Role of Glossopharyngeal Nerve Stimulation in Stabilizing the Lateral Pharyngeal Wall and Ventilation in OSA

A Pilot Study

To the Editor:

OSA is a highly prevalent condition that is independently linked with common health morbidities and decreased quality of life.[1] Positive airway pressure therapy is the first-line treatment for OSA, but patient compliance rates are suboptimal, and surgical interventions, including hypoglossal nerve stimulation, are not universally efficacious. Oropharyngeal lateral wall collapse decreases surgical responder rates and remains challenging to treat.[2] Our group recently proposed ansa cervicalis stimulation as a novel respiratory neurostimulation therapy for OSA,[3] which has been observed to stabilize the oropharyngeal lateral wall by pulling the pharynx caudally.[4] In addition, the stylopharyngeus muscle is capable of directly pulling the oropharyngeal wall laterally, suggesting that it plays a pivotal role in stabilizing the pharynx and that some individuals may benefit from additional neurostimulation strategies.[5]

The stylopharyngeus muscle originates from the styloid process of the temporal bone and inserts medially into the oropharyngeal lateral wall between the superior and middle constrictor muscles. It is innervated by the glossopharyngeal nerve, which also contributes to the pharyngeal plexus motor branches innervating the constrictor muscles. Guilleminault et al[6] observed electromyography activity in these muscles during human inspiratory activity and proposed the "tent hypothesis," in which coactivation of the stylopharyngeus muscle and pharyngeal constrictor muscles stiffens the oropharyngeal wall and pulls it laterally to stabilize it during inspiration.[6] Animal experiments support these observations. Pre-inspiratory glossopharyngeal nerve activity was preserved in rodents even after pontomedullary transection disrupted facial and hypoglossal nerve activity.[7] Kuna[8] stimulated the glossopharyngeal nerve in a decerebrate feline model and observed that it increased oropharyngeal area to a greater degree than hypoglossal nerve stimulation.[8]

Here we describe a novel technique for percutaneous glossopharyngeal nerve stimulation (GNS) to investigate Guilleminault's tent hypothesis. Our initial results suggest that GNS pulls the oropharyngeal wall laterally, reducing pharyngeal collapsibility.

Methods

This study was approved by the Vanderbilt University Medical Center institutional review board (IRB #212305). After signing consent, a participant was screened with in-laboratory polysomnography for moderate-to-severe OSA. He then underwent unilateral GNS under propofol anesthesia with a modified version of a previously described drug-induced sleep endoscopy protocol.[3,9]

We iteratively developed a technique for percutaneous placement of a hook-wire electrode proximate to the glossopharyngeal nerve by localizing it within identifiable surrounding anatomic landmarks, similar to our approaches to other upper airway motor nerve targets.[10] Briefly, the ultrasound probe was placed in a paraxial plane approximating a line between the mastoid tip and the hyoid bone[11] and was then rolled rostrally until the styloid process and its superficial musculature was visualized. An electromyography needle carrying a hook-wire electrode was advanced in plane anteromedially, superficial to the internal jugular vein and deep to the external carotid artery, following the path of the glossopharyngeal nerve as it courses across the lateral surface of the stylopharyngeus muscle. The hook wire was fixed in place for the subsequent GNS experiment after brief stimulation pulses confirmed ipsilateral oropharyngeal wall movement laterally on endoscopic examination.

