Evaluation of Therapeutic Positive Airway Pressure as a Hypoglossal Nerve Stimulation Predictor in Patients With Obstructive Sleep Apnea

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IMPORTANCE Recent retrospective hypoglossal nerve stimulation (HGNS) outcomes data suggest that patients with low therapeutic positive airway pressure (PAP) levels achieve greater success than patients with high therapeutic PAP levels.

OBJECTIVE To examine the use of therapeutic nasal PAP levels at the soft palate in predicting the outcomes of HGNS for patients with obstructive sleep apnea.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study used drug-induced sleep endoscopy (DISE) to evaluate the predictive capacity of therapeutic PAP levels in HGNS outcomes. In an academic sleep surgery center, 27 consecutive patients with obstructive sleep apnea who underwent DISE before implantation of an HGNS device were evaluated. The study was conducted from May 1, 2018, to June 26, 2019.

EXPOSURES Positive airway pressure delivered through a nasal mask during DISE.

MAIN OUTCOMES AND MEASURES Improvement in apnea-hypopnea index as measured from full-night preoperative and postoperative efficacy studies.

RESULTS Twenty-seven patients met all inclusion criteria. The mean (SD) age was 62.0 (14.4) years, 14 participants were men (51.9%), and mean body mass index was 28.1 (4.0). Responders to HGNS therapy (n = 18) had significantly lower mean (SD) palatal opening pressure compared with nonresponders (n = 9) (3.0 [2.8] vs 9.2 [3.7] cm H₂O, respectively; mean difference, −4.2; 95% CI, −6.8 to −1.6 cm H₂O). After adjusting for age, sex, and body mass index, the mean palatal opening pressure value for the responders remained 3.5 cm H₂O lower (95% CI, −6.7 to −0.4 cm H₂O) than that of nonresponders. A palatal opening pressure cutoff level less than 8 cm H₂O demonstrated a positive predictive value of 82.4%; sensitivity, 77.8%; and specificity, 66.7%.

CONCLUSIONS AND RELEVANCE In this small prospective cohort study, therapeutic nasal PAP levels during DISE differed significantly between responder and nonresponders to HGNS. Because DISE represents a mandatory, relatively standardized diagnostic tool for HGNS candidacy, the use of therapeutic nasal PAP through DISE can be broadly implemented and studied across multiple centers to possibly improve patient selection for HGNS.

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Obstructive sleep apnea (OSA) is a disorder that involves complete or partial blockage in airflow during sleep. The resulting hypoxia and sympathetic activation place patients at an increased risk for metabolic syndrome, neurocognitive decline, hypertension, stroke, and other cardiovascular sequelae.1,2 The primary therapy for OSA is positive airway pressure (PAP); however, although PAP treatment is beneficial, recommended adherence to therapy ranges from 17% to 54%.3 Consequently, there exists a need for treatment alternatives to PAP therapy.

One class of alternatives to PAP therapy is upper airway surgery, which includes soft tissue surgery, skeletal surgery, tracheostomy, and hypoglossal nerve stimulation (HGNS). Hypoglossal nerve stimulation, the most recent development in OSA surgery, involves stimulation of select branches of the hypoglossal nerve resulting in tongue protrusion and upper airway dilation during sleep. The HGNS device used consists of 3 implantable components: a respiratory sensor, pulse generator (battery), and an electrode cuff (Inspire; Inspire Medical Systems). Upon inspiration, the respiratory sensor detects changes in the intrathoracic space and signals the pulse generator to stimulate the hypoglossal nerve. Stimulation persists through the end of expiration and then briefly deactivates to avoid overstimulation.

