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Original Article

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Polysomnographic endotypes of successful multilevel upper airway surgery for obstructive sleep apnea

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ABSTRACT

Study Objectives: Multilevel upper airway surgery is effective for some patients with obstructive sleep apnea (OSA), but predicting the response to surgery remains a challenge. The underlying endotypes of OSA include upper airway collapsibility, muscle compensation, loop gain, and the arousal threshold. This study aimed to explore the effect of surgery on polysomnography (PSG)-derived OSA endotypes and establish a surgical response prediction model.

Methods: Our study included 54 Chinese patients with OSA who underwent multilevel upper airway surgery. Participants underwent PSG before and after surgery with a median follow-up time of 6.5 months. Using $AHI_{Baseline}/AHI_{post\text{-}surgery} \geq 2$ and $AHI_{post\text{-}surgery} < 10$ events/h as criteria, participants were classified as surgery responders and non-responders. The surgical success rate was 26%. These endotypic traits were derived from a standard PSG data by validated methods.

Results: The surgery altered both anatomical and non-anatomical endotypic traits, including increased Vpassive (baseline vs post-surgery: 51.5 [18.7–84.2] vs 86.8 [67.4–93.7] %Veupnea, $p < .001$), decreased loop gain (baseline vs post-surgery: 0.7 [0.7–0.8] vs 0.6 [0.5–0.6]; $p < .001$), and a higher arousal threshold (baseline vs post-surgery: 202.9 [183.7–222.0] vs 160.7 [143.9–177.4] %Veupnea; $p < .001$). However, it did not significantly affect muscle compensation. Fully adjusted logistic regression analyses indicated that a favorable response to surgery was independently associated with a lower LG (OR [CI 95%], 0.1 [0.0–0.5], $p = .032$). In patients with improved muscle compensation or a more collapsible airway (lower Vpassive), a lower loop gain was more strongly indicative of success. However, when muscle compensation was lower or collapsibility was less severe (higher Vpassive), a lower loop gain was less predictive of success.

Conclusions: This study demonstrated that multilevel upper airway surgery altered both anatomical and non-anatomical endotypes in Chinese patients with OSA. An endotype based regression model may meaningfully predict surgical success.

Key words: obstructive sleep apnea; upper airway surgery; loop gain; arousal threshold; pharyngeal collapsibility; muscle compensation

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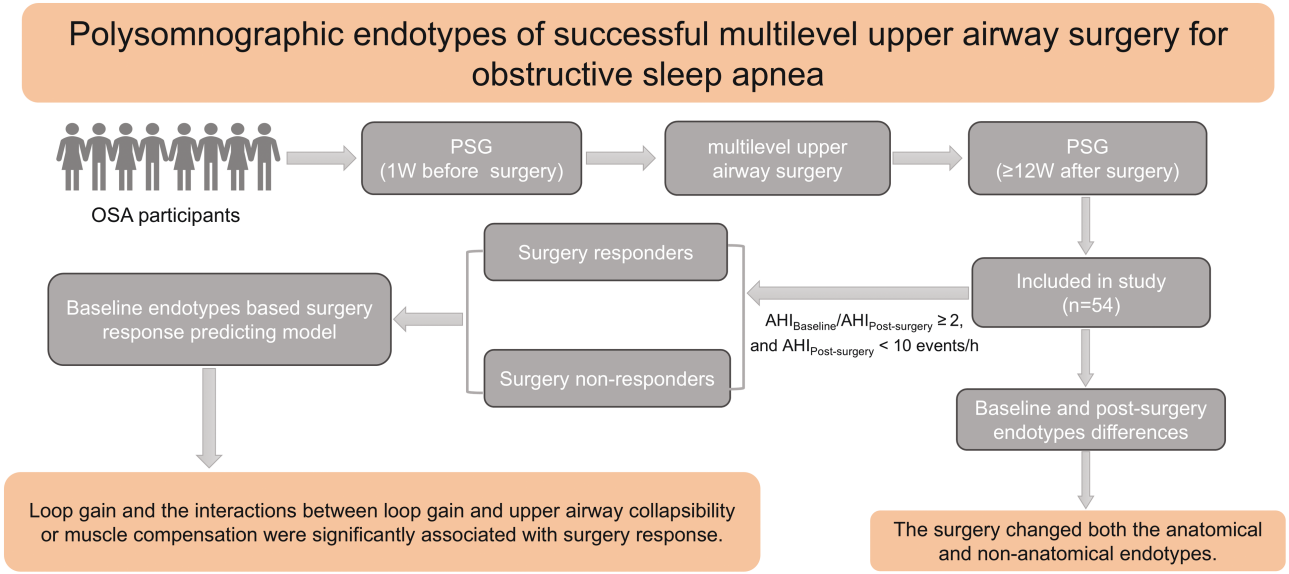
Graphical Abstract



Statement of Significance

The prediction of multilevel upper airway surgery response in OSA patients remains a challenge, OSA endotypes maybe effective in the response prediction. This research indicated LG and endotype interactions are effective determinants of surgical response. Specifically, favorable surgery response was independently associated with lower LG. Moreover, in patients with improved muscle compensation or more collapsible airway, lower LG was associated with higher probability of surgical success. In patients with decreased muscle compensation or reduced collapsibility, lower LG was less predictive of success. An endotype-based regression model may effective in predicting surgical success and provided theoretical foundations for precision medicine.

Introduction

Obstructive sleep apnea (OSA) is characterized by repeated upper airway obstruction during sleep and is an independent risk factor for cardiovascular and metabolic diseases, cognitive impairment, and all-cause mortality [1, 2]. Multilevel upper airway surgery is an alternative for a considerable proportion of patients with OSA who are intolerant to continuous positive airway pressure (CPAP) treatment [3, 4]. Surgery can be curative in some patients with OSA; however, meta-analysis indicates that the long-term efficacy of uvulopalatopharyngoplasty (UPPP) in unselected adult patients is only 44% [5], with a mean follow-up time of at least 34 months. Patient selection for OSA is crucial for improving the efficacy of multilevel upper airway surgery. Although considerable research has focused on preoperative prognostic factors, these predictive systems have limited predictive efficiency and are only applicable to oropharyngeal surgery.