Nasal airflow was measured with the mouth sealed on and off GNS across a range of positive airway pressures to quantify acute changes in metrics of upper airway obstruction including tidal volume, peak

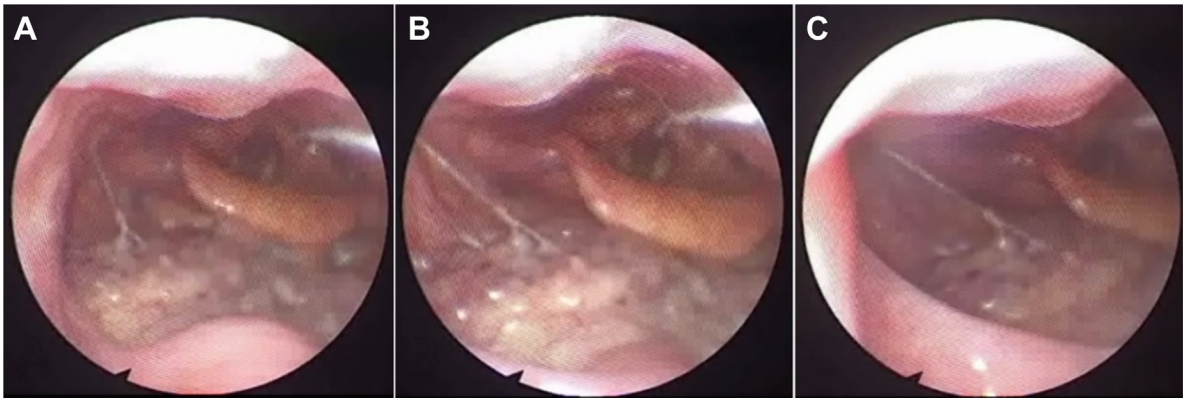

Figure 1 – *Glossopharyngeal nerve stimulation pulled the right oropharyngeal wall laterally by activating the stylopharyngeus muscle from baseline (A). As the stylopharyngeus muscle contracted (B), the endoscope had to move laterally to keep the oropharyngeal lateral wall within view (C).*

inspiratory flow rates ($V_I$max), and negative effort dependence (NED) ratio (mid-inspiratory airflow/$V_I$max).[12] A regression line was plotted through $V_I$max values from flow-limited inspirations to derive the critical closing (P_{CRIT}) pressure with and without GNS.[9]

Results

The participant had a BMI of 30.7 and apnea-hypopnea index of 41.1 events/h. His standard clinical drug-induced sleep endoscopy examination demonstrated partial circumferential collapse of the palate, complete lateral pharyngeal wall collapse, and partial tongue base collapse.

GNS was stably captured for a period of approximately 5 minutes, with 35 unstimulated baseline inspirations and

