CHEST

Ansa Cervicalis Stimulation

A New Direction in Neurostimulation for OSA

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BACKGROUND: Hypoglossal nerve stimulation (HNS) is an alternative treatment option for patients with OSA unable to tolerate positive airway pressure but implant criteria limit treatment candidacy. Previous research indicates that caudal tracheal traction plays an important role in stabilizing upper airway patency.

RESEARCH QUESTION: Does contraction of the sternothyroid muscle with ansa cervicalis stimulation (ACS), which pulls the pharynx caudally via thyroid cartilage insertions, increase maximum inspiratory airflow ($V_I$max)?

STUDY DESIGN AND METHODS: Hook-wire percutaneous electrodes were used to stimulate the medial branch of the right hypoglossal nerve and right branch of the ansa cervicalis innervating the sternothyroid muscle during propofol sedation. $V_I$max was assessed during flow-limited inspiration with a pneumotachometer.

RESULTS: Eight participants with OSA were studied using ACS with and without HNS. Compared with baseline, the mean $V_I$max increase with isolated ACS was 298%, or 473 mL/s (95% CI, 407-539). Isolated HNS increased mean $V_I$max from baseline by 285%, or 260 mL/s (95% CI, 216-303). Adding ACS to HNS during flow-limited inspiration increased mean $V_I$max by 151%, or 205 mL/s (95% CI, 174-236) over isolated HNS. Stimulation was significantly associated with increase in $V_I$max in both experiments ($P < .001$).

INTERPRETATION: ACS independently increased $V_I$max during propofol sedation and drove further increases in $V_I$max when combined with HNS. The branch of the ansa cervicalis innervating the sternothyroid muscle is easily accessed. Confirmation of the ansa cervicalis as a viable neurostimulation target may enable caudal pharyngeal traction as a novel respiratory neurostimulation strategy for treating OSA. CHEST 2021; 159(3):1212-1221

KEY WORDS: ansa cervicalis; hypoglossal nerve stimulation; OSA; sternothyroid muscle; tracheal traction

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ABBREVIATIONS: ACS = ansa cervicalis neurostimulation; BIS = bispectral index score; DISE = drug-induced sleep endoscopy; HNS = hypoglossal nerve stimulation; RNS = respiratory neurostimulation; $V_I$max = maximum inspiratory flow

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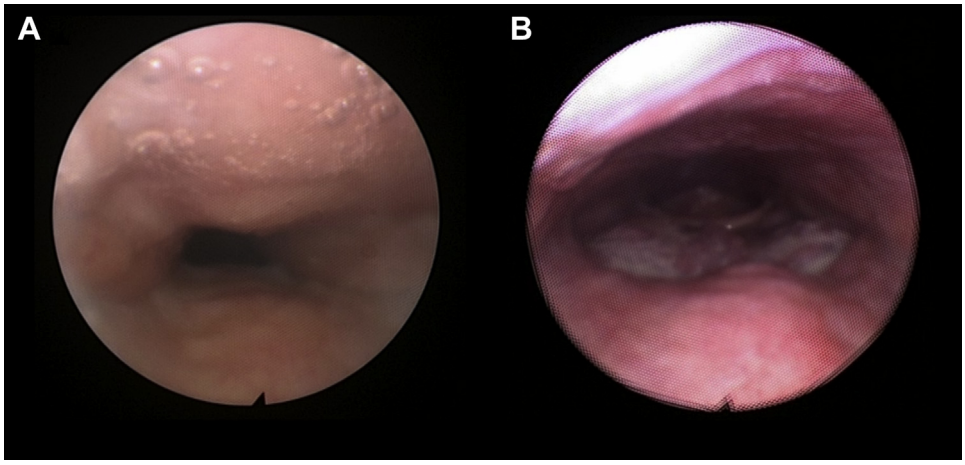

Figure 1 – *A-B, Awake nasopharyngoscopy images at the level of the velopharynx. A, A participant with increased mass and convexity in the lateral wall tissues during awake pharyngoscopy. This participant displayed complete lateral wall and circumferential palatal collapse during drug-induced sleep endoscopy. B, A patient (not a study participant) with no examination findings suggestive of increased lateral wall bulk. No palatal collapse was observed in this patient during drug-induced sleep endoscopy.*

OSA is a common disorder characterized by repetitive upper airway collapse with associated sequelae affecting almost half a billion people worldwide.[1-7] Positive airway pressure modifies the health consequences of OSA and remains the reference standard for treatment,[8,9] but 39% to 50% of patients fail to maintain compliance.[9,10] Although surgical therapies can effectively reduce OSA disease burden in select patients, success rates are variable.[11] Despite the promising development of hypoglossal nerve stimulation (HNS), its indications are limited, and a significant proportion of eligible patients remain inadequately treated.[12,13]