OSA is induced by multiple interactive anatomical and non-anatomical physiological mechanisms, including upper airway collapsibility, pharyngeal dilator muscle compensation, ventilation control hypersensitivity (loop gain [LG]), and arousal threshold (ArTH) [6, 7]. These baseline traits of physiological mechanisms are valuable in predicting the response to OSA treatments [8–10]. However, the gold-standard measurement techniques for assessing these endotypes are invasive and rigorous, involving esophageal catheters to assess ventilation and CPAP drops during overnight sleep. Sands et al. [11] developed non-invasive techniques to determine the four key physiological traits from the ventilation flow pattern recorded during standard laboratory-based polysomnography (PSG) [8, 11], which was widely used thereafter. A positive response to hypoglossal nerve stimulation therapy has been associated with a higher PSG-estimated ArTH, greater compensation, and lower LG [9]. Responders to the mandibular advancement device exhibited a lower PSG-estimated LG at baseline than non-responders [12]. Bamagoos et al. showed that greater oral appliance efficacy is associated with favorable nonpharyngeal traits, moderate pharyngeal collapsibility, and weaker muscle compensation [8]. With these established criteria, individuals with different endotypic traits could potentially receive personalized precision OSA therapy.

However, the effects of upper airway surgery on OSA endotypes remain unclear. Schwartz et al. [13] measured upper airway collapsibility using the pharyngeal critical closing pressure in 13 patients who underwent UPPP. They demonstrated that no baseline clinical, polysomnographic, or physiological factors could predict the response to surgery [13]. Recent studies have also calculated PSG-derived non-anatomical traits and indicated that an elevated LG is associated with a poorer upper airway surgery treatment response [14]. Wong et al. [15] utilized CPAP dial-down and PSG-derived methods to assess the influence of upper airway surgery on all 4 key endotypes in 23 individuals with OSA. They found that upper airway surgery unpredictably alters upper airway collapsibility but does not alter non-anatomical endotypes, and there are no baseline predictors of response to surgery [15].

Considering the significant variation in research findings and the several key unanswered questions, further investigation is needed: (i) How do physiological endotypes change after

multilevel upper airway surgery in Chinese patients with OSA? (ii) Previous studies have reported conflicting results on the role of physiological endotypes in predicting treatment outcomes. What role do these endotypes play in predicting the response to multilevel upper airway surgery? In this study, we analyzed baseline and post-treatment endotype differences between responders and non-responders and determined whether baseline characteristics could predict multilevel upper airway surgery responses.

Methods

Participants

Study participants were ethnically Chinese individuals with OSA aged ≥ 18 years who underwent multilevel upper airway surgery (majority received palate-based surgery) and at least one other type of surgery (tonsillectomy, or tongue-based surgery); further details of the upper airway surgery types received by each participant are provided in Supplementary Table S1. Participants were retrospectively enrolled between December 29, 2011 and October 22, 2020 at our sleep center. Individuals who had undergone palate-or tongue-based surgery prior to this study; those with comorbid sleep disorders; and those taking anxiolytics, antidepressants, antipsychotics, or hypnotic drugs were excluded. The study was approved by the Ethics Committee of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (Approval No: 2019-KY-050[K]) and registered in the Chinese Clinical Trial Registry (No. ChiCTR1900025714). All the participants provided informed consent.

Sleep evaluation and clinical evaluation

All participants underwent routine overnight PSG (Alice 5/6 Sleep Diagnostic System; Respironics Inc., Pittsburgh, PA, USA) no more than 1 week before surgery. Sleep and arousal were scored in 30-s epochs using the electroencephalogram, electrooculogram, electrocardiogram, and electromyogram channels, following standard criteria. Obstructive sleep, mixed sleep, and hypopnea were defined according to the 2012 American Academy of Sleep Medicine criteria [16]. Two experienced technicians manually generated reports using Sleepware software (Respironics Inc.) according to established guidelines. The data collected included the total apnea hypopnea index (AHI), baseline AHI ($AHI_{Baseline}$), post-surgery AHI ($AHI_{Post\text{-}surgery}$), AHI in the supine position (AHI_{Supine}), AHI in the non-supine positions($AHI_{Non\text{-}supine}$), AHI during non-rapid eye movement sleep stages (AHI_{NREM}), AHI during rapid eye movement sleep stages (AHI_{REM}), arousal index (ArI), total sleep time (TST), sleep efficiency, proportion of each sleep stage (including N1, N2, N3, and REM), 3% oxygen desaturation index (ODI3), cumulative time of oxygen saturation < 90% in TST (CT90), mean oxygen saturation ($MSaO_2$), and lowest oxygen saturation ($LSaO_2$).

Clinical characteristics were calculated as the mean of two consecutive measurements before PSG. The measurements included height (m), weight (kg), neck circumference (NC) (cm), waist circumference (WC) (cm), and hip circumference (HC) (cm). Tonsil and tongue positions were evaluated and classified according to the Friedman Score [17]. Body mass index (BMI) was calculated as weight divided by height in meters squared (kg/m^2).

PSG and clinical characteristic measurements were repeated during postoperative visits, with a median follow-up time of 6.5 months. Using a post-surgery AHI criterion of ≥50% reduction from baseline and a value of less than 10 events/h to defined effective treatment [18], participants were classified as surgery responders and non-responders.

Calculation of pathophysiological traits

To quantify the physiological OSA traits from the scored PSGs, we used recently published and validated techniques developed by previous study [11, 19] This method was found to have high within and across night repeatability [20, 21]. Data from the staged and scored PSGs were converted into European Data Format file and imported into MATLAB (MathWorks, Inc., Natick, MA). Ventilation refers to an uncalibrated breath-by-breath ventilation time series (tidal volume × respiratory rate) derived from the nasal pressure airflow signal and is presented as a percentage of the average neighboring values (%Veupnea). The polysomnographic data were divided into 7 min windows, and the ventilatory drive was calculated based on each window using a simplified chemoreflex feedback control model. The ventilatory drive reflects the intended ventilation and is calculated for each breath based on the prior values of ventilation by fitting a physiologically constrained regression model. Endotypic traits can be estimated using ventilation and ventilatory drive and are presented as median values.