Although studies have cited significant improvements in both objective and subjective outcomes following HGNS,4,6 there exists a need to determine factors predictive of surgical outcomes. A previous study showed that a therapeutic PAP
level less than 8 cm H₂O had a 92% positive predictive value for surgical success, whereas success was achieved in only 44% of patients with PAP levels greater than or equal to 8 cm H₂O. This retrospective study had inherent limitations, such as heterogeneous data from nonstandardized mask interfaces and varied PAP data (autoPAP downloads, nonstandardized titration tables between laboratories, and exclusion of patients intolerant of PAP). With 44% of patients in the high-pressure group being responders, the need for an understanding of the individualized anatomic effects of positive pressure became apparent.

Drug-induced sleep endoscopy (DISE) is a procedure performed by otolaryngologists to characterize the upper airway collapse patterns during sleep. All patients considering HGNS as a treatment option undergo DISE as part of determining candidacy for HGNS. Those with complete concentric collapse or total airway blockage resulting from simultaneous collapse of the soft palate and oropharyngeal lateral walls are not eligible for HGNS. Within DISE, there are opportunities to manipulate the airway using oral appliance simulation as well as PAP. In a double-blind study of 16 patients, Civelek et al reported that titration pressures during DISE were correlated with higher continuous PAP (CPAP) levels during natural sleep. Lan et al reported that lateral wall and circumferential velum collapse during DISE were correlated with higher continuous PAP (CPAP) levels during natural sleep. Safiruddin et al suggested that a poor anatomic opening at the retropalatal level is found in HGNS failures. The previously mentioned findings taken together suggest that patients with collapse at the level of the soft palate requiring high distention pressures may be poor responders to HGNS.

Therefore, we sought to examine the use of therapeutic nasal PAP during DISE on palatal opening pressure (POP). Our primary aim was to examine whether POP observed with therapeutic nasal PAP administered during DISE differs between responders and nonresponders to HGNS when response is defined as a 50% reduction in the apnea-hypopnea index (AHI) level from baseline to a 3-month postoperative home sleep study. We hypothesized that the mean POP would be lower in responders than nonresponders. Our secondary aim was to examine whether POP differs between responders and nonresponders to HGNS when response to therapy is defined as a 50% reduction in AHI level from baseline to in-lab titration residual supine AHI level. We hypothesized that the mean POP would be lower in responders than nonresponders when using this secondary definition based on supine residual AHI level.

Methods
Participants
This prospective cohort study was performed at a single academic institution, Emory University, Atlanta, Georgia. Participants were consecutively recruited from a sleep surgery clinic via written informed consent from May 17, 2018, to June 21, 2019. The study was conducted from May 1, 2018, to June 26, 2019. Inclusion criteria were as follows: age greater than or equal to 22 years, baseline AHI level between 15 and 65 events/h, previous PAP intolerance, and lack of complete concentric collapse at the palate during DISE. Complete concentric collapse was defined as 100% palatal collapse and 100% lateral wall collapse. Patients were excluded for having greater than or equal to 25% of respiratory events classified as central or mixed apneas on baseline polysomnographic testing. The study was approved by the Emory University Institutional Review Board. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies. Participants did not receive financial compensation.

Drug-Induced Sleep Endoscopy
The standard DISE procedure at Emory University at the time of the study consisted of an otolaryngologist (R.C.D.), anesthesiologist or nurse anesthetist, and supporting nursing staff. The patient is brought to the endoscopy suite and is laid in the supine position on 1 pillow. Before sedation, a bispectral index monitor is placed on the patient’s forehead that monitors sedation depth during the procedure, with a target range of 50 to 70. Next, viscous lidocaine, 4%, is administered to a single nostril via cotton-tipped applicators. A propofol bolus is delivered at the discretion of the anesthesia provider, followed by a propofol infusion at 75 μg/kg/min. Once the patient is sedated, the laryngoscope is passed through the nostril. The velum, oropharynx, tongue base, and epiglottis are characterized via the VOTE (velum, oropharynx, tongue base, and epiglottis) classification system by the otolaryngologist. Both the extent of collapse (an estimated percentage reduction in cross-sectional area) and pattern of collapse (eg, anterior to posterior) are recorded. The clinical staff then performs a mandibular advancement to simulate an oral appliance and records the underjet and open bite (millimeters) in addition to the effect on the airway via VOTE classification. The patient is then moved to the lateral position via a supportive wedge, and a final VOTE classification is recorded.