HNS dilates the airway at multiple levels primarily by drawing the tongue ventrally, and findings suggest that favorable HNS responses can be attributed to a strong mechanical linkage between the tongue and other pharyngeal structures, including the soft palate.[14-19] Nonresponders may experience a plateau effect in which further electrical current fails to completely relieve airway obstruction, suggesting that the effects of HNS are localized and insufficient for some recipients despite stringent selection criteria.[12,15,20] Supraphysiological protrusion of the tongue with HNS may also result in pain, tongue abrasion, and xerostomia.[12]

The pharynx is attached to mobile structures ventrally (the mandible and hyoid bone) and caudally (the thyroid cartilage), permitting dynamic modification of its shape and tension in both directions. Caudal tracheal traction is a well-documented method for increasing pharyngeal patency by unfolding and stretching the pharyngeal walls longitudinally to reduce compliance, and by decompressing peripharyngeal tissue pressure.[21-34] Substantial rostro-caudal movement of the hyolaryngeal complex is possible in humans due to adaptations for speech and swallowing that are partially mediated by the cervical strap muscles.[35,36] Previous experiments in animals with less mobile larynges showed significant improvements in airway collapsibility and decreases in peripharyngeal tissue pressure with infra-hyoid muscle traction and electrical stimulation.[32,37-39]

The purpose of the current study was to investigate whether sternothyroid muscle contraction via ansa cervicalis stimulation (ACS) increases pharyngeal patency in humans with OSA. Participants underwent acute studies evaluating the effects of isolated and combined ACS and HNS on pharyngeal patency during propofol sedation. Our findings show substantial increases in maximum inspiratory airflow ($V_I$max) and highlight the potential role of ACS as a novel respiratory neurostimulation (RNS) strategy for treating OSA.

Patients and Methods

Study Design

This study was approved by the Vanderbilt University Medical Center Institutional Review Board (IRB# 181078). Participants were recruited from a group of patients with OSA scheduled to undergo drug-induced sleep endoscopy (DISE) as part of their regular clinical care. Eligible participants were required to have moderate to severe OSA (apnea-hypopnea index ≥15 events/hour) with no history of pharyngeal

surgery aside from tonsillectomy, and no palatine tonsillar hypertrophy (grade III or IV).

Participants most likely to exhibit continued inspiratory airflow limitation during HNS were recruited. Under these circumstances, any further increase in $V_I$max during ACS would reflect reductions in pharyngeal collapsibility with ACS.[15,18] Previous studies have shown that nonresponders to HNS and soft tissue surgery tend to have greater collapse of the retropalatal space and oropharyngeal lateral walls.[14,20,40] Participants were therefore preferentially recruited if physical examination was suggestive of increased lateral wall bulk in the velopharynx or oropharynx, as indicated by increased mass, laxity, and convexity in the lateral wall tissues during awake pharyngoscopy (Fig 1). The increased chance of persistent flow limitation during HNS allowed us to investigate multiple RNS strategies, including isolated ACS, isolated HNS, and HNS combined with ACS.

Experimental Procedures

Drug-Induced Sleep Endoscopy: DISE was completed in the operating room using methods as previously described.[41] A propofol infusion was continuously titrated intraoperatively to maintain flow-limited inspiration with a bispectral index score (BIS) < 70, although lower scores were often required to prevent arousal during neurostimulation experiments. Pharyngeal collapse patterns were assessed during the standard clinical DISE examination using the VOTE classification, a visual endoscopic grading system characterizing the pattern and degree of collapse of the velum (soft palate), oropharyngeal lateral walls, tongue base, and epiglottis.[42] In the VOTE classification, the degree of each structure's collapse is graded by using a unitless value of 0 (no collapse), 1 (partial collapse), or 2 (complete collapse). The velum can collapse anteroposteriorly, circumferentially, or lateromedially. The epiglottis can collapse anteroposteriorly or lateromedially. The tongue base collapses anteroposteriorly, whereas the oropharyngeal lateral walls collapse lateromedially.

Nerve Localization and Electrode Placement: The ansa cervicalis and the hypoglossal nerve were localized by using ultrasound prior to propofol sedation.[43,44] Topical anesthesia was injected subcutaneously, and percutaneous hook-wire monopolar electrodes (0.008-inch perfluoroalkoxy-coated stainless steel monofilament; A-M Systems) were placed, under ultrasound guidance, proximal to the branch of the ansa cervicalis innervating the right sternothyroid muscle. An additional percutaneous electrode was placed proximal to the medial branch of the right hypoglossal nerve, under ultrasound guidance, in a subgroup of participants to assess the effects of combined ACS and HNS (see Results below). Electrodes were connected to a Grass S88 stimulator unit (Grass Instruments Co.). Stimulation pulses (300 μs, 3 Hz) at 1.0 to 1.5 mA confirmed motor nerve activation with target muscle contraction at amperages too low to substantially activate muscle fiber. Desired muscle contraction was additionally confirmed via ultrasound.