LG is quantified as the size of the increased ventilatory drive observed in response to a prior reduction in ventilation [22]; higher LG values represent a greater contribution of ventilatory control to sleep apnea owing to either chemoreflex or pulmonary mechanisms. ArTH was quantified as the ventilatory drive that occurs in breaths immediately preceding the scored EEG arousals from sleep [22], with lower values reflecting greater arousability from sleep [23]. Pharyngeal collapsibility (Vpassive) was defined as the median ventilation during sleep in the normal/eupneic ventilatory drive [24]; lower values of Vpassive reflect a more collapsible airway. Pharyngeal muscle compensation (Vcomp) is the increase in ventilation with rising ventilatory drive; lower values represent a greater neuromuscular contribution to sleep apnea [24]. Vcomp is calculated by Vactive minus Vpassive, where Vactive is the ventilation when the ventilatory drive is at the ArTH. The median values during all sleep stages and sleep positions were used for each participant.

Statistical analysis

Categorical data are presented as proportions. Simple comparisons of variables were performed using the *t*-test, Mann–Whitney *U* test, and chi-square test, as appropriate.

The values of LG, ArTH, Vpassive, and Vcomp were not square-root-based transformed in our research. The endotypes and other continuous variables included in the logistic regression models were standardized using Z-score normalization. All patients with OSA were classified as responders or non-responders according to the criteria mentioned in the Methods section. The surgical effect (responders or non-responders) was defined as the dependent variable in logistic regression analyses. In the preliminary bivariate logistic regression analyses, endotypes were included, and AHI was adjusted as a confounder. The multivariate logistic regression model included all endotypes, AHI, and interactions between the endotypes. Interactions were included in the model based on backward selection ($p < 0.157$), and endotypes were retained in the logistic regression model to avoid underestimating the p values. The removal of endotypes was considered only if collinearity existed (the variance inflation factor for endotypes in this study was <5). The sensitivity and specificity of the logistic regression model were tested, and the efficacy of the model was evaluated using the area under the receiver operating characteristic curve (AUC) value.

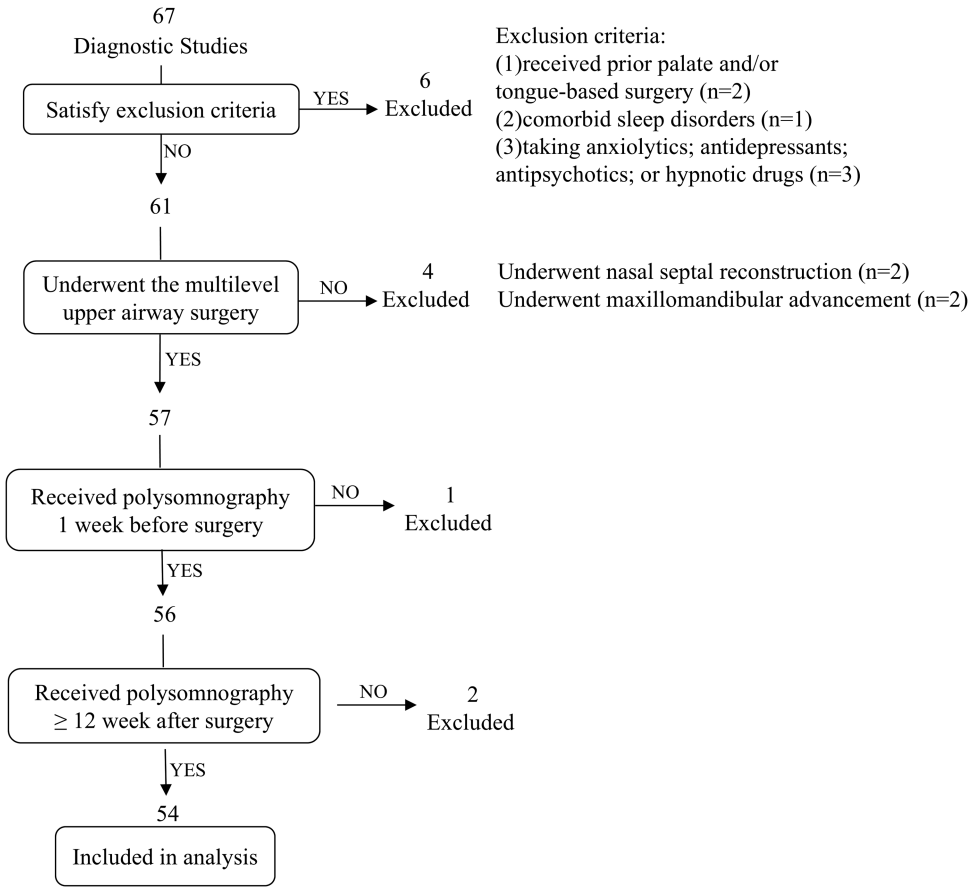


Figure 1. Participant flow diagram showing the number of participants identified at each inclusion/exclusion steps.

Statistical analyses were performed using SPSS software (version 27.0; IBM Corp., Armonk, NY, USA) and R software (version 4.2.2; R Foundation, Vienna, Austria). Statistical significance was set at $p < .05$.

Results

Baseline characteristics of participants with OSA

Fifty-four participants were included in the research analysis (Figure 1). The baseline demographics characteristics of the 54 participants are shown in Table 1. Participants were aged 36.5 [33.0–44.5] y, overweight (27.2 [25.0–29.0] kg/m^2), and had severe OSA (58.0 [31.4–67.4] events/h).

Effect of the multilevel upper airway surgery on sleep characteristics and OSA endotypes

The effects of surgery on sleep-disordered breathing, sleep architecture, and OSA endotypes are summarized in Table 2. Surgery was associated with a significant reduction in AHI (baseline vs post-surgery: 51.3 [45.6–57.0] vs 29.7 [23.7–35.8] events/h; $p < .001$; Figure 2), ODI3 (baseline VS post-surgery: 51.6 [45.3–57.9] vs 28.9 [22.9–34.9] events/h; $p < .001$), CT90 (baseline VS post-surgery: 12.9 [3.6–30.2] vs 2.2 [0.1–13.7] %; $p < .001$), and improvement in the $LSaO_2$ (baseline vs post-surgery: 70.8 [67.3–74.2] vs 77.9 [74.3–81.4] %; $p < .001$). Moreover, no significant differences in the sleep efficiency, total REM and NREM sleep duration, proportion REM and NREM sleep stage (all $p > .05$) existed before and after surgery. Conversely, after surgery, TST (baseline vs post-surgery: 438.0

Table 1. Baseline demographics characteristics of the OSA participants.

