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Hypoglossal nerve stimulation therapy on peripheral arterial tonometry in obstructive sleep apnea: a pilot study

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Abstract

Purpose Hypoglossal nerve stimulation (HGNS) is being increasingly utilized in the setting of moderate-severe obstructive sleep apnea (OSA). While moderate-severe OSA confers excess cardiovascular risk, the impact of HGNS on cardiovascular requires further investigation. With the advent of peripheral arterial tonometry (PAT), one can non-invasively study real-time changes to the autonomic nervous system. This study evaluates the effect of HGNS therapy on autonomic output, using PAT-integrated polysomnography.

Methods Subjects included adult patients undergoing 2-month post-operative HGNS titration studies with PAT-integrated polysomnography. Apneic and hypopneic events with arousal during stage 2 sleep were identified at increasing levels of stimulation. With each event, PAT signal attenuations were recorded, processed, and analyzed.

Results Nine subjects were enrolled, and eight met inclusion criteria (mean age 67.8 ± 12.4 years; 50% female). The PAT signal did not significantly change before and during stimulation (mean pre-stimulation 43.4 ± 1.7, mean intra-stimulation 41.1 ± 22.5, $p = 0.53$) in any patient. The ratio of the PAT signal maximum and minimum amplitudes during sleep breathing events largely demonstrated very weak correlation ($R^2 = <0.12$). Across all subjects, poor linear correlation was present between HGNS and PAT signal attenuation ($R^2 = 0.028$) in both adjusted and unadjusted analyses.

Conclusions Using PAT-integrated polysomnography, PAT output does not appear to be affected by HGNS stimulation at clinical thresholds. These findings support the absence of autonomic system alterations by twelfth nerve stimulation and support the clinical use of PAT-based devices for post-HGNS monitoring. Larger studies examining hard cardiovascular endpoints with HGNS are needed.

Keywords Hypoglossal nerve stimulation · Peripheral arterial tonometry · Obstructive sleep apnea · Sympathetic activity · Polysomnography

Introduction

As the prevalence of obstructive sleep apnea (OSA) continues to increase with the obesity epidemic and the aging population [1–3], OSA has become a significant public health concern, due to its measureable impacts on healthcare costs and quality of life [4, 5]. Specifically, untreated moderate-severe OSA has been associated with neurocognitive impairment, motor vehicle accident risk, and increased health risks [6, 7]. More importantly, OSA has been reported to be associated with higher risk of hypertension and fatal/nonfatal cardiovascular events [8, 9].

First-line treatment of OSA remains continuous positive airway pressure (CPAP), as it has well-documented efficacy and overall lowered morbidity [10]. Despite these benefits, patient adherence remains CPAP's major drawback, ranging from 29 to 83% [11, 12]. Other treatment options for OSA do exist, including oral appliance therapy [13], positional therapy [14], weight loss [15], and upper airway reconstructive surgery [16]. In 2014, the Federal Drug Administration approved hypoglossal nerve stimulation (HGNS) for the treatment of patients with moderate-severe OSA who are unable to use

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CPAP. The HGNS procedure involves the implantation of a device with three components: (1) implantable pulse generator, which is placed in a subcutaneous pocket in the right chest, (2) stimulation lead with a cuff electrode placed on the medial branch of the hypoglossal nerve in the right submandibular space, and (3) sensing lead to detect ventilator effort in the intercostal space facing the pleura [17]. Together, these components coordinate the stimulation of the medial branch of the hypoglossal nerve with respiration to selectively innervate the extrinsic genioglossus muscle and intrinsic medial inferior longitudinal, transverse, and vertical muscles [17, 18]. This enables the protrusion of a stiffened tongue and opening of the airway during inspiration and expiration [17]. Thus, HGNS devices may impact both the anatomic and neuromuscular sources of OSA [17]. Recent studies with HGNS have shown average nightly usage between 6.5 and 7 h [19, 20].