Neurostimulation: The standard clinical DISE examination was completed following electrode placement. Under continued sedation, ACS amperage was titrated upward in 0.1- to 0.5-mA increments until maximal sternothyroid muscle contraction without arousal was achieved as observed by ultrasonography and by observation of thyroid notch descent. Maximal contraction was achieved when further increases in amperage did not increase the degree of thyroid notch descent or repeatedly caused arousal. Arousal was primarily identified by clinical response to noxious stimuli such as body movement or grimacing, which was occasionally accompanied by persistent elevation of BIS. In participants undergoing HNS, the process was repeated until maximal tongue protrusion was achieved as observed by oral tongue protrusion and endoscopic visualization of the hypopharynx. Maximal tongue protrusion was achieved when further increases in amperage did not increase the degree of tongue protrusion or repeatedly caused arousal. Nerves were stimulated with square-wave pulse trains with a pulse width of 300 μs, a frequency of 30 Hz, and amperage of 1 to 2 mA depending on clinical response.

Experimental Protocol

A Hans Rudolph RSS-100HR pneumotachometer (Hans Rudolph, Inc.) connected to an oronasal mask (ResMed F20; ResMed Inc.), was placed on each participant prior to the RNS experiments. Baseline levels of upper airway obstruction and responses in airway patency to stimulation were established by measuring $V_I$max with and without stimulation under conditions of inspiratory airflow limitation, as previously described.[15,18] Because airway collapsibility varies between breaths, ACS was applied in periodic (alternating) 0.3 s on-off bursts to evaluate $V_I$max responses within single inspirations. In five participants, periodic ACS was superimposed on 5 to 6 s bursts of continuous HNS stimulation to evaluate the effect of ACS during HNS stimulation on $V_I$max. A secondary evaluation of responses to isolated HNS compared with adjacent unstimulated breaths was performed from data obtained during the HNS with ACS experiment.

Stimulation was activated manually; periodic stimulation continued with a fixed burst duty cycle that was not synchronized to the respiratory cycle. Stimulation was terminated, and data were discarded if arousal occurred during any experimental trial, prompting further adjustments in stimulation amperage and propofol infusion to prevent repeated arousal. A deeper plane of anesthesia than usual during DISE was often required to suppress arousals and subsequent nonspecific increases in airway patency, sometimes resulting in complete apnea.

It was critical for this study to achieve stable periods of inspiratory airflow limitation from which $V_I$max responses could be assessed. Complete airway collapse during RNS experiments created an undesirable floor effect on $V_I$max measurements, as complete absence of airflow prevented detection of changes in pharyngeal collapsibility. A limited jaw-thrust maneuver was therefore occasionally applied by the examiner (D. T. K.) using gentle anterior pressure against the mandibular angles. Aggressive jaw thrust created a state as problematic as complete apnea due to a ceiling effect: if the pharynx was not resistive to airflow, decreased collapsibility with RNS was not reflected in $V_I$max changes. If jaw thrust was used, care was therefore taken to maintain it constantly prior to, during, and following stimulation runs, with comparable degrees of flow limitation prior to and following stimulation. Head and neck positions were maintained in the neutral position throughout the entire study. Multiple stimulation trials were conducted in each participant.

Data Analysis

Variable Definitions: The primary dependent variable was $V_I$max, a marker of upper airway patency.[15,18] Periodic ACS stimulation in both experiments caused multiple transient increases, or peaks, in airflow during flow-limited inspiration. To isolate ACS effects from the natural tidal excursions in inspiratory airflow, only locally bounded maxima during ACS bursts or local plateaus correlating with return to unstimulated flow-limited inspiration prior to the next stimulation were included in analyses of any given breath, as previously described (an illustrative example is provided in the Results).[15,18] Within each breath, the average $V_I$max across the transient peaks was compared with the average value without stimulation between each peak to reduce the impact of natural interbreath variability in $V_I$max on outcomes. To

improve experimental efficiency and reduce time under anesthesia, average $V_I$max during isolated HNS in the combined stimulation experiment was compared with average $V_I$max of the unstimulated breaths immediately prior to and following each stimulation trial, enabling us to obtain measurements of HNS with and without ACS from the same experimental condition. $V_I$max changes were collected across multiple breaths in each stimulation trial, and multiple stimulation trials were conducted in each patient.

The main independent variable was RNS, which consisted of three different interventions from the two experiments: isolated ACS, isolated HNS, and HNS combined with ACS. Palatal collapse pattern from the standard DISE examination was also included as an independent fixed regression model effect as circumferential palatal collapse is known to have substantial negative impacts on HNS response.[20] Subject identifier and stimulation trial number were incorporated as random effects.