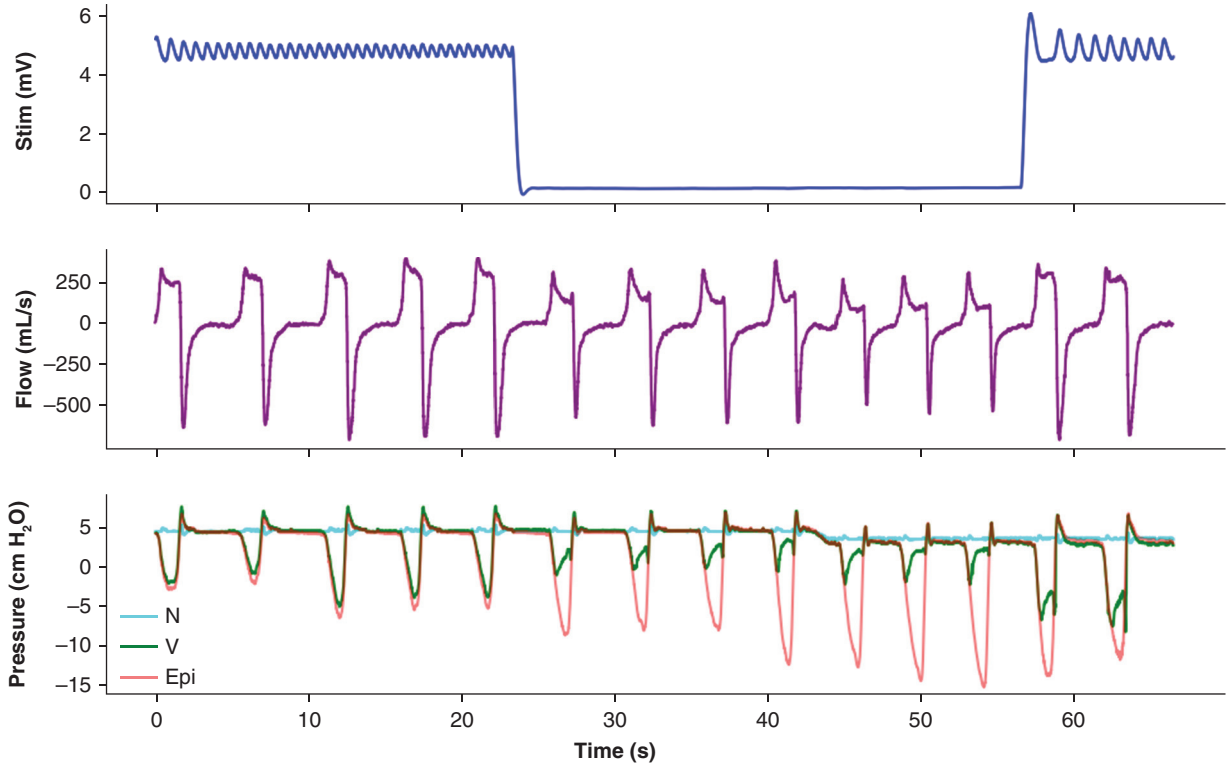

Figure 2 – *Physiologic signals during unilateral glossopharyngeal nerve stimulation (GNS). GNS (elevated dark blue tracing) increased peak inspiratory airflow (purple tracing). Pressure catheters in the velopharyngeal (green tracing) and oropharyngeal (red tracing) pressure catheters indicated an oropharyngeal site of flow limitation at baseline as nasal pressure (light blue tracing) is decreased during the course of the experiment.*

27 inspirations with GNS available for analysis. Robust movement of the oropharyngeal wall laterally was observed with simultaneous posterior displacement of the soft palate during application of GNS (Fig 1 and Video[13]). GNS decreased the pharyngeal P_{CRIT} pressure by 1.2 cm H_2O, increased tidal volume by 141 mL, and increased peak inspiratory airflow by 120 mL/s at baseline P_{CRIT} (nasal pressure, 2 cm H_2O). During an isolated period of flow-limited inspirations with stable ventilatory drive, GNS decreased NED ratio from 0.44 to 0.19 at 5 cm H_2O of nasal pressure, and from 0.71 to 0.23 at 4 cm H_2O of nasal pressure (Fig 2).

Discussion

This feasibility study demonstrated that GNS generated significant change in multiple measures of airway collapsibility in a patient with severe OSA. Specifically, GNS pulled the oropharyngeal wall laterally, increasing peak inspiratory airflow and tidal volume and reducing negative effort dependence. Our initial findings support Guilleminault's hypothesis that lateral movement of the oropharyngeal wall increases upper airway patency and suggest that GNS may have value as a respiratory neurostimulation strategy for OSA.

We observed several interesting anatomic and physiologic phenomena during this experiment. First, GNS pulled the oropharyngeal wall laterally, implying robust contraction of the stylopharyngeus muscle with potential additional activation of the pharyngeal constrictor muscles. Although contraction of the stylopharyngeus could not be directly confirmed, no other muscles in the parapharyngeal space would be expected to directly pull the oropharyngeal wall laterally.[5] Possibly increased tone in the pharyngeal constrictor muscles may have contributed to pharyngeal stabilization. Prior feline experiments suggest that constrictor activation can stabilize the airway in a state-dependent fashion when the airway is collapsed.[14] In humans, the glossopharyngeal nerve additionally innervates a unique, specialized neuromuscular compartment of the constrictor muscles that appears to be responsible for subtle gradations of tonic muscle tone.[15] Second, we observed an increase in $V_I$max and a decrease in NED directly associated with movement of the oropharyngeal wall laterally on endoscopy. The site of flow limitation shifted simultaneously from the oropharynx to the velopharynx, implying that GNS had stabilized the oropharynx and highlighting the interconnections between pharyngeal flow-limiting structures. Further research is required to elucidate the mechanisms underlying these observations.