As several longitudinal studies have demonstrated a strong association between moderate-severe OSA and heightened cardiovascular risk [7, 21], the impact of HGNS on cardiovascular risk requires investigation. The link between OSA and cardiovascular consequences can be largely explained by autonomic imbalance during repeated episodes of nocturnal airway obstruction [22]. Peripheral arterial tonometry (PAT) can measure changes in arterial volume in the fingertip, as a means of quantifying vasoconstriction as a marker of sympathetic activation to the peripheral vasculature. It continuously measures the pulsatile volume change using a pneumo-optic probe, which reflects the relative change in blood volume in the finger [23]. Finger blood flow, as captured by the PAT signal, attenuates immediately following obstructive breathing events during sleep [24]. Digital blood flow captured by PAT has repeatedly been shown to be mediated by sympathoadrenergic alpha receptors, a key component of the peripheral autonomic system [25]. Nocturnal surges in blood pressure at the termination of obstructive apneas are also strongly correlated with attenuations in PAT signal [26]. The noninvasive, real-time PAT signal provides an unparalleled view of the sympathetic nervous system disturbances in the setting of sleep-disordered breathing.

While the PAT signal provides a measure of sympathetic activity, it does not capture measures of sleep staging and respiratory flow, which are important measures to assess the effectiveness of OSA therapies. In order to evaluate the effect of OSA therapy on cardiovascular measures, the PAT signal requires integration to the input channels (e.g., electroencephalogram, nasal pressure transducer) found from in-lab polysomnography (PSG). In November 2016, the Emory Sleep Center successfully executed the integration of peripheral arterial tonometry into the polysomnograph amplifier.

Using this unique platform, two mechanistic questions related to HGNS therapy during sleep and sympathetic activity could be pursued. Does stimulation of the twelfth cranial nerve modulate afferent signals via hypoglossal or adjacent nerves (e.g., vagus), altering baseline sympathetic outflow to the digital vascular bed? Does increasing the voltage level of HGNS therapy reduce the degree of post-obstructive PAT signal attenuation (measure of sympathetic activation) in a dose-response manner? In testing these research questions, this study would provide clinical insight into the application of PAT-based measuring devices for post-HGNS monitoring.

Methods

Study design

All subjects were drawn from an ongoing, prospective sleep surgery study run by the senior author (R.C.D.) at the Sleep Surgery Center at Emory University Midtown Hospital. All patients were recruited into this study during their 2-week postoperative follow-up appointment, after undergoing implantation of HGNS for OSA (performed by R.C.D.). Approval from the Emory Institutional Board was obtained for this prospective study (IRB00088693). All patients were 21 years old or older and able to provide informed consent. All patients met criteria for HGNS therapy, including having moderate-severe OSA with < 25% central events, inability to use positive airway pressure therapy, body mass index < 32 kg/m^2, and drug-induced sedated endoscopy showing absence of complete circumferential collapse at velopharynx. Exclusion criteria included active smokers, unstable and untreated coronary or peripheral artery disease, severe and inadequately controlled arterial hypertension, active use of alpha-blocker medication, and previous sympathectomy or disorder of autonomic function.

HGNS activation

All subjects underwent activation of the HGNS device at 1-month post-procedure at the Emory Sleep Center. At this initial visit, the functional threshold (in volts) was obtained based on tongue motion during device stimulation. Over the following month, the stimulation strength was increased by 0.1 V every two or three nights until the upper limit was reached. All subjects returned to Emory Sleep Center for overnight PAT-integrated PSG 2 months after surgery.

Polysomnography and PAT signal integration

A level-I polysomnography (in accordance with 2014 American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events) was performed with standard parameters: electroencephalography (EEG), right and left electrooculography, electromyography of the bilateral tibialis anterior muscle, electrocardiography, and oxygen