Statistical Analysis

Statistical analyses were designed to test the primary hypothesis that RNS increased $V_I$max. We constructed generalized linear mixed models and Wilcoxon rank sum tests in the R statistical programming language and software environment.[45] The models evaluated the independent effect of RNS and palatal collapse pattern because repeated stimulation trials in a single participant were nonindependent measurements and changes in $V_I$max did not always follow a normal distribution. A separate model was constructed for each stimulation modality using a log link function that was exponentially transformed to normalize effects, meaning that each reported effect estimate indicated a multiplicative effect on baseline $V_I$max.

The Wilcoxon rank sum test was used to evaluate for demographic differences between the two experimental groups. Statistical significance was inferred at a P value $< .05$.

Results

Eight participants underwent neurostimulation experiments (Table 1).[42] The study cohort was largely composed of obese older men, consistent with many other OSA cohorts. All participants had severe OSA (mean apnea-hypopnea index, 43.2 ± 8.9 events/h). Three participants (37.5%) had complete circumferential palatal collapse during DISE, and seven (87.5%) had partial or complete lateral wall collapse. ACS was the only experiment evaluated in the first three participants. The experimental protocol was subsequently modified to explore ACS combined with HNS in another five participants. The percutaneous ACS electrode was dislodged in three of these participants by hyolaryngeal movement during the initial combined stimulation experiment, precluding assessment of subsequent responses to isolated ACS. Thus, each group had five participants, with two of them completing both the ACS and HNS with ACS experimental protocols. No significant demographic differences were observed between the two groups (Table 2).

RNS trials were conducted as described in Table 3. Mean ± SD BIS over the course of the RNS trials was 51.0 ± 11.5. In five participants undergoing isolated ACS (Fig 2), the mean $V_I$max increase over 52 stimulated breaths was 298%, or 473 mL/s (95% CI, 407-539) (Fig 3). Flow-limited inspiration persisted during isolated HNS over 66 stimulated breaths in the five participants undergoing continuous HNS with superimposed periodic 0.3 s ACS (Fig 4). Isolated HNS increased mean $V_I$max from baseline by 285%, or 260 mL/s (95% CI, 216-303) compared with unstimulated breaths prior to and following each experimental trial. Adding ACS to HNS

TABLE 1] Demographic Information From Participants in the Neurostimulation Experiments

Participant	Age (y)	Sex	BMI (kg/m^2)	AHI (events/h)	O2 Nadir (%)	VOTE Classification[42]				RNS Experiment
						V	O	T	E	
1	31	M	28.0	32.5	88	2a	1	0	0	ACS
2	75	M	29.7	48	74	2a	2	0	0	ACS
3	64	F	34.2	54.3	66	2a	0	1	0	ACS
4	60	F	30.0	40	71	2c	2	0	0	Both
5	58	M	33.5	30.6	82	2c	2	0	0	Both
6	42	M	35.1	51	83	1a	2	1	0	HNS with ACS
7	59	F	32.6	39.1	57	2c	1	2	0	HNS with ACS
8	49	M	33.7	49.7	78	1a	2	1	0	HNS with ACS
Mean ± SD or ratio	54.8 ± 13.7	5:3	32.1 ± 2.5	43.2 ± 8.9	74.9 ± 10.1					

The VOTE classification grades the degree of collapse of four pharyngeal structures (velum, oropharynx, tongue base, and epiglottis) using a unitless value of 0 (no collapse), 1 (partial collapse), or 2 (complete collapse). The velum can collapse in an anterior-posterior (a), circumferential (c), or lateral pattern. ACS = ansa cervicalis stimulation; AHI = apnea-hypopnea index; HNS = hypoglossal nerve stimulation; RNS = respiratory neurostimulation.

TABLE 2] Comparison of Demographic Variables Between Experimental Groups

Variable	ACS	HNS With ACS	*P*
Age, y	57.6 ± 16.3	53.6 ± 7.8	.38
BMI, kg/m^2	31.1 ± 2.6	33 ± 1.9	.29
AHI, events/h	41.1 ± 10.1	42.1 ± 8.4	.97
Oxygen nadir, %	76.2 ± 8.8	74.2 ± 10.7	.99

Data are presented as mean ± SD. No significant differences were observed between groups. ACS = ansa cervicalis stimulation; AHI = apnea-hypopnea index; HNS = hypoglossal nerve stimulation.

increased mean $V_I$max within the same breath by 151%, or 205 mL/s (95% CI, 174-236) beyond the partial improvements in flow limitation obtained with isolated HNS (Fig 5).