Oropharyngeal lateral wall collapse broadly decreases treatment response rates across a range of surgical procedures.[2] Our early findings create intriguing possibilities for a neurostimulation treatment to directly stabilize the oropharyngeal lateral wall via recruitment of natural physiologic mechanisms. Nevertheless, this feasibility study in a single patient provides limited data for analysis, and which patients with OSA might benefit from GNS is not yet clear. The supraphysiologic stimulation applied in this experiment caused robust activation of the stylopharyngeus muscle that likely does not reflect normal physiologic activity. The simultaneous posterior displacement of the soft palate suggests that GNS may benefit from combination with respiratory neurostimulation strategies that stabilize the pharynx anteriorly, such as hypoglossal or ansa cervicalis stimulation.[3] Further research is underway to better quantify the effects of GNS on upper airway mechanics.

David T. Kent, MD
John J. Ceremsak, MD
Yike Li, MD, PhD
Nashville, TN
Pratyusha Yalamanchi, MD
Ann Arbor, MI
Kyle Mannion, MD
David Zealear, PhD
Matthew S. Shotwell, PhD
Megan E. Hall, BS
Nashville, TN
Christopher J. Lindsell, PhD
Durham, NC
Holly A. Budnick, MSN, FNP-C
Silvana Bellotto, MD
Katherine E. Estes, RPSGT
Carol LeeAnn Wells, RPSGT
Alan R. Schwartz, MD
Nashville, TN

AFFILIATIONS: From the Department of Otolaryngology—Head and Neck Surgery (D. T. K., J. J. C., Y. L., K. M., D. Z., H. A. B., S. B., K. E. E., C. L. W., and A. R. S.), Vanderbilt University Medical Center; the Department of Otolaryngology Head and Neck Surgery (P. Y.), University of Michigan; the Department of Biostatistics (M. S. S. and M. E. H.), Vanderbilt University Medical Center; the Duke Clinical Research Institute (C. J. L.), Duke University; the Department of Otorhinolaryngology (A. R. S.), University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; and the Universidad Peruana Cayetano Heredia School of Medicine (A. R. S.), Limu, Peru.

This work was presented in poster form at the 2025 International Surgical Sleep Society 2024 Educational Update meeting, September 27, 2024, Miami, FL.

CORRESPONDENCE TO: David T. Kent, MD; email: david.kent@vumc.org

DOI: https://doi.org/10.1016/j.chest.2025.02.009

Funding/Support

This work is supported by National Institutes of Health (R01HL161635).

Financial/Nonfinancial Disclosures

The authors have reported to *CHEST* the following: D. K. has received research support from Invicta Medical, Inspire Medical System, and Nyxoah SA. He is a consultant to Invicta Medical and Nyxoah SA and is a scientific advisory board member with Nyxoah SA. He is an inventor on patents pending licensed by Nyxoah SA that is relevant to this work. He is the guarantor of this work. C. L. has received grants from NIH and Department of Defense and research funds from the CDC, biomeme, Novartis, bioMerieux, AstraZeneca, AbbVie, Entegrion Inc, and Endpoint Health outside the submitted work; patents for risk stratification in sepsis and septic shock issued to Cincinnati Children's Hospital Medical Center; service on DSMBs unrelated to the current work; stock options in Bioscape Digital unrelated to the current work; editor in chief of the *Journal of Clinical and Translational Science.* A. S. is a scientific advisor for Apnimed, HuMannity Foundation, Invicta Medical, Itamar/Zoll, LivaNova, Lunair, Nyxoah SA, Periodic Breathing LLC, Respicardia/Zoll, and Sonosa. None declared (J. C., Y. L., P. Y., K. M., D. Z., M. S., M. H., H. B., S. B., K. E., C. W.).