PAP is performed at the end of the standard DISE examination as previously described. A CPAP machine (Phillips Respironics) is used with a nasal mask custom fitted with a bronchoscopy adapter to allow passage of the laryngoscope into

### Key Points

**Question** Is therapeutic nasal positive airway pressure at the soft palate during drug-induced sleep endoscopy associated with response to hypoglossal nerve stimulation in patients with obstructive sleep apnea?

**Findings** In this cohort study of 27 consecutive patients with obstructive sleep apnea undergoing therapeutic nasal positive airway pressure during drug-induced sleep endoscopy, those who responded to hypoglossal nerve stimulation had significantly lower palatal opening pressures than nonresponders (5.0 vs 9.2 cm H₂O, respectively). A palatal opening pressure cutoff level less than 8 cm H₂O was associated with a positive predictive value.

**Meaning** Airway distensibility, as measured by the palatal opening pressure in administration of therapeutic nasal positive airway pressure during drug-induced sleep endoscopy, those who did not receive financial compensation.
the upper airway. The CPAP machine is preprogrammed to 18 cm H_2O, with a ramp from 4 to 18 cm H_2O over 5 minutes and no expiratory pressure relief setting. The custom nasal PAP mask and headgear is then secured to the patient by one of us (E.G.S. when at Emory University). On completion of the standard DISE examination, CPAP is initiated to ramp from 4 cm H_2O up to 18 cm H_2O. In this way, the opening pressure can be determined in real time by viewing the PAP machine display and videoendoscopy screen simultaneously. In the event of mask leakage due to an improper seal or mouth opening, mask adjustment or manual lip closure is performed while maintaining the patient’s natural jaw position. Therapeutic pressure is determined at each collapsing level of the upper airway: the velum, oropharynx, tongue base, and epiglottis. Patients with less than 100% collapse at the velum were determined to have a POP of 0 cm H_2O; these patients were excluded from sensitivity analyses.

Sleep Study Data
All sleep data were extracted from the patient’s medical record. For patients with multiple baseline or split-night sleep studies, the mean AHI level of all studies dated 3 years before device implantation was determined. Owing to inherent reporting variation across regional sleep facilities, 3% or 4% hypopnea definitions were used for baseline studies. Postoperative, full-night studies were performed through Emory Sleep Center, an outpatient facility associated with Emory University Hospital. Either 3% or 4% hypopnea scoring was used to match the definition used at baseline for individual participants. To achieve positional parity between DISE and polysomnographic measures, the residual supine AHI level was extracted from the titration data and separately analyzed. Residual supine AHI level during titration was calculated by determining a weighted mean at each voltage setting tested. In this way, an overall residual supine AHI level was used as opposed to an AHI level at one particular voltage setting. If the patient did not sleep in the supine position, they were excluded from this secondary analysis. Home efficacy studies were performed at least 3 months after the procedure and were conducted on one voltage setting (WatchPAT; Itamar Medical).