Results of generalized linear mixed models evaluating $V_I$max response to isolated ACS, HNS, and HNS with ACS are summarized in Table 4. $V_I$max distribution analyses showed that isolated ACS was best approximated by the normal distribution, whereas isolated HNS and HNS with ACS were best approximated with a gamma distribution (goodness-of-fit testing for both models, $P > .5$). We thus constructed a model with Gaussian distribution errors and a log link function for isolated ACS, and separately constructed models with gamma distribution errors and a log link function for the other two.

Model effect estimates indicate multiplicative effects on $V_I$max. For example, isolated ACS caused a 3.03-fold (95% CI, 2.43-3.79) increase in $V_I$max, whereas complete circumferential palatal collapse caused a nonsignificant .94-fold (95% CI, 0.82-1.07) decline. The three RNS modalities significantly increased $V_I$max in both experiments to a considerable degree ($P < .001$). Circumferential palatal collapse had the least effect during isolated ACS, but the difference was not statistically significant between any RNS modality. A true effect cannot be excluded due to the wide CIs and small sample size.

Discussion

The current study showed that stimulation of the ansa cervicalis branch to the sternothyroid muscle independently increased inspiratory airflow in patients with OSA during DISE. Stimulating the ansa cervicalis also increased airflow response during flow-limited HNS, representing further improvements in upper airway patency. Taken together, our findings suggest that ACS independently stabilized pharyngeal patency in patients with OSA and could further improve airway patency in patients with incomplete responses to HNS.

Pharyngeal stabilization with ACS is likely due to caudal pharyngeal traction from the sternothyroid muscle. This muscle pulls the thyroid cartilage caudally, mimicking the effects of tracheal traction observed in previous animal and human studies. In animal studies, caudal traction has been shown to improve upper airway patency by decreasing peripharyngeal tissue pressure and pharyngeal wall compliance, and by increasing caudal tension along the distal edge of the soft palate.[23,31,46,47] The active tension of caudal traction on the soft palate may explain why circumferential palatal collapse had less of a suppressive effect on $V_I$max during isolated ACS, although this theory should be interpreted with caution as the effect was not statistically significant

TABLE 3] Responses in $V_I$max to RNS Modalities

RNS Modality	Comparison	No.	Mean Baseline $V_I$max (mL/s)	Mean Stimulated $V_I$max (mL/s)	Mean ΔV_Imax (mL/s)	Mean ΔV_Imax (%)
ACS	Intrabreath unstimulated	5	238 (190-287)	711 (665-757)	473 (407-539)	298
HNS	Interbreath unstimulated	5	140 (112-169)	400 (349-452)	260 (216-303)	285
HNS with ACS	Intrabreath HNS	5	400 (349-452)	605 (531-679)	205 (174-236)	151

Mean $V_I$max and change in $V_I$max under each experimental condition with 95% CIs in parentheses. ACS = ansa cervicalis stimulation; HNS = hypoglossal nerve stimulation; RNS = respiratory neurostimulation; $V_I$max = maximum inspiratory flow.

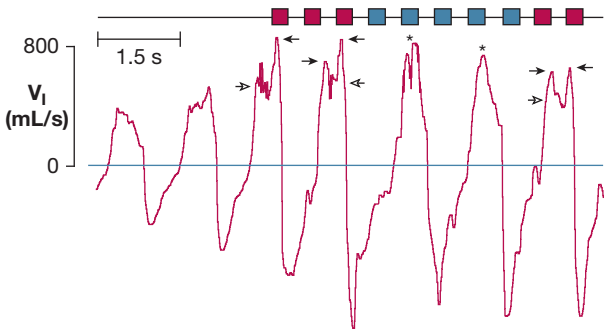

Figure 2 – *An example of periodic ansa cervicalis neurostimulation (thick vertical bars) with 0.3 s stimulation bursts during flow-limited inspirations in a single patient. Periodic stimulation induced a transient increase in V_I (black arrows) as the sternothyroid muscle contracted, reflecting increases in airway patency from the unstimulated state (open arrows) within the same breath. Blue bars indicate stimulation periods excluded from analysis because they occurred during expiration or overlapped the entire period of potential flow limitation, preventing comparison vs unstimulated airflow (examples indicated by asterisks). V_I increased during stimulated vs unstimulated periods (P < .001). V_I = inspiratory airflow.*

in any RNS modality. In humans, tracheal traction has been shown to improve pharyngeal patency by decreasing its collapsibility, leading to concomitant reductions in airflow obstruction during sleep.[21,24,26-30,47] Our results show that caudal traction on upper airway structures from sternothyroid muscle contraction also generates sizable improvements in airway patency.