Variables	All participants (n = 54)
Gender	48M:6F
Age (y)	36.5 (33.0–44.5)[b]
BMI (kg/m^2)	27.2 (25.0–29.0)[b]
AHI (events/h)	58.0 (31.4–67.4)[b]
Follow-up time (months)	6.5 (4.0–13.3)[b]
NC (cm)	40.8 (39.8–41.8)[a]
WC (cm)	97.9 (95.6–100.2)[a]
HC (cm)	103.1 (101.5–104.7)[a]
Friedman	
I (%)	17.3
II (%)	57.7
III (%)	21.2
IV (%)	3.9
Tonsil	
I (%)	33.3
II (%)	45.5
III (%)	21.2

Abbreviations: AHI, apnea hypopnea index; BMI, body mass index; NC, neck circumference; HC, hip circumference; WC, waist circumference.
[a]Data are presented as mean and 95%CI.
[b]Indicates data presented as median and first to third quartiles.

[393.7–470.3] vs 413.8 [373.5–449.5] min; $p = .022$) and the proportion of N1 sleep stage (baseline vs post-surgery: 21.9 [17.6–26.2] vs 15.3 [11.9–18.6] %; $p = .017$) were reduced, while the proportion of N2 sleep stage (baseline vs post-surgery: 51.8 [47.7–56.0] vs 59.6 [56.3–62.9] %; $p = .007$) increased.

As for OSA endotypes measured using clinical PSG methods, results (Table 2) indicated that surgery significantly decreased LG (baseline vs post-surgery: 0.7 [0.6–0.8] vs 0.6 [0.5–0.6]; $p < .001$; Figure 3, A), ArTH (baseline vs post-surgery: 202.9 [183.7–222.0] vs 160.7 [143.9–177.4] %Veupnea; $p < .001$; Figure 3, B) and increased Vpassive (baseline vs post-surgery: 51.5 [18.7–84.2] vs 86.8 [67.4–93.7] %Veupnea; $p < .001$; Figure 3, C). However, there were no significant differences between baseline and post-surgery Vcomp values (baseline vs post-surgery: 2.3 [–4.4–8.9] vs –1.7 [–9.5–6.2]) %Veupnea; $p = .343$; Figure 3, D).

Baseline and post-surgery characteristics of surgery non-responders and responders

Using post-surgery AHI criterion of ≥50% reduction from baseline and a value of less than 10 events/h as criteria, 14 (26%) patients were classified as responders, while 40 were non-responders. The baseline and postoperative characteristics of non-responders and responders are shown in Table 3 and Supplementary Table S2.

As shown in Table 3, responders had lower baseline age (non-responders vs responders: 38.0 [33.8–47.5] vs 34.0 [30.0–35.8]; $p = .034$), BMI (non-responders vs responders: 27.7 [25.3–30.1] vs 26.1 [24.8–26.9] kg/m^2; $p = .003$), ODI3 (non-responders vs responders: 55.2 [48.2–62.3] vs 39.9 [26.6–53.2] events/h; $p = .031$), CT90 (non-responders vs responders: 18.7 [10.5–35.5] vs 2.9 [1.1–6.4]

Table 2. Effect of the multilevel upper airway surgery on sleep characteristics and endotypes.

Variables	Before surgery ($n = 54$)	After surgery ($n = 54$)	Difference	p value
BMI (kg/m^2)	27.1 (25.0–28.9)[b]	26.0 (24.5–28.7)[b]	0.0 (– 0.3–1.6)[b]	.262
AHI (events/h)	51.3 (45.6–57.0)[a]	29.7 (23.7–35.8)[a]	20.9 (14.0–27.7)[a]	<.001
AHI_{REM} (events/h)	50.3 (45.0–55.7)[a]	31.7 (24.2–39.3)[a]	16.8 (8.0–25.6)[a]	<.001
AHI_{NREM} (events/h)	51.6 (45.6–57.6)[a]	29.5 (23.4–35.6)[a]	21.8 (14.5–29.0)[a]	<.001
AHI_{Supine}(events/h)	43.1 (35.4–50.8)[a]	27.6 (19.4–35.8)[a]	17.2 (5.6–28.9)[a]	.005
$AHI_{Non\text{-}supine}$ (events/h)	46.5 (39.8–53.3)[a]	21.9 (15.9–28.0)[a]	23.1 (13.7–32.5)[a]	<.001
$ODI3_{Total}$ (events/h)	51.6 (45.3–57.9)[a]	28.9 (22.9–34.9)[a]	22.5 (15.9–29.1)[a]	<.001
$ODI3_{REM}$ (events/h)	51.3 (44.9–57.7)[a]	32.2 (24.8–39.5)[a]	17.1 (8.6–25.6)[a]	<.001
$ODI3_{NREM}$ (events/h)	52.0 (46.0–58.1)[a]	27.4 (20.9–33.8)[a]	25.3 (18.6–32.1)[a]	<.001
ArI (events/h)	39.9 (33.5–46.3)[a]	26.8 (21.6–31.9)[a]	12.8 (5.5–20.1)[a]	<.001
$MSaO_2$ (%)	92.8 (91.9–93.6)[a]	94.7 (94.2–95.3)[a]	–1.9 (– 2.7–[– 1.2])[a]	<.001
$LSaO_2$ (%)	70.8 (67.3–74.2)[a]	77.9 (74.3–81.4)[a]	–7.04 (– 9.8–[– 4.3])[a]	<.001
CT90 (%)	12.9 (3.6–30.2)[b]	2.2 (0.1–13.7)[b]	10.8 (6.5–15.1) [a]	<.001
TST (min)	438.0 (393.7–470.3)[b]	413.8 (373.5–449.5)[b]	17.2 (– 25.3–84.3)[b]	.022
Sleep efficiency (%)	94.9 (85.6–99.0)[b]	96.0 (85.0–99.0)[b]	0.0 (– 5.4–5.4)[b]	.975
REM sleep duration (min)	52.6 (46.3–59.0)[a]	45.4 (38.7–52.1)[a]	15.5 (– 11.0–28.1)[b]	.096
Stage REM (%)	12.5 (11.0–13.9)[a]	11.3 (9.7–12.9)[a]	2.0 (0.0–3.9)[a]	.246
NREM sleep duration (min)	373.1 (356.9–389.4)[a]	354.4 (334.3–374.6)[a]	26.1 (1.1–51.1)[a]	.093
Stage NREM (%)	87.5 (86.1–89.0)[a]	88.7 (87.2–90.3)[a]	–2.0 (– 3.9–0)[a]	.238
N1 sleep duration (min)	92.0 (73.8–110.2)[a]	58.8 (47.1–70.6)[a]	16.8 (–10.1–76.8)[b]	.005
Stage N1 (%)	21.9 (17.6–26.2)[a]	15.3 (11.9–18.6)[a]	5.3 (– 0.7–11.32)[a]	.017
N2 sleep duration (min)	221.5 (200.9–242.0)[a]	238.3 (219.7–256.9)[a]	–10.9 (– 43.4–21.5)[a]	.235
Stage N2 (%)	51.8 (47.7–56.0)[a]	59.6 (56.3–62.9)[a]	–8.0 (– 14.3–[– 1.6])[a]	.007
N3 sleep duration (min)	59.7 (46.0–73.3)[a]	57.3 (45.9–68.7)[a]	7.2 (– 11.6–26.0)[a]	.775
Stage N3 (%)	13.8 (10.9–16.7)[a]	13.9 (11.3–16.4)[a]	0.7 (– 3.6–4.9)[a]	.976
Endotypes				
LG	0.7 (0.7–0.8)[a]	0.6 (0.5–0.6)[a]	0.2 (0.1–0.2)[a]	<0.001
ArTH (%Veupnea)	202.9 (183.7–222.0)[a]	160.7 (143.9–177.4)[a]	38.6 (14.9–62.2)[a]	<0.001
Vpassive (%Veupnea)	51.5 (18.7–84.2)[b]	86.8 (67.4–93.7)[b]	–24.0 (– 33.8–[– 14.2])[a]	<0.001
Vcomp (%Veupnea)	2.3 (– 4.4–8.9)[a]	–1.7 (– 9.5–6.2)[a]	5.4 (– 3.6–14.5)[a]	.343