Statistical Analysis
Data collection and analyses were performed with Microsoft Excel (Microsoft Corp) and Stata/SE, version 14.2 (StataCorp LLC). Categorical data are presented using frequencies and percentages, and continuous data are summarized using means (SDs). Where applicable, changes or percent changes in measures were calculated as postoperative minus preoperative values. The primary definition of therapy response was considered a 50% overall reduction in AHI level from baseline to home efficacy study. Comparisons between therapy responders and nonresponders are presented as estimated differences in means or proportions along with the associated 95% CI. Analyses of primary outcomes were performed both unadjusted and controlling for established clinical covariates of age, sex, and body mass index (BMI)\[1\] using linear regression models, with responder status as a binary predictor. To understand the predictive ability of POP and clinical covariates, both alone and in combination, we calculated the area under the receiver operating characteristic curve and 95% CI for each variable individually, for the 3 covariates combined, and for the combination of covariates and POP. To facilitate comparisons with previously reported values\[2\] and further understand the predictive characteristics of POP, measures of sensitivity, specificity, positive predictive value, and negative predictive value were calculated for cut points ranging from 4 to 12 cm H_2O. In secondary analyses, we repeated analyses excluding 3 patients with POP of 0 cm H_2O. Moreover, we used linear regression to evaluate the association between continuous POP and continuous AHI percent changes, with results presented as the estimated change in AHI response for a 1-cm H_2O decrease in POP, as well as the variance in AHI percent change explained by POP (eg, R\(^2\)). Using guidelines provided by Cohen, values of 1% (r = 0.1) can be interpreted as small; 9% (r = 0.3), moderate; and 25% (r = 0.5), large.\[16\]

Results
Sample Characteristics
Twenty-seven patients met all study inclusion criteria. Patient demographics and baseline statistics are listed in Table 1. Overall, the study cohort was older than those in a previous trial\[3\] (mean [SD] age, 62.0 [14.4] years) and overweight (mean [SD] BMI, 28.1 [4.0]; calculated as weight in kilograms divided by height in meters squared), 14 participants were men (51.9%), and 26 were of white race (96.3%). One patient had neurologic disease (trismus 2I). There were 18 responders and 9 nonresponders to HGNS. Responders were 4.9 (95% CI, −14.7 to 5.0) years younger and BMI was 1.4 (95% CI, −4.8 to 2.0) lower than in nonresponders, and the response cohort included half as many men (38.9% vs 77.8%) (Table 1). Responders also demonstrated a mean of 9.3 (95% CI, −7.3 to 25.8) events/h more severe baseline AHI.

Associations With Primary Outcome
Figure 1 illustrates a representative airway at the level of the soft palate before application of nasal PAP and following therapeutic nasal PAP. Table 2 presents the percent collapse and POP at the velum during preoperative therapeutic nasal PAP during DISE, stratified according to responder status. There was no clinically meaningful difference in percent collapse at the velum between responders and nonresponders. Overall, POP ranged from 0 to 15 cm H_2O, with all responders demonstrating a POP less than 10 cm H_2O. Responders showed a clinically meaningful lower mean (SD) POP than nonresponders (5.0 [2.8] vs 9.2 [3.7] cm H_2O, respectively; mean difference, −4.2; 95% CI, −6.8 to −1.6 cm H_2O), which remained after accounting for differences in age, sex, and BMI (mean difference, −3.5; 95% CI, −6.7 to −0.4 cm H_2O). Similar results were observed in sensitivity analyses excluding patients with no palatal collapse (POP, 0 cm H_2O, in unadjusted [mean difference, −3.2; 95% CI, −5.5 to −0.9 cm H_2O] and covariate-adjusted [mean difference, −2.6; 95% CI, −5.3 to 0.0 cm H_2O]) comparisons. Regression analysis of percent change in AHI level and POP suggested that, for each 1-cm H_2O decrease in POP, the percent

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[1] BMI: Body Mass Index
[2] POP: Pressure Overlap
[3] SD: Standard Deviation
A reduction in AHI level increased by nearly 6% (model estimate, −5.8%; 95% CI, −12.1% to 0.4% change; $R^2 = 12.9%$). Results were attenuated, but consistent, after covariate adjustment, with each 1-cm H$_2$O decrease in POP resulting in a 4% greater percent reduction in AHI (model estimate, −3.8%; 95% CI, −10.8% to 3.2% change).