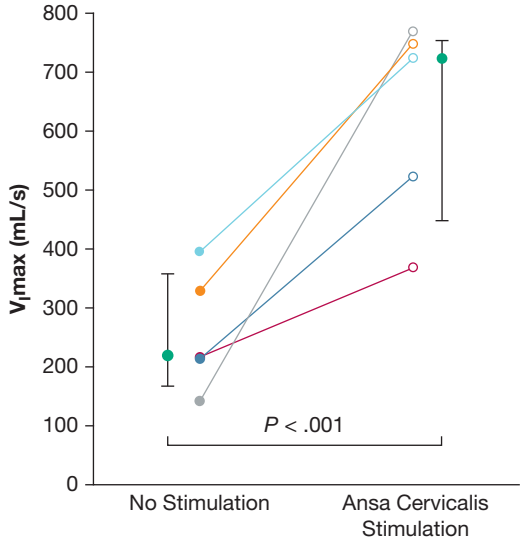

Figure 3 – *Isolated ansa cervicalis stimulation response. $V_I$max increased from baseline with stimulation of the branch of the ansa cervicalis innervating the sternothyroid muscle. Median and quartile values for each cohort are depicted. Stimulation had a significant effect on $V_I$max in a generalized linear mixed model evaluating $V_I$max response (P < .001). $V_I$max = maximum inspiratory airflow.*

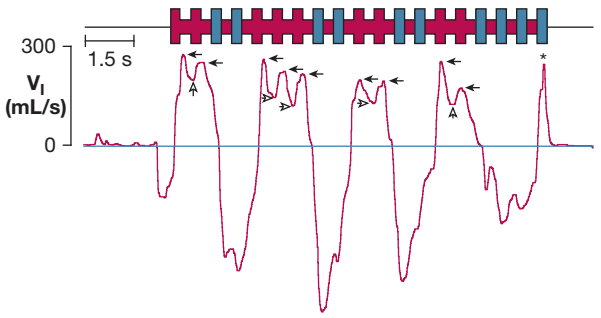

Figure 4 – *An example of periodic ansa cervicalis neurostimulation (thick vertical bars) of 0.3 s bursts superimposed over continuous hypoglossal nerve stimulation (thick horizontal bar) during flow-limited inspiration in a single patient. Periodic stimulation induced a transient increase in V_I (black arrows) as the sternothyroid muscle contracted, reflecting increases in airway patency from isolated hypoglossal nerve stimulation (open arrows) within the same breath. Blue bars indicate stimulation periods excluded from analysis because they occurred during expiration or overlapped the entire period of potential flow limitation, preventing comparison vs unstimulated airflow (example is indicated by the asterisk). V_I increased during stimulated vs unstimulated periods (P < .001). Stimulation significantly improved maximum V_I with immediate return to baseline flow-limited inspiration, indicating that the participant did not arouse from sedation during the experiment. V_I = inspiratory airflow.*

We observed further improvements in pharyngeal patency when ACS was superimposed on HNS, suggesting different mechanisms for stabilizing pharyngeal patency. In 1996, Rowley et al[23] observed synergistic effects of tongue protrusion and tracheal traction on pharyngeal collapsibility in an isolated feline upper airway model, in which the combined response exceeded that of either one in isolation. These investigators postulated that tracheal traction decreased pharyngeal wall compliance by increasing longitudinal tension. Tongue displacement, on the other hand, primarily exerted outward dilating forces on the pharynx. Simultaneous modification of both mechanisms generated the greatest overall changes in pharyngeal collapsibility as tongue displacement effects were amplified when pulling on stiffened pharyngeal walls. Our findings showed a similar synergistic effect when HNS and ACS were combined. Our observed average increase in $V_I$max of > 200 mL/s suggest substantial decreases in airway collapsibility that produced marked reductions in OSA severity in other studies.[48,49]

The sternothyroid muscle was specifically targeted for stimulation in the current RNS study. First, this muscle is known to exert caudal traction on the pharynx in rabbits and humans, who both have a