saturation using pulse oximetry with a finger probe on the right ring finger. Electromyography of the bilateral submentalis was modified such that the right-sided electrode was placed directly over the neck incision (Fig. 1a). Respiratory variables were recorded via oral airflow by means of an external thermistor and nasal pressure by a nasal pressure cannula. Respiratory effort was measured using piezo respiratory effort belts across the chest and abdomen. A microphone recorded snoring qualitatively, and body position was monitored using a piezo-electrical sensor. In addition to these elements, a peripheral arterial tonometry (PAT) probe (WatchPAT 200, Itamar Medical, Caesarea, Israel) was placed on the ring finger of the opposite hand bearing the oximetry probe (Fig. 1b). The signal from this probe was directly inserted into the polysomnograph amplifier (Embla N7000, Natus Medical, Pleasanton, CA USA) and appeared as an independent signal on the screen montage (Fig. 2). It is important to understand that the PAT signal provides a relative value without units as opposed to an absolute value of peripheral arterial tonometry. An apnea is defined as a drop in peak thermal sensor excursion by ≥ 90% for at least 10 s. A hypopnea is defined as a drop in nasal pressure signal excursion by ≥ 30% and ≥ 4% desaturation for at least 10 s (using AASM alternative definition).

Overnight polysomnography experimental protocol

After the lights were turned off, the subjects were monitored for sleep onset. Once the subject had attained two consecutive epochs of stage 2 NREM, the subject was monitored, without treatment, until the occurrence of five discrete apneas or hypopneas in stage 2 NREM (baseline PAT). At this juncture, the device was activated at 0.4 V below functional threshold. At this stimulation level, the subject was monitored until the occurrence of five obstructive apneas or hypopneas in stage 2 NREM. As the stepwise clinical titration of stimulation with 0.2 V increases occurred, the subject was maintained until the occurrence of five obstructive apneas or hypopneas in stage 2 NREM. The titration continued until a NREM therapeutic amplitude was reached. All efforts were made to maintain a consistent body position of the subject throughout the study.

PAT signal processing

To test our first aim, to assess the presence of attenuations in PAT signal during HGNS device stimulation, the mean PAT signal was calculated for 4 s before and for 4 s during stimulation, via the chin EMG channel. These channels allowed the precise timing of the neurostimulation to be identifiable, and the 4-s duration represented the standard maximum stimulation time with HGNS.

To test our second aim, to examine the impact of HGNS voltage level on PAT signal attenuation, the start times of the apneic or hypopneic events with arousals in stage 2 NREM and the associated HGNS device stimulation voltages were recorded. After identification of events of interest, the PAT signal and PSG tracings were aligned and exported together at a sampling rate of 100 Hz in RemLogic Software. Using Matlab, the raw PAT signal tracing was smoothed using a median window of 5 s to create a smoothed PAT signal tracing. This smoothed PAT signal tracing was then subtracted from the raw PAT signal tracing to create the adjusted PAT signal tracing. Using the smoothed PAT tracing, the minimum value was identified between 10 and 60 s after the start time of the event of interest. Using this minimum value as reference, the maximum and minimum difference in adjusted PAT signal amplitude was identified 15 s before and 15 s after the minimum value, respectively (Fig. 3). Event selection was initially reviewed by the first author (A.K.I.), and any ambiguous events were adjudicated via group review with the study team (R.C.D., E.G.S.).

Statistical analysis

To test our first aim, to assess the presence of attenuations in PAT signal during HGNS device stimulation, we examined the first five stimulations at the highest voltage achieved during the sleep study. The mean PAT signal amplitudes comparing

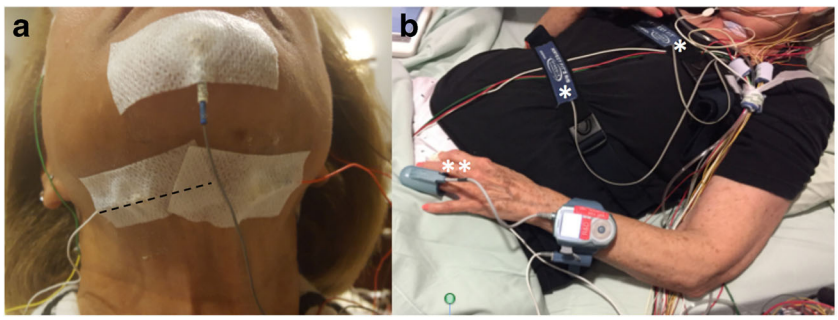

Fig. 1 PAT-integrated polysomnography. **a** Electromyography electrodes were placed on bilateral submental regions, with the right-sided electrode placed directly over the neck incision (noted as dotted line). **b** Patient in supine position with piezo respiratory effort belts placed over chest and abdomen (noted as *). WatchPAT 200 is placed on patient's left ring finger (noted as **)