Abbreviations: AHI, apnea hypopnea index; AHI_{NREM}, apnea and hypopnea index in non-rapid eye movement stage; $AHI_{non\text{-}supine}$, apnea and hypopnea index in non-supine sleep position; AHI_{REM}, apnea and hypopnea index in rapid eye movement stage; ArI, arousal index; ArTH, arousal threshold; AHI_{supine}, apnea and hypopnea index in supine sleep position; BMI, body mass index; CT90, the cumulative time spent at oxygen saturation below 90% in total sleep time; LG, loop gain; $LSaO_2$, lowest oxygen saturation; $MSaO_2$, mean oxygen saturation; NREM, non-rapid eye movement ODI3, 3% oxygen desaturation index; $ODI3_{REM}$, 3% oxygen desaturation index in rapid eye movement stage; $ODI3_{NREM}$, 3% oxygen desaturation index in non-rapid eye movement stage; REM, rapid eye movement; TST, total sleep time.
[a]Data are presented as mean and 95%CI.
[b]Indicates data presented as median and first to third quartiles.

%; $p < .001$) and higher $MSaO_2$ (non-responders vs responders: 93.0 [91.0–94.0] vs 95.5 [94.3–96.0] %; $p < .001$) and $LSaO_2$ (non-responders VS responders: 67.8 [63.6–72.1] vs 78.5 [74.4–82.6] %; $p = .006$) than those of non-responders. Baseline AHI, ArI, TST, and sleep efficiency were not significantly different between the two groups. Baseline physiological endotype analysis indicated that responders had lower LG (non-responders vs responders: 0.7 [0.7–0.8] vs 0.6 [0.5–0.7]; $p = .047$; Figure 4, A) than that of non-responders. However, no significant differences were noted among the values of ArTH (non-responders vs responders: 208.0 [146.5–278.7] vs 158.4 [131.7–212.7] %Veupnea; $p = .167$; Figure 4, B), Vpassive (non-responders vs responders: 41.4 [10.1–83.4] vs 72.9 [40.7–89.5] %Veupnea; $p = .066$; Figure 4, C), and Vcomp (non-responders vs responders: 1.6 [−4.3–7.3] vs 13.9 [−13.3–24.0] %Veupnea; $p = .333$; Figure 4, D).

Analysis of post-surgery physiological endotypes (Supplementary Table S2) indicated that responders had significantly lower AHI (non-responders vs responders: 38.6 [32.9–44.3] vs 4.6 [3.0–6.1] events/h; $p < .001$), ODI3 (non-responders vs responders: 37.4 [31.5–43.3] vs 4.6 [2.7–6.5] events/h; $p < .001$), ArI (non-responders vs responders: 26.6 [18.8–37.2] vs 12.2 [8.2–15.7] events/h; $p = .002$), LG (non-responders vs responders: 0.6 [0.5–0.7] vs 0.4 [0.3–0.5]; $p = .001$), and ArTH (non-responders vs responders: 161.3 [129.7–210.8] vs 107.6 [104.6–115.3] %Veupnea, $p < .001$). In contrast, Vpassive (non-responders vs responders: 81.8 [59.6–89.8] vs 94.5 [91.1–97.2] %Veupnea, $p = 0.001$) and Vcomp (non-responders vs responders:−1.1 [−25.3–10.1] vs 6.6 [4.9–13.0] %Veupnea; $p = .027$) values were higher than non-responders.