Table 3 presents the predictive characteristics (sensitivity, specificity, negative predictive value, and positive predictive value) at various cutoff levels based on therapeutic nasal PAP levels during DISE for response to HGNS using both overall postoperative home sleep AHI and residual supine AHI levels. For overall postoperative home sleep AHI, higher cutoff values increased sensitivity but decreased specificity. Cutoff levels of both 6 and 8 cm H$_2$O resulted in similar positive predictive values of 83.3% and 82.4%, respectively, although less than 8 cm H$_2$O resulted in relatively good balance across other measures of sensitivity (77.8%), specificity (66.7%), and a negative predictive value (60.0%). When excluding patients with a POP of 0, a therapeutic nasal PAP during DISE cutoff level less than 7 cm H$_2$O was associated with the maximum positive predictive value of 85.7%.

In addition, to understand the overall predictive ability of therapeutic nasal PAP during DISE and typical clinical factors for our primary responder definition, we evaluated the area under the receiver operating characteristic curve as reported in Table 4. Individually, therapeutic nasal PAP during DISE resulted in an area under the receiver operating characteristic curve of 0.818 (95% CI, 0.629-1.000), which was higher than...
any of the individual covariates alone. The combination of age, sex, and BMI resulted in an area under the receiver operating characteristic curve of 0.790 (95% CI, 0.578–1.000), which was improved to 0.895 (95% CI, 0.766–1.000) with the addition of therapeutic nasal PAP during DISE to the predictive model (Figure 2).

**Associations With Secondary Outcome**

As a secondary aim, we examined differences between responders and nonresponders based on the change in preoperative AHI to postoperative residual supine AHI level from the titration study; 10 patients were excluded due to no recorded supine data on titration. Similar to primary analyses, there was a clinically meaningful difference in POP (mean difference, −4.4; 95% CI, −7.9 to −1.0 cm H₂O) between HGNS responders and nonresponders (eTable 1 in the Supplement). Results again were consistent when adjusted for differences in age, sex, and BMI (mean difference, −3.9; 95% CI, −9.1 to 1.3 cm H₂O). When excluding patients with POP of 0 cm H₂O, results remained clinically meaningful in both unadjusted (mean difference, −2.9; 95% CI, −5.8 to 0.0 cm H₂O) and covariate-adjusted (mean difference, −3.7; 95% CI, −8.4 to 1.1 cm H₂O) comparisons.

For hypothesis-generating outcomes, we evaluated percent collapse and opening pressures of the oropharynx, tongue base, and epiglottis stratified by responder status (eTable 2 in the Supplement). There was no clinically meaningful difference in the percentage of collapse between responders and nonresponders at any site. Nonresponders had higher mean pressure requirements at all sites, although differences were smaller than those observed at the velum.

**Discussion**

To our knowledge, this is the first study to investigate the use of therapeutic nasal PAP during DISE as a predictor of response to surgical therapy for OSA. This investigation may further the insight gained from recent work demonstrating the predictive power of preoperative PAP levels on HGNS outcomes.7 In our present study, the findings suggest that responders to HGNS therapy have more distensible airways at the soft palate compared with nonresponders during DISE. These POP values remained meaningful predictors using either postoperative home sleep AHI data or supine AHI titration data to define response.

These data add to the growing body of literature on predictors for HGNS outcomes. Thaler et al17 reported sex differences, with men as worse responders. These findings are consistent with our study sample in which men were less likely to meet responder criteria. The body of anatomic predictors includes (1) the absence of palatal complete circumferential collapse during DISE,18 (2) increased retropalatal opening in response to stimulation,19 and (3) decreased soft palate volume.19 The importance of distensibility at the soft palate has been