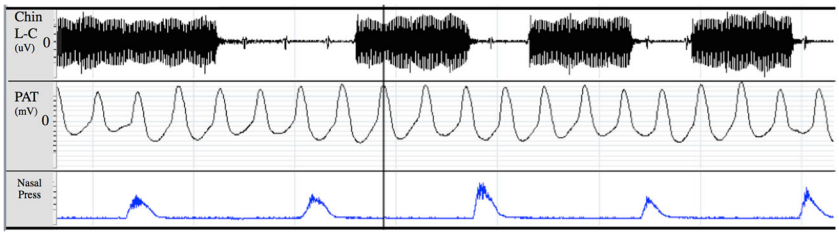

Fig. 2 HGNS stimulation (marked by Chin "L-C") does not alter PAT signal amplitude. This is a polysomnography (PSG) montage. (1) Chin L-C captures stimulation "on" by EMG artifact. (2) PAT signal captures peripheral arterial tonometry. (3) Nasal pressure transducer (noted as Nasal Press) demonstrates synchrony of PAT with traditional PSG inputs

the 4 s before (pre-stimulation) and the first 4 s during the stimulations (intra-stimulation). After a Shapiro-Wilk normality test confirmed the normal distribution of the data, a Student's *t* test was performed on the difference in mean PAT signal amplitudes between pre-stimulation and intra-stimulation values.

To test our second aim, to examine the impact of HGNS voltage level on PAT signal attenuation, we calculated the average ratio between the maximum and minimum PAT amplitudes for the events of interest at each HGNS stimulation voltage applied for each patient. A linear regression was performed for each subject with stimulation level as the main effect variable and PAT signal amplitude ratio as the outcome variable, adjusting for AHI at each voltage.

Results

Population characteristics

Nine subjects were enrolled. One subject was excluded due to having no events of interest during polysomnography due to minimal sleep time. Table 1 shows demographic information for these eight patients.

Effect of HGNS stimulation on PAT signal

HGNS voltage levels in this study ranged from 0 to 3.4 V. The mean maximum HGNS voltage during the sleep studies was 2.9 ± 0.52 V. The mean PAT signal prior to highest stimulation was 42.3 ± 20.7 and 40.4 ± 21.3 during stimulation, ($p = 0.16$). For each patient, there was no significant change in the mean PAT signal 4 s before and 4 s during HGNS stimulation at the identified highest achieved voltage (mean difference = 0.8 ± 9.4, $p = 0.53$) (see Table 2 for details).

HGNS therapy does not correlate with PAT signal attenuation during episodes

During stage 2 sleep, the mean number of events of interests per subject was 24.1 ± 22.7, with 12% representing apneic events with arousal and 88% hypopneic events with arousal. The mean ratio of maximum and minimum amplitudes per events of interest was 4.75 ± 3.91, occurring at voltages