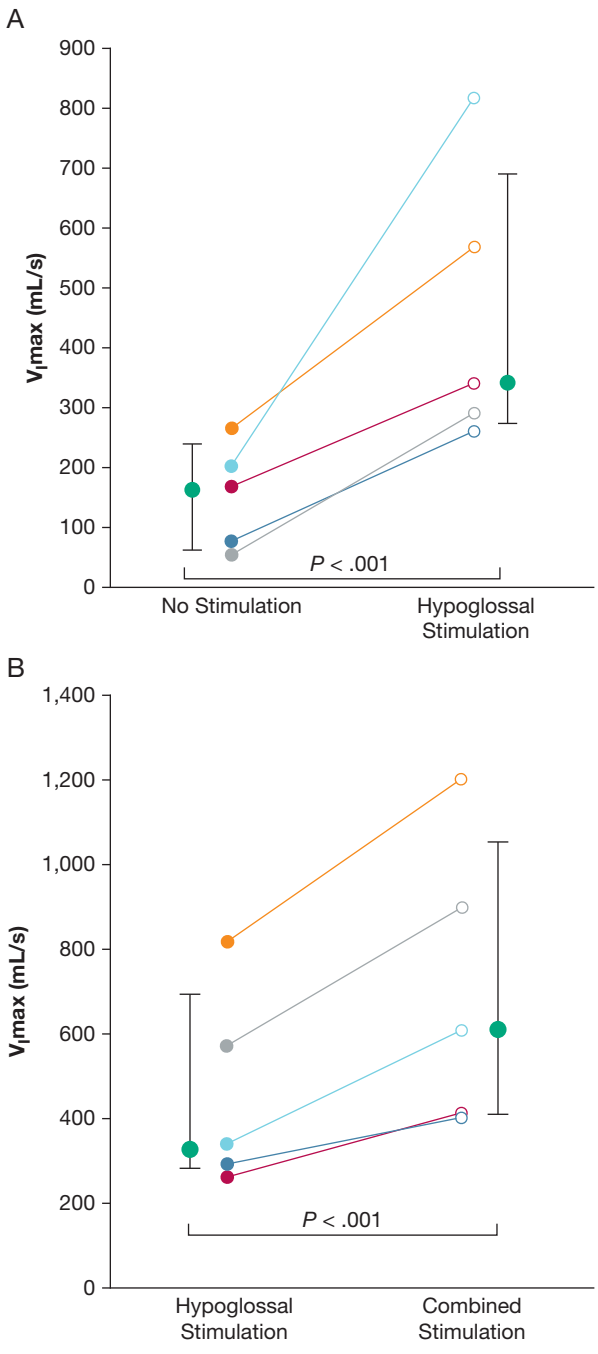

Figure 5 – *A-B, Increases in $V_I$max during an experiment with flow-limited continuous hypoglossal nerve stimulation and supplemental periodic ansa cervicalis neurostimulation. Median and quartile values for each cohort are depicted. A, Hypoglossal nerve stimulation had a significant effect on $V_I$max compared with $V_I$max from unstimulated baseline breaths prior to and following each stimulation trial in a generalized linear mixed model evaluating airflow response (P < .001). B, Ansa cervicalis stimulation had a significant effect on $V_I$max compared with hypoglossal nerve stimulation within the same breath in a generalized linear mixed model evaluating airflow response (P < .001). $V_I$max = maximum inspiratory airflow.*

freely suspended and mobile hyolaryngeal complex.[46] In rabbits, the sternothyroid muscle was found to have a marked mechanical advantage over the sternohyoid muscle, with the greatest improvements in airway caliber observed endoscopically in the nasopharynx and oropharynx.[38] Second, the innervation of the sternothyroid muscle is readily accessible and anatomically reliable. Although ansa cervicalis innervation of sternohyoid and omohyoid muscles can be highly variable with dual innervation to separate bellies, the sternothyroid muscle is reliably innervated by a single branch that is located 1 to 2 cm above the clavicle at the lateral border of the muscle (Fig 6).[50,51]

Several limitations of this pilot study should be considered in interpreting our findings. First, we recognize that the study sample size is relatively small, potentially limiting the generalizability of our findings. Nonetheless, the sample size was comparable to those of early pilot studies reporting HNS efficacy,[17,18,52] and we observed robust improvements in pharyngeal patency with ACS despite the small sample size. Second, the small sample was biased toward patients with lateral pharyngeal wall collapse, which is generally considered undesirable for HNS therapy.[12] Further studies with more diverse populations will be required to ascertain what anatomic characteristics, including palatal collapse pattern, are most responsive to ACS. Third, periodic stimulation was used to discern the physiological effects of ACS within single breaths as opposed to a more conventional continuous stimulation. We thus caution against direct comparisons of the ACS and HNS data, as the underlying stimulation patterns are different. Nonetheless, we found substantial response to ACS in both experimental conditions, suggesting that significant reductions in airway collapsibility may be achievable with more sustained stimulation. Fourth, a difference in $V_I$max during baseline flow-limited inspiration can be observed between the two experimental conditions, which we hypothesized was due to differences in the degree of jaw thrust necessary to achieve stable flow-limited inspirations. Nevertheless, we acknowledge that jaw thrust intensity was not explicitly measured. Previous acute HNS studies have required similar experimental strategies, deploying anesthetics, narcotics, benzodiazepines, and positive pressure support to balance arousal against airway collapsibility while seeking stable flow-limited inspiration.[17,18,53,54] These various tools may have limited generalizability to natural sleep, but the substantial effect sizes of HNS suggested that the

TABLE 4] Generalized Linear Mixed Models Constructed for Three Neurostimulation Modalities Across Both Experimental Conditions