**Table 2. Comparison of DISE and Sleep Study Data in HGNS Responders and Nonresponders**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD) Responders (n = 18)</th>
<th>Mean (SD) Nonresponders (n = 9)</th>
<th>Effect size (95% CI)</th>
<th>Adjusted effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISE data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Velum % collapse</td>
<td>92.2 (20.5)</td>
<td>100 (0)</td>
<td>−7.8 (−22.0 to 6.4)</td>
<td>−6.5 (−20.9 to 8.0)</td>
</tr>
<tr>
<td>Velum opening pressure, cm H₂O</td>
<td>5.0 (2.8)</td>
<td>9.2 (3.7)</td>
<td>−4.2 (−6.8 to −1.6)</td>
<td>−3.5 (−6.7 to −0.4)</td>
</tr>
<tr>
<td>Sleep study data, events/h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline AHI</td>
<td>40.5 (20.6)</td>
<td>31.2 (17.6)</td>
<td>9.3 (−7.3 to 25.8)</td>
<td>10.4 (−5.9 to 26.8)</td>
</tr>
<tr>
<td>Treatment AHI</td>
<td>9.3 (8.8)</td>
<td>34.5 (14.8)</td>
<td>−25.2 (−34.5 to −15.9)</td>
<td>−26.3 (−36.6 to −15.9)</td>
</tr>
<tr>
<td>Absolute AHI change</td>
<td>−31.2 (14.2)</td>
<td>3.3 (12.8)</td>
<td>−34.4 (−46.0 to −22.9)</td>
<td>−36.7 (−48.7 to −24.7)</td>
</tr>
<tr>
<td>% AHI change</td>
<td>−78.8 (11.3)</td>
<td>24.2 (56.7)</td>
<td>−103.0 (−131.1 to −74.9)</td>
<td>−103.1 (−137.7 to −68.5)</td>
</tr>
</tbody>
</table>

**Table 3. Comparison of Predictive Characteristics for Nasal PAP Levels During DISE as Cutoff Values for Prediction of Response to HGNS®**

<table>
<thead>
<tr>
<th>Measure</th>
<th>&lt;4</th>
<th>&lt;6</th>
<th>&lt;8</th>
<th>&lt;10</th>
<th>&lt;12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall efficacy AHI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>16.7 (3.6–41.4)</td>
<td>55.6 (30.8–78.5)</td>
<td>77.8 (52.4–93.6)</td>
<td>100 (81.5–100.0)</td>
<td>100 (81.5–100.0)</td>
</tr>
<tr>
<td>Specificity</td>
<td>100 (66.4–100.0)</td>
<td>77.8 (40.0–97.2)</td>
<td>66.7 (29.9–92.5)</td>
<td>33.3 (7.5–70.1)</td>
<td>22.2 (2.8–60.0)</td>
</tr>
<tr>
<td>PPV</td>
<td>100 (29.2–100.0)</td>
<td>83.3 (51.6–97.9)</td>
<td>82.4 (56.6–96.2)</td>
<td>75.0 (53.3–90.2)</td>
<td>72.0 (50.6–87.9)</td>
</tr>
<tr>
<td>NPV</td>
<td>37.5 (18.5–59.4)</td>
<td>46.7 (21.3–73.4)</td>
<td>60.0 (26.2–87.8)</td>
<td>100 (29.2–100.0)</td>
<td>100 (15.8–100.0)</td>
</tr>
<tr>
<td>Residual supine AHI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>25.0 (5.5–57.2)</td>
<td>58.3 (27.7–84.8)</td>
<td>75.0 (42.8–94.5)</td>
<td>100 (73.5–100.0)</td>
<td>100 (73.5–100.0)</td>
</tr>
<tr>
<td>Specificity</td>
<td>100 (54.1–100.0)</td>
<td>83.3 (35.9–99.9)</td>
<td>83.3 (35.9–99.9)</td>
<td>33.3 (4.3–77.7)</td>
<td>16.7 (0.4–64.1)</td>
</tr>
<tr>
<td>PPV</td>
<td>100 (29.2–100.0)</td>
<td>87.5 (47.3–99.7)</td>
<td>90.0 (55.5–99.7)</td>
<td>75.0 (47.6–92.7)</td>
<td>70.6 (44.0–89.7)</td>
</tr>
<tr>
<td>NPV</td>
<td>40.0 (16.3–67.7)</td>
<td>50.0 (18.7–81.3)</td>
<td>62.5 (24.5–91.5)</td>
<td>100 (15.8–100.0)</td>
<td>100 (25.0–100.0)</td>
</tr>
</tbody>
</table>

Abbreviations: AHI, apnea-hypopnea index; DISE, drug-induced sleep endoscopy; HGNS, hypoglossal nerve stimulation.

a Therapy response defined as a 50% or greater reduction in AHI level.
b Estimated difference in means or percentage between responders and nonresponders and associated 95% CI.
c Adjusted for age, sex, and BMI.