Acknowledgments

Author contributions: D. K.: conceptualization, methodology, validation, investigation, resources, visualization, supervision, funding acquisition, writing—review & editing. J. J. C., P. Y., and K. M.: methodology, investigation, writing—review & editing. Y. L.: methodology, software, formal analysis, investigation, data curation, writing—original draft, review & editing, and visualization. D. Z.: conceptualization, methodology, investigation, resources, writing—review & editing. M. S., M. H., and C. L.: methodology, formal analysis, writing—review & editing. H. B., K. E., and C. W.: investigation. S. B.: methodology, writing—review & editing. A. S.: conceptualization, methodology, investigation, writing—review & editing. All authors have discussed and approved the manuscript. D. K. is the guarantor of the manuscript.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

References

1. Veasey SC, Rosen IM. Obstructive sleep apnea in adultsSolomon CG, ed. *N Engl J Med*. 2019;380(15):1442-1449.
2. Green KK, Kent DT, D'Agostino MA, et al. Drug-induced sleep endoscopy and surgical outcomes: a multicenter cohort study. *The Laryngoscope*. 2019;129(3):761-770.
3. Kent DT, Zealear D, Schwartz AR. Ansa cervicalis stimulation: a new direction in neurostimulation for obstructive sleep apnea. *Chest*. 2021;159(3):1212-1221.
4. Li Y, Schwartz AR, Zealear D, et al. Ansa cervicalis stimulation effects on upper airway patency: a structure-based analysis. *Eur Respir J*. 2025;65(1):2400901.
5. Dewald D. Rethinking the muscles of obstructive sleep apnea. *CRANIO®*. 2022;40(5):389-391.
6. Guilleminault C, Hill MW, Simmons FB, Dement WC. Obstructive sleep apnea: electromyographic and fiberoptic studies. *Exp Neurol*. 1978;62(1):48-67.
7. Kola G, Hamada E, Dhingra RR, et al. Persistent glossopharyngeal nerve respiratory discharge patterns after ponto-medullary transection. *Respir Physiol Neurobiol*. 2024;327:104281.
8. Kuna ST. Effects of pharyngeal muscle activation on airway size and configuration. *Am J Respir Crit Care Med*. 2001;164(7):1236-1241.
9. Li Y, Richard KE, Schwartz AR, et al. Quantitative effects of ansa cervicalis stimulation in obstructive sleep apnea. *Am J Respir Crit Care Med*. 2023;207(8):1097-1099.
10. Kent DT, Schwartz AR, Zealear D. Ultrasound localization and percutaneous electrical stimulation of the hypoglossal nerve and ansa cervicalis. *Otolaryngol Head Neck Surg*. 2021;164(1):219-225.
11. Azman J, Pintaric TS, Cvetko E, Vlassakov K. Ultrasound-guided glossopharyngeal nerve block a cadaver and a volunteer sonoanatomy study. *Reg Anesth Pain Med*. 2017;42(2):252-258.
12. Genta PR, Owens RL, Edwards BA, et al. Influence of pharyngeal muscle activity on inspiratory negative effort dependence in the human upper airway. *Respir Physiol Neurobiol*. 2014;201:55-59.
13. Kent DT, Ceremsak JJ, Li Y, et al. Glossopharyngeal nerve stimulation stabilizes the lateral pharyngeal wall and ventilation in OSA: a pilot study. Media posted November 1, 2024. figshare website. https://doi.org/10.6084/m9.figshare.27478782
14. Kuna ST. Respiratory-related activation and mechanical effects of the pharyngeal constrictor muscles. *Respir Physiol*. 2000;119:155-161.
15. Mu L, Sanders I. Neuromuscular specializations within human pharyngeal constrictor muscles. *Ann Otol Rhinol Laryngol*. 2007;116(8):604-617.