not compare surface and intramuscular GG stimulation in the sleep study, as conducting both protocols (including coactivation) in a single sleep study was infeasible. However, in our first AnS patients, we could verify endoscopically that surface GG stimulation failed to enlarge the pharynx. Also, the difference in response to the two modes of stimulation could not be explained by differences between patients groups and was similar to our previous findings with the two types of electrodes (22, 23). A sex-related bias may be present, as we studied men only. Instrumentation, particularly the pharyngoscope, could affect our results, but their effect was found to be negligible (24). In the present study we did not assess the effect of tongue muscle stimulation on the oropharynx, as the site of collapse was at the level of the velopharynx in all AnS patients. Isono et al. (16) reported that whole tongue stimulation (that may have coactivated tongue retractors) slightly decreased oropharyngeal compliance. In a recent study, we (24) found that intramuscular stimulation of the GG did not alter oropharyngeal compliance, but the change in Pcrit was larger than that observed at the

level of the velopharynx. It should also be noted that the mode of stimulation used in the present studies differs substantially from the physiological, central activation of these muscles. Therefore, it is likely that the magnitude of responses during coordinated coactivation may be much more effective than that observed under the experimental conditions. Stimulation was applied always after pressure reductions, and it is possible that application of electrical stimulation before reductions in Pn could have produced different results, improving the effects of GG stimulation. However, resistance to reopening could be expected during complete obstruction but would be unlikely during mild to moderate partial obstruction. Also, if resistance to reopening would have occurred, a gradual improvement in airflow over the first breaths would have been expected, and this did not occur. Another concern is the use of anesthesia. Although propofol has no direct effect on muscle contraction (12), upper airway muscles may be more relaxed during anesthesia (6). On the other hand, the mechanical properties of the pharynx during propofol anesthesia were found to predict the severity of disturbance during sleep (5). As GG stimulation in our studies was ineffective during sleep compared with anesthesia, this difference cannot be explained by increased relaxation during anesthesia. The similar baseline Pcrit and the similar decrease in Pcrit during coactivation in the AnS and SIS, in patient groups with similar AHI, suggests that the confounding mechanical effect of anesthesia (compared with sleep) in our study was of minor relevance. This is also supported by the finding that in our previous study in sleeping OSA patients (23), the mean decrease in Pcrit during GG stimulation via fine wires was similar to that observed with the same technique in the present study in the AnS.

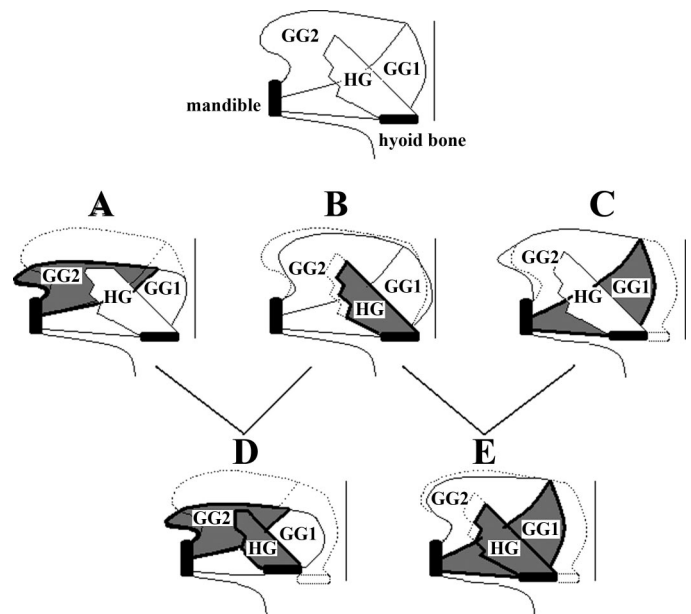


Fig. 5. Schematic presentation of the forces applied by the GG and the HG on the tongue. GG1, longitudinal GG fibers that advance and protrude the tongue. GG2, vertically oriented GG fibers that depress the tongue. A, B, and C illustrate the isolated effects of GG2, HG, and GG1 contraction, respectively. D and E show effects of coactivation. To enable tongue retraction by the HG, the hyoid bone has to be stable, and the GG relaxed. However, when the HG contracts together with the GG, and the muscles that stabilize the hyoid bone are relaxed, coactivation is expected to move the hyoid bone (and the tongue) anteriorly. See text for additional explanations.