Discussion

To our knowledge, this is the first study to investigate the use of therapeutic nasal PAP during DISE as a predictor of response to surgical therapy for OSA. This investigation may further the insight gained from recent work demonstrating the predictive power of preoperative PAP levels on HGNS outcomes.7 In our present study, the findings suggest that responders to HGNS therapy have more distensible airways at the soft palate compared with nonresponders during DISE. These POP values remained meaningful predictors using either postoperative home sleep AHI data or supine AHI titration data to define response.

These data add to the growing body of literature on predictors for HGNS outcomes. Thaler et al17 reported sex differences, with men as worse responders. These findings are consistent with our study sample in which men were less likely to meet responder criteria. The body of anatomic predictors includes (1) the absence of palatal complete circumferential collapse during DISE,18 (2) increased retropalatal opening in response to stimulation,19 and (3) decreased soft palate volume.19 The importance of distensibility at the soft palate has been
Table 4. Area Under the Receiver Operating Characteristic Curve for Clinical Factors and Therapeutic Nasal PAP During DISE in Prediction of Response to HGNS*

<table>
<thead>
<tr>
<th>Model</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual measures</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.559 (0.330-0.787)</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.694 (0.510-0.879)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.630 (0.404-0.855)</td>
</tr>
<tr>
<td>Nasal PAP during DISE</td>
<td>0.818 (0.629-1.000)</td>
</tr>
<tr>
<td>Combined measures</td>
<td></td>
</tr>
<tr>
<td>Age, male sex, and BMI</td>
<td>0.790 (0.578-1.000)</td>
</tr>
<tr>
<td>Age, male sex, BMI, and nasal PAP during DISE</td>
<td>0.895 (0.766-1.000)</td>
</tr>
</tbody>
</table>

Abbreviations: AHI, apnea-hypopnea index; AUC, area under the receiver operating characteristic curve; BMI, body mass index; DISE, drug-induced sleep endoscopy; HGNS, hypoglossal nerve stimulation; PAP, positive airway pressure.

* Therapy response defined as a 50% or greater reduction in AHI level.

intimated by the results of Safiruddin et al13 and further solidified by Lan et al’s14 findings of high PAP levels associated with circumferential palatal and lateral wall collapse. Our present work appears to be supportive of the findings from these previous endeavors.

Positional OSA may play a role in predicting HGNS therapy response, as patients with complete resolution of supine events are rare from our clinical experience. Steffen et al20 studied 44 patients with HGNS, including 31 patients with positional OSA, and found that, although the overall AHI level was significantly reduced relative to baseline, the supine AHI was still higher than the total night AHI level. There was no clear cutoff in supine AHI level for predicting responders. We did not have access to baseline supine AHI data, which was a limitation of our study.