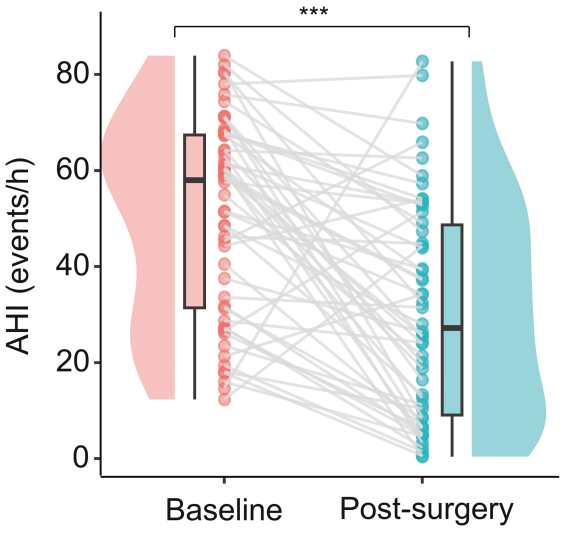


Figure 2. Effect of the multilevel upper airway surgery on AHI. AHI, apnea hypopnea index. *** indicates p-value < 0.001.

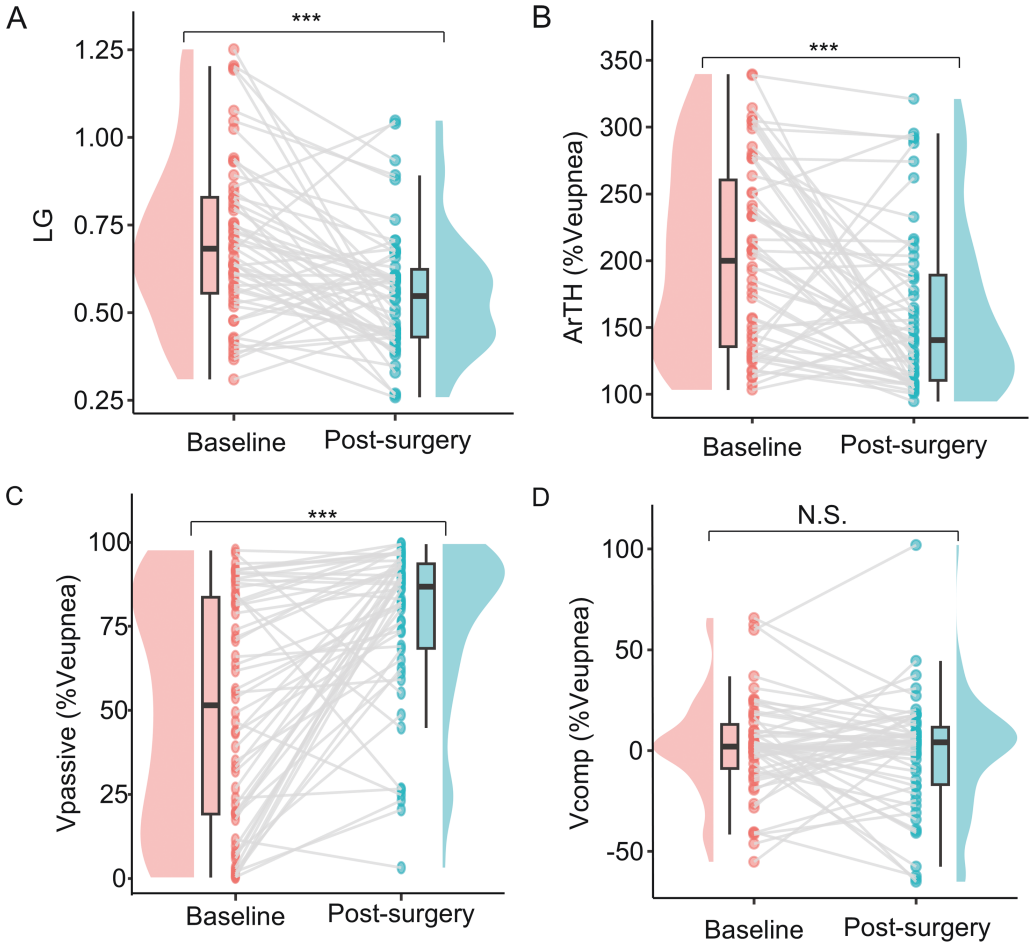


Figure 3. Effect of the multilevel upper airway surgery on OSA endotypes. A, B, C, and D demonstrate the effect of surgery on LG (A), ArTH (B), Vpassive (C), and Vcomp (D), respectively. ArTH, arousal threshold; LG, loop gain. N.S. indicates that the difference did not reach statistical significance; *** indicates p value < .001.

Effect of endotypic characteristics on predicting surgery responses

Each endotypic trait was incorporated into the model in the preliminary bivariate logistic regression analysis (Table 4). LG (OR [CI 95%], 0.4 [0.2–0.8]; $p = .018$) was significantly associated with surgical response, while ArTH, Vpassive, and Vcomp were not. After adjusting for AHI, similar results were obtained (Table 4 and Supplementary Figure S1).

Furthermore, AHI, all endotypic traits, and interactions were incorporated into the analysis model, and multivariate regression analyses were conducted. Results (Table 5 and Figure 5,A–F) indicated that a favorable response to surgery was independently associated with a lower LG (OR [CI 95%], 0.1 [0.0–0.5], $p = .032$, Figure 5, A), whereas ArTH, Vpassive, and Vcomp were not significantly associated with surgery response. Endotype interactions were also present; lower LG was associated with surgical response in patients with an improved Vcomp (Figure 5, E) or a more collapsible airway (lower Vpassive); higher LG was related to surgical success in patients with a decreased Vcomp (Figure 5, E) or a less collapsible airway (higher Vpassive, Figure 5, F). Supplementary Figures S2–S4 for slope plots of the model.

Predicting efficacy of the multivariable regression analyses

We used the multivariable regression model to predict surgery response, and the equation used for this purpose was:

$$\text{Logit(P)} = -1.3 \times \text{AHIBaseline} - 2.5 \times \text{LG} + 0.1 \times \text{ArTH} - 0.3 \times \text{Vpassive} - 0.4 \times \text{Vcomp} + 3.8 \times \text{LG} \times \text{Vpassive} - 2.5 \times \text{LG} \times \text{Vcomp}.$$

Table 3. Baseline sleep and enotypic characteristics of surgery non-responders and responders.