As in previous studies (16, 17), we used the slope of the CSA:Pn curve in the AnS as an indicator of the compliance of the area of collapse. This method has the advantage of focusing on the collapsible segment of the pharynx, rather than measuring compliance of the whole isolated upper airway, possible only in animals. On the other hand, this method includes confounders like lung volume effects on pharyngeal size and compliance and changes in muscles length-tension relationships associated with alterations in pharyngeal size. Therefore, the CSA:Pn relationships results from a complex interaction of multiple effects (17). It should also be noted that the complete CSA:Pn relationships of the pharynx is typically exponential, with little dilation occurring at high Pn levels (15). However, as we were interested only in the CSA:Pn range close to Pcrit, which is associated with flow limitation (14), we limited our measurements to this nearly linear portion of the curve, as previously suggested (16, 17). The lack of response of velopharyngeal CSA:Pn to tongue muscle stimulation in our study is similar to the response observed by Isono et al. (16) during whole tongue stimulation, and responses in animals (17).

The results of the present study provide additional evidence on the effect of tongue muscle contraction on velopharyngeal patency and collapsibility. Although the exact mechanism by which the tongue affects the soft palate cannot be determined from our experiments, it is likely due to changes in the external tissue pressure at the site of collapse, as previously suggested (27). The close relationships between the direction of movement of the tongue and the size of the velopharynx observed in the present study, as well as the correlation between the magnitude of tongue advancement and enlargement of the retropalatal space during GG stimulation in our recent study (24), suggest that the tongue compresses the site of collapse. Anterior tongue advancement may unload the velopharyngeal area and decrease the pressure exerted by the tongue on the ventral surface of the soft palate, thereby increasing the transmural pressure (i.e., intraluminal minus external pressure). The possibility that palatoglossal and/or palatopharyngeal fibers near the posterior edge of the sublingual electrode could have been activated during retractor muscle stimulation cannot be excluded. These fibers, which pull the anterior palatal arch, could possibly enlarge the retropalatal airway. However, as this potential effect did not prevent velopharyngeal obstruction during retractor stimulation, their effect, if present, was probably minimal. On the other hand, displacement of the tongue may exert a direct mechanical effect on the soft palate, as the tongue connects anatomically to the soft palate by the palatoglossus muscle and arch.

Previous studies that evaluated the effects of tongue protrusion and retractor coactivation on the pharynx used nerve stimulation and compared stimulation of the median hypoglossus branch, which activates the GG (and intrinsic muscles), with stimulation of the whole hypoglossus, which activates all intrinsic and extrinsic (i.e., both retractor and protrusion) tongue muscles (1, 3, 8, 11, 17, 18, 32). Taken together, the animal studies indicated that the mechanical effects of tongue muscle stimulation depend on a complex interaction between the muscles stimulated, the pharyngeal region (i.e., caudal and rostral oropharynx and nasopharynx), and the transmural pressure. In addition, results depended also on the mechanical parameter evaluated (i.e., size, compliance, resistance, or Pcrit). Most studies found no advantage to coactivation by

stimulating the whole hypoglossus nerve over stimulation of its medial branch (1, 3, 17, 18). On the other hand, pharyngeal resistance decreased during coactivation more than during GG stimulation (32). In patients with OSA, a similar increase in airflow was found during whole hypoglossus nerve and medial branch stimulation (8). Although differing substantially from our study in the mode of stimulation and, therefore, in the pattern of muscle recruitment, these results corroborate our finding that once the transverse GG fibers are activated, coactivation of the retractors provides little or no additional mechanical advantage. However, isolated supramaximal stimulation of the GG is unlikely to occur under physiological conditions. Our findings suggest that tongue retractors may provide a mechanical advantage during specific muscle recruitment patterns. The coactivation observed regularly when EMG of the retractor and protrusion muscles is recorded (10) suggests that such specific patterns of recruitment are likely to be the norm during physiological, central activation of the tongue muscles.

In conclusion, our findings emphasize the importance of discerning the mechanical action of the deeper, transversely oriented GG fibers, which advance the tongue and enlarge the pharynx, from "nonadvancing" GG fibers, which have other mechanical effects. Similarly, tongue retractors function differently, and the HG may help advancing the base of the tongue when pulled by the GG, unopposed by muscles that stabilize the hyoid bone. Accordingly, a beneficial effect of tongue retractor and protrusion coactivation depends on the pattern of muscle recruitment. Coactivation may enlarge the pharynx and improve flow dynamics during specific modes of tongue muscle activation (for example, contraction of the HG + nonadvancing GG fibers), while little or no benefit of coactivation is observed when the transverse GG fibers are activated.

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