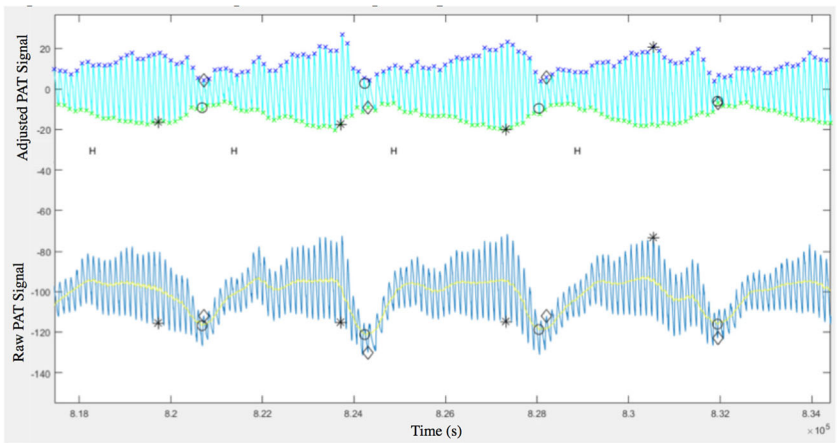

Fig. 3 WatchPAT signal processing (sample from patient 7). Bottom tracing is raw peripheral arterial tonometry (PAT) signal (noted as dark blue line) is presented as a relative value without units, with time in seconds along the *x*-axis. To analyze, we smoothed the raw PAT signal tracing using a median window of 5 s to create a smoothed PAT signal tracing (noted as yellow line), using Matlab. This smoothed PAT signal tracing was then subtracted from the raw PAT signal tracing to create the adjusted PAT signal tracing (noted as light blue line, top tracing). Using the smoothed PAT tracing, the minimum value (noted as circle) was identified between 10 and 60 s after the start time of the event of interest (noted as H). Using this minimum value as reference, the maximum and minimum difference (noted as * and diamond, respectively) in adjusted PAT signal amplitude was identified 15 s before and 15 s after the minimum value, respectively

Table 1 Patient characteristics. Demographics of eight patients with moderate-severe OSA who underwent HGNS device placement and 2-month post-procedure PAT-integrated polysomngraphy. Mean (standard deviation) presented. *SD* standard deviation, *F* female, *M* male, *AA* African American

	Mean (SD)
Age (years)	67.8 (12.4)
Gender	4F/4M
Race	5 White, 2 AA, 1 Asian
BMI (kg/m2)	27.5 (2.4)
Pre-operative Apnea-Hypopnea Index (events/hr)	45.6 (26.8)
Pre-operative Epworth Sleepiness Scale*	11.5 (5.45)
Pre-operative Insomnia Severity Index**	20.5 (4.44)

*Epworth Sleepiness Scale categories. 0–10 normal, 11–16 sleepy, 17–24 very sleepy (reference)

**Insomnia Severity Index categories. 0–7 = no clinically significant insomnia, 8–14 = subthreshold insomnia, 15–21 = clinical insomnia (moderate severity), 22–28 = clinical insomnia (severe) (reference)

ranging from 0.0–3.4 V. Seven out of the eight cases demonstrated low correlation between HGNS therapy and PAT signal attenuation ($R^2 = < 0.12$), and one patient's polysomnography with PAT monitoring reflected moderate correlation ($R^2 = 0.193$). Cumulatively, a weak linear correlation was present between HGNS therapy and PAT signal attenuation ($R^2 = 0.028$) (Fig. 4). These findings remained unchanged during adjusted analysis, controlling for AHI at each voltage level.

Discussion

This is the first study to examine peripheral arterial tonometry in the context of hypoglossal nerve stimulation for OSA. We analyzed the PAT signal for any attenuation, which would be detected by changes in the baseline sympathetic outflow to the digital vascular bed, specifically before and during overnight HGNS device stimulation. This pattern could be caused by the HGNS therapy unintentionally stimulating nearby afferent nerves, including hypoglossal and vagus nerves, and if present, could alter our interpretations during events of interest. Next, we examined the impact of incremental increases in HGNS therapy on the degree of post-obstructive PAT signal attenuation, a measure of sympathetic activation. The lack of association between HGNS stimulation and PAT amplitude in our study confers confidence in the use of PAT-based devices in patients with HGNS.

The implanted HGNS device is composed of a cuff electrode placed on the medial branch of the hypoglossal nerve for stimulation and a sensing lead to detect ventilator effort in the intercostal space facing the pleura. The placement of these leads is important due to its close proximity to surrounding muscles and nerves. The hypoglossal nerve exits through the

Table 2 Mean PAT signal 4 s before and during highest HGNS device stimulation achieved during sleep. Matlab was used to calculate the mean PAT signal amplitude over the 4 s prior to (noted as pre) and during (noted as during) the highest HGNS device stimulation achieved during sleep. The difference between the two means was calculated for each of the first five stimulations per patient (noted as diff). The pre and during mean PAT signal and standard deviation for each patient is reported and presented as mean (standard deviation). Paired *T* test *p* values are in italic. *SD* standard deviation