Baseline variables	Non-responders ($n = 40$)	Responders ($n = 14$)	Difference	p value
Age(y)	38.0(33.8–47.5)[b]	34.0(30.0–35.8)[b]	8.2(– 1.7–18.2)[a]	.034
Gender	38M:2F	10M:4F		.033
BMI (kg/m^2)	27.7(25.3–30.1)[b]	26.1(24.8–26.9)[b]	1.7(– 0.2–3.7)[a]	.003
AHI (events/h)	59.0(45.1–67.5)[b]	31.5(26.4–62.4)[b]	7.9(– 10.7–26.6)[a]	.110
AHI_{REM} (events/h)	54.9(45.5–64.6)[b]	45.3(27.0–61.0)[b]	2.0(– 18.2–22.3)[a]	.125
AHI_{NREM} (events/h)	59.6(46.2–68.2)[b]	36.0(24.2–62.3)[b]	6.3(– 14.5–27.0)[a]	.221
AHI_{Supine} (events/h)	57.2(15.0–67.1)[b]	40.5(17.0–66.5)[b]	–6.9(– 35.1–21.3)[a]	.913
$AHI_{Non\text{-}supine}$ (events/h)	55.8(36.6–69.2)[b]	23.7(14.4–59.6)[b]	17.2(– 1.5–36.0)[a]	.027
ODI3 (events/h)	55.2(48.2–62.3)[b]	39.9(26.6–53.2)[b]	9.8(– 10.4–30.0)[a]	.031
$ODI3_{REM}$ (events/h)	53.7(47.2–60.2)[b]	42.7(25.8–59.6)[b]	2.0(– 20.8–24.9)[a]	.141
$ODI3_{NREM}$ (events/h)	59.3(47.3–68.6)[b]	42.4(20.4–53.1)[b]	9.1(– 9.5–27.7)[a]	.046
ArI (events/h)	43.9(25.4–62.7)[b]	21.5(16.2–36.3)[b]	4.1(– 18.1–26.1)[a]	.064
$MSaO_2$ (%)	93.0(91.0–94.0)[b]	95.5(94.3–96.0)[b]	–1.3(– 3.0–0.4)[a]	<.001
$LSaO_2$(%)	67.8(63.6–72.1)[b]	78.5(74.4–82.6)[b]	–7.2(– 16.6–2.2)[a]	.006
CT90 (%)	18.7(10.5–35.5)[b]	2.9(1.1–6.4)[b]	10.4(– 2.5–23.3)[a]	<.001
TST (min)	426.3(405.7–447.0)[b]	426.6(402.2–451.0)[b]	–29.9(– 85.0–25.3)[a]	.989
Sleep Efficiency (%)	94.1(85.1–99.0)[b]	95.5(90.3–98.8)[b]	–5.0(– 15.9–5.9)[a]	.736
REM sleep duration (min)	54.1(47.4–60.7)[b]	52.5(36.4–68.5)[b]	–3.2(– 21.8–15.4)[a]	.974
Stage REM (%)	12.8(11.3–14.3)[b]	12.4(8.6–16.2)[b]	0.2(– 4.0–4.3)[a]	.955
N1 sleep duration (min)	81.8(35.4–133.3)[b]	65.5(36.5–102.4)[b]	15.3(– 40.6–71.2)[a]	.708
Stage N1 (%)	17.1(8.8–35.9)[b]	14.2(8.4–25.6)[b]	4.9(– 10.0–19.8)[a]	.686
N2 sleep duration (min)	223.7(198.5–249.0)[b]	222.9(184.4–261.3)[b]	–12.4(– 82.3–57.5)[a]	.936
Stage N2 (%)	52.1(47.1–57.1)[b]	52.4(44.0–60.8)[b]	–0.7(– 15.9–14.5)[a]	.879
N3 sleep duration (min)	42.5(22.6–84.8)[b]	52.0(23.9–88.5)[b]	–21.2(– 61.1–18.7)[a]	.813
Stage N3 (%)	11.3(5.2–20.8)[b]	13.5(6.2–18.7)[b]	–4.3(– 12.5–3.8)[a]	.767
Endotypes				
LG	0.7(0.7–0.8)[b]	0.6(0.5–0.7)[b]	0.1(– 0.1–0.3)[a]	.047
ArTH (%Veupnea)	208.0(146.5–278.7)[b]	158.4(131.7–212.7)[b]	25.4(– 40.8–91.7)[a]	.167
Vpassive (%Veupnea)	41.4(10.1–83.4)[b]	72.9(40.7–89.5)[b]	–14.5(– 45.5–16.6)[a]	.066
Vcomp (%Veupnea)	1.6(– 4.3–7.3)[b]	13.9(– 13.3–24.0)[b]	–6.0(– 29.5–17.5)[a]	.333

Abbreviations: AHI, apnea hypopnea index; AHI_{REM}, apnea and hypopnea index in rapid eye movement stage; AHI_{NREM}, apnea and hypopnea index in non-rapid eye movement stage; $AHI_{non\text{-}supine}$, apnea and hypopnea index in non-supine sleep position; ArI, arousal index; ArTH, arousal threshold; AHI_{supine}, apnea and hypopnea index in supine sleep position; BMI, body mass index; CT90, the cumulative time spent at oxygen saturation below 90% in total sleep time; LG, loop gain; $LSaO_2$, lowest oxygen saturation; $MSaO_2$, mean oxygen saturation; NREM, non-rapid eye movement ODI3, 3% oxygen desaturation index; $ODI3_{REM}$, 3% oxygen desaturation index in rapid eye movement stage; $ODI3_{NREM}$, 3% oxygen desaturation index in non-rapid eye movement stage; REM, rapid eye movement; TST, total sleep time.

[a]Data are presented as mean and 95%CI.

[b]Indicates data presented as median and first to third quartiles.