Strengths and Limitations

In addition to lack of data on baseline supine AHI, we acknowledge several other key limitations of this study. First, we did not monitor airflow during therapeutic nasal PAP during DISE. While the CPAP machine has the capability to monitor this airflow, the pressure ramps too quickly to analyze the results at any given pressure level. We have since started using a flow-based home sleep study during DISE for a more objective measure of airway patency, but procedure time is still a limiting factor. In addition, we did not capture objective measures of mask leakage despite some patients having mouth opening. For future experiments, we are acquiring equipment to objectively measure leakage. Second, nasal obstruction can also contribute to elevations in POP levels.21-24 However, evidence suggests that elevations in nasal resistance will increase POP levels only modestly.24,25 Third, we only captured pressure requirements when patients were in the supine position, yet pressure requirements for side sleepers are likely lower. For this reason, we presented residual supine AHI data from the in-lab titration study. Fourth, our data set did not include adequate baseline PAP levels for most patients for comparison with POP levels; we are prospectively gathering these data for all patients for future analysis. Fifth, POP was primarily determined by one of us (R.C.D.) with input from another (E.G.S.). This method is susceptible to interrater reliability concerns akin to other DISE scoring systems. In future studies, we plan to use measures of flow and pressure to obtain objective, rather than subjective, POP values. Sixth, rapid eye movement sleep-related OSA may represent the source of HGNS failure in some patients, and we do not have in-lab polysomnographic studies at one voltage to determine rapid eye movement sleep AHI levels. Furthermore, we do not have the capability to induce rapid eye movement sleep during DISE, which has been shown to be more closely related to non-rapid eye movement sleep.26,27 In addition, our sample size was relatively small and contained a high proportion of patients who were white. Thus, our DISE findings and POP levels may not generalize to other racial groups, and larger studies are warranted to confirm the observed associations.

Conversely, this study has some strengths. For the primary outcome variable, we followed the highest standards by using full-night data rather than treatment AHI from titration.26 We extracted only the residual supine AHI level from the titration study to prevent positional OSA burden and achieve uniformity in body position between polysomnographic testing and DISE.

The utility of therapeutic nasal PAP during DISE may be a notable aspect of our study. Because all patients undergo DISE before HGNS device implantation to determine their candidacy for surgery, use of therapeutic nasal PAP during DISE represents a potential low-risk, low-cost option to predict treatment outcomes. DISE has been traditionally analyzed using the

Figure 2. Therapeutic Nasal Positive Airway Pressure (PAP) During Drug-Induced Sleep Endoscopy (DISE) as a Predictor for Hypoglossal Nerve Stimulation Response, Defined as a 50% Reduction in Overall Apnea-Hypopnea Index (AHI) Level

Receiver operating characteristic curve for overall efficacy AHI level based on prediction models using age, sex, and body mass index (BMI) only (area under the receiver operating characteristic curve [AUC], 0.790; 95% CI, 0.578-1.000) and the 3 covariates plus therapeutic nasal PAP during DISE (AUC, 0.895; 95% CI, 0.766-1.000). The addition of therapeutic nasal PAP during DISE resulted in improved predictive ability as evidenced by an increase in the AUC.
Conclusions

To our knowledge, this is the first study to use a therapeutic nasal PAP interface and PAP ramp during DISE. We used a nasal mask, which is preferable over oronasal interfaces since the latter may worsen obstruction by displacing the tongue base posteriorly. In addition, oronasal masks are associated with higher pressure requirements and mask leak—2 confounders we aimed to minimize when determining POP levels.

Nasal PAP involves a single airstream acting directly on the palate, which was important for consistent measurements of our primary outcome. One drawback of the nasal mask, however, is the need for manual mouth closure to prevent oral leak in mouth-breathing patients. When performing a manual mouth closure, we attempted to close the lips while maintaining natural jaw position.

Future studies analogous to our exploratory analyses can include prospective, detailed examination of other anatomic sites (ie, inferior lateral wall and epiglottis) in treatment success. This study suggests the need for broad OSA endotyping of patients receiving HGNS. Both anatomic and nonanatomic (insomnia, loop gain, and sleep stage physiologic characteristics) factors are paramount to refine patient selection of this treatment modality. Because all patients undergo DISE before HGNS device implantation to determine their candidacy for surgery, use of therapeutic nasal PAP during DISE may represent an available low-risk, cost-effective prognostic tool. We suggest that therapeutic nasal PAP during DISE be broadly implemented and studied across multiple centers to further understand its role in patient selection for HGNS.

REFERENCES