RNS Modality	Fixed Effect	Estimate (95% CI)	*P*
ACS	Intercept	241 (196-298)	< .001
	Circumferential collapse	0.94 (0.82-1.07)	.351
	Stimulation	3.03 (2.43-3.79)	< .001
HNS	Intercept	204 (97-431)	< .001
	Circumferential collapse	0.56 (0.22-1.44)	.231
	Stimulation	3.48 (2.86-4.22)	< .001
HNS with ACS	Intercept	824 (423-1605)	< .001
	Circumferential collapse	0.56 (0.22-1.41)	.218
	Stimulation	1.51 (1.38-1.65)	< .001

Circumferential palatal collapse was not a significant predictor of maximum inspiratory flow outcome in either experiment, although the effect size CIs were large. Stimulation represents a multiplicative effect of baseline maximum inspiratory flow at the intercept in both experiments. All three stimulation modalities had a significant effect ($P < .001$; boldface). ACS = ansa cervicalis stimulation; HNS = hypoglossal nerve stimulation; RNS = respiratory neurostimulation.

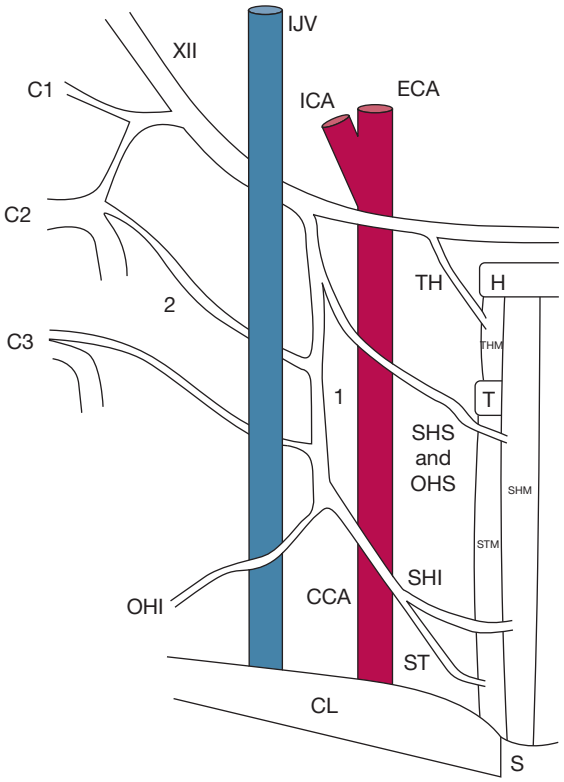

Figure 6 – *The ansa cervicalis nerve plexus. A single common trunk (ST) to the STM is observed. In this example, the inferior root (2) passes posterior to the IJV to join the superior root (1). The omohyoid muscle is not depicted. C1, C2, and C3 = first, second, and third cervical ventral rami; CCA = common carotid artery; CL = clavicle; ECA = external carotid artery; H = hyoid bone; ICA = internal carotid artery; IJV = internal jugular vein; OHI = inferior omohyoid nerve; OHS = superior omohyoid nerve; S = sternum; SHI = inferior sternohyoid nerve; SHM = sternohyoid muscle; SHS = superior sternohyoid nerve; ST = sternothyroid; STM = sternothyroid muscle; T = thyroid cartilage; TH = thyrohyoid nerve; THM = thyrohyoid muscle; XII = hypoglossal nerve. (Adapted, with permission, from Banneheka.*[51]*)*

observed effects were valid. Although we used limited jaw thrust for partial airway support in this study, we posit that the observed effects of ACS were similarly substantial, suggesting reductions in pharyngeal collapsibility. Fifth, participant arousal during RNS can confound our ability to assess responses. We controlled for arousal by monitoring for it clinically and with BIS, discarding experimental data if it were observed during any trial, and by referencing RNS response to the immediately adjacent unstimulated airflow values. Lastly, this study was conducted under propofol sedation. Future studies will need to investigate ACS during natural sleep to determine whether it produces meaningful changes to OSA severity. Future studies will also help to evaluate any differences between unilateral vs bilateral sternothyroid muscle stimulation, the precise mechanisms for ACS responses, and optimal stimulation patterns.

To improve upon HNS, future RNS strategies must ultimately move beyond the hypoglossal nerve. The branch of the ansa cervicalis to the sternothyroid muscle is easily accessed, and the robust stimulation responses observed in this study suggest that ACS markedly improves pharyngeal patency synergistically with HNS. ACS harnesses the known beneficial effects of caudal traction on pharyngeal patency and differs substantially from current surgical treatments for OSA that primarily displace the tongue and other pharyngeal soft tissues ventrally. Nevertheless, further study is required to determine the role of ACS among surgical and neurostimulation treatment strategies.

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