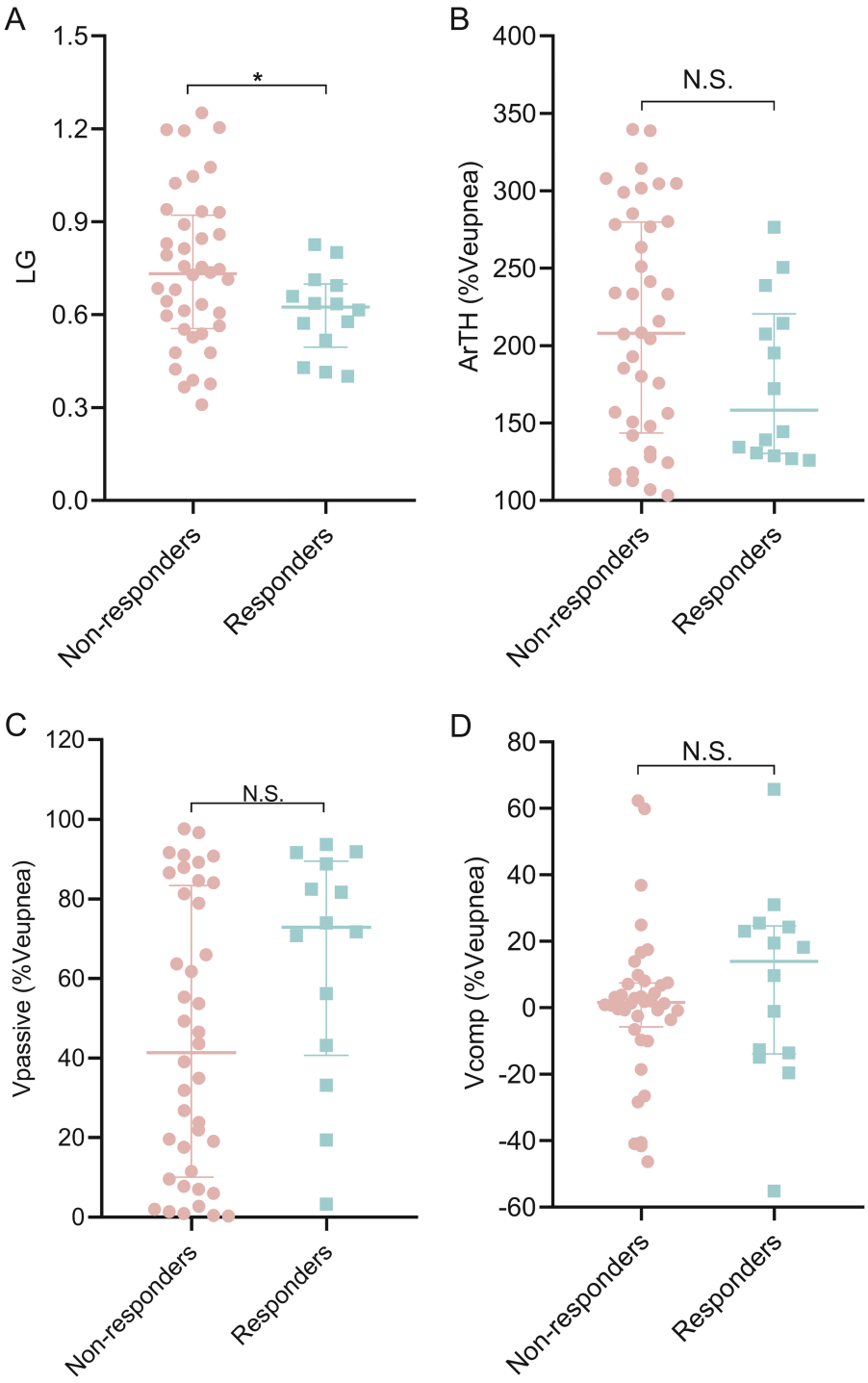


Figure 4. Endotypic differences between surgery responders and non-responders. A, B, C, and D demonstrate difference of LG (A), ArTH (B), Vpassive (C), and Vcomp (D), respectively, between surgery responders and non-responders. ArTH, arousal threshold; LG, loop gain. N.S. indicates that the difference did not reach statistical significance; *indicates p value < .05.

Predictive value of the multivariable regression model was assessed via receiver operating characteristic analysis, resulting in the AUC is 0.88 [0.78–0.98] (Supplementary Figure S5). Sensitivity and specificity were 75% and 88%, respectively. The model correctly identified 64.3% of responders based on its positive predictive value. In terms of negative predictive value, 92.5% of non-responders were correctly identified by the model. The AHI in predicted surgery responders was substantially reduced compared with that in predicted surgery non-responders (responders vs non-responders: 6.6 [2.9–27.8] vs 33.4 [18.2–53.2] events/h, p = .003, Supplementary Figure S6). The characteristics of the predicted responders and non-responders are described in Table 6.

Discussion

This study is the first to explore the effect of multilevel upper airway surgery on four key traits of OSA endotypes in Chinese individuals, and to compare baseline and post-surgery OSA endotypes

Table 4. Preliminary bivariate logistic regression analyses of upper airway surgery responds and endotypic characteristics.

Logistic regression analyses	Unadjusted model OR (CI 95%)	*p* Value	Model 1 OR (CI 95%)	*p* Value
LG	0.4 (0.2–0.8)	.018	0.5 (0.2–1.0)	.049
ArTH (%Veupnea)	0.6 (0.3–1.1)	.122	0.8 (0.3–1.9)	.593
Vpassive (%Veupnea)	1.9 (1.0–3.8)	.066	1.4 (0.5–4.0)	.487
Vcomp (%Veupnea)	1.3 (0.7–2.5)	.384	1.1 (0.6–22.2)	.695

In the unadjusted model, LG, ArTH, Vpassive, Vcomp was respectively included in the logistic regression model; Model 1 was further adjusted for AHI on the base of unadjusted model.
Abbreviation: ArTH, arousal threshold; LG, loop gain; OR values represent the odds of response per 1-SD increase in each endotype or endotypic interaction.

Table 5. Multivariate logistic regression analyses of upper airway surgery responds and endotypic characteristics.

Multivariate regression analyses	SD values of variables	OR (CI 95%)	*p* value
LG	0.1	0.1 (0.0–0.5)	.032
ArTH (%Veupnea)	70.2	1.1 (0.2–6.7)	.916
Vpassive (%Veupnea)	24.4	0.8 (0.1–7.0)	.787
Vcomp (%Veupnea)	34.0	0.7 (0.2–2.1)	.556
LG × Vpassive	12.0	43.9 (3.9–2764.5)	.018
LG × Vcomp	15.0	0.1 (0.0–0.5)	.033

This model included LG, ArTH, Vpassive, Vcomp, AHI, and the interactions in the