Pt	Stimulation 1			Stimulation 2			Stimulation 3			Stimulation 4			Stimulation 5			Mean value (mean SD)		*p* value
	Pre	During	Diff	Pre	During	Diff	Pre	During	Diff	Pre	During	Diff	Pre	During	Diff	Pre	During	
1	43.8	43.6	−0.2	48.9	55.0	6.1	56.4	27.9	−28.4	22.8	12.0	−10.8	12.4	15.3	2.9	36.8 (18.5)	30.8 (18.4)	*0.62*
2	57.8	36.7	−21.1	38.5	29.8	−8.6	27.3	25.8	−1.5	27.5	31.8	4.3	31.5	40.2	8.7	36.5 (12.7)	32.9 (5.7)	*0.57*
3	63.3	49.0	−14.2	50.1	45.9	−4.2	49.6	59.0	9.5	60.0	60.0	0.1	61.7	62.9	1.2	56.9 (6.7)	55.38 (7.4)	*0.74*
4	9.2	7.2	−2.0	7.9	7.1	−0.7	7.0	8.2	1.1	8.5	8.6	0.2	8.7	7.4	−1.3	8.3 (0.8)	7.7 (0.7)	*0.28*
5	73.0	74.3	1.3	74.8	68.7	−6.1	69.1	63.8	−5.4	34.6	18.3	−16.3	20.2	17.2	−3.0	54.4 (25.2)	48.5 (28.3)	*0.74*
7	74.8	61.0	−13.8	69.0	76.1	7.1	76.3	66.6	−9.7	57.8	54.8	−3.0	67.7	75.1	7.4	69.1 (7.3)	66.7 (9.1)	*0.66*
8	58.0	57.8	−0.3	61.7	71.5	9.8	43.4	49.0	5.6	49.5	51.7	2.2	53.9	71.3	17.4	53.3 (7.2)	60.2 (10.7)	*0.26*
9	50.7	35.9	−14.8	37.1	23.1	−14.0	24.3	24.2	0.0	22.9	22.4	−0.5	23.5	25.8	2.3	31.7 (12.1)	26.3 (5.5)	*0.39*

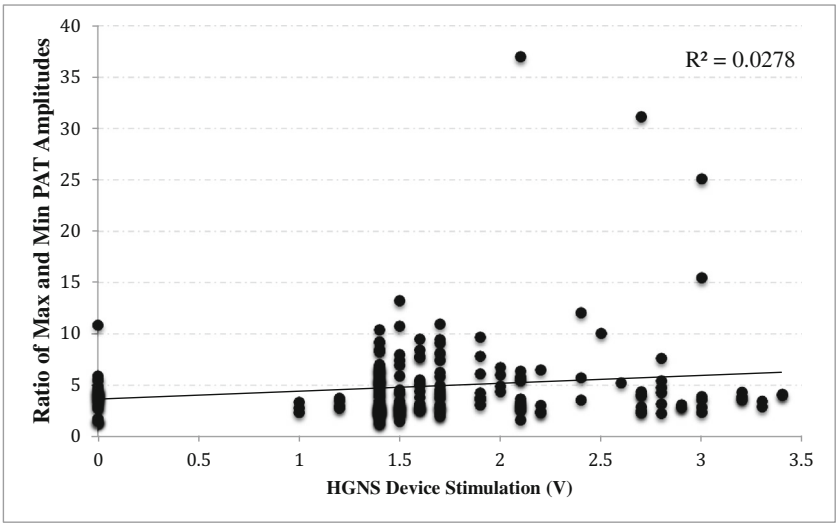

Fig. 4 HGNS device stimulation (V) vs ratio of maximum and minimum PAT amplitudes during events of interest. Weak linear correlation was present between HGNS device stimulation and ratio of maximum and minimum PAT amplitudes during events of interest ($R^2 = 0.028$)

hypoglossal foramina and tracks along with a branch from the anterior ramus of C1. Then the nerve runs very close to the vagus nerve and spinal division of the accessory nerve. The hypoglossal nerve travels down into the neck between the internal carotid artery and internal jugular vein, with the vagus nerve lying on the carotid sheath. At the angle of the mandible, the hypoglossal nerve loops around the occipital artery and tracks anteriorly and deeply to the hyoglossus and stylohyoid muscles, where the HGNS cuff is conventionally placed. Due to the intricate trail of the hypoglossal nerve, it is important to identify any potential effect HGNS therapy may have on sympathetic outflow, specifically our PAT signal. It is plausible that stimulation of the hypoglossal nerve activates the ipsilateral vagus nerve or cervical sympathetic trunk, both known mediators of the autonomic nervous system. In our analysis of PAT signal changes prior to and during HGNS stimulation, we did not see any evidence to support peripheral autonomic activation during stimulation "on" periods.

The current pathway for HGNS patients includes a 2-month in-lab PSG titration. However, some patients may not be adequately titrated during this single night or have limited sampling time at the recommended setting. For this reason, home sleep testing should be performed to sample an entire night of sleep with HGNS. While several home sleep tests are currently available, some pose compatibility challenges with the HGNS wireless telemetry systems. For example, respiratory inductance plethysmography (RIP) thoracoabdominal belts disrupt the HGNS wireless telemetry systems, impeding remote control communication with the device. WatchPAT-based device has become 200 is a well-validated, commercially available type of home sleep study, which utilizes PAT to detect sleep-disordered breathing [27, 28]. Our use of PAT-integrated PSG in this study shows the absence of an intrinsic signal modification with HGNS therapy.

There are several limitations of this study. The small sample size ($n = 8$) limits the generalizability of the findings from this pilot study. Additionally, the power of our analyses is admittedly poor. That being said, given the very small effect size from these data, a sample of 2568 participants would be required (assume alpha 0.05) to achieve a power of 0.9. As this number is not feasible, we feel that the strikingly similar point estimates of "pre" and "during" stimulation (42.3 vs 40.4) in this pilot data set suggest little effect of HGNS on PAT signal. The number and distribution of apneic and hypopneic events with arousals for each patient varied across HGNS stimulation voltages. We only included events in stage 2 NREM sleep associated with an arousal to maintain consistency. Obstructive events, which terminate in an arousal, likely potentiate post-event drop in PAT signal. [23] In narrowing our event subtypes to stage 2 NREM with arousals, we have introduced sampling bias, as there are alterations in sympathetic nerve activity during different stages of NREM sleep [29]. More specifically, stages of NREM sleep have been reported to have lower sympathetic nerve activity, with sympathetic bursts in the presence of arousal stimuli [29]. Also, we focused on only one adjustable stimulation parameter with HGNS, amplitude (in volts). In our experience, amplitude has shown to be the primary titration parameter, and to avoid confounding, we avoided manipulation of the other three stimulation parameters (frequency, pulse width, electrode configuration) during the titration study. However, these other adjustable parameters or any combination of them could prove to affect the autonomic system in an unknown manner. Finally, our study aim was not to evaluate the WatchPAT (Itamar Medical, Israel) algorithm, which includes heart rate variability and oxygen saturation, for detection of events, rather, to determine the effect of HGNS on the PAT signal in isolation.

In conclusion, we observed that HGNS therapy does not immediately alter the PAT signal before or during the stimulation achieved during sleep. Additionally, we found that PAT signal attenuation was independent of HGNS therapy stimulation. While not definitive as a pilot study, our work provides support for use of PAT-based home sleep testing for HGNS patients and lays groundwork for further studies of autonomic function in patients with moderate-severe OSA having undergone HGNS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (place name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Comment

It will be very important in the future to study the effects of upper airway stimulation on the sympathetic system. We still have patients as non-responders with this therapy. Probably with a higher amount of patients, we can figure out why... This could be an explanation... Even due to the small sample size, I think it is important to show/publish these results. We need to encourage the authors to go on with their study.

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This is the first study showing that PAT signal does not change with HGNS. Thus, although preliminary, with small sample size and limit to stage 2 sleep, the results provide support for the potential usage of PAT-based home sleep testing in patients treated with HGNS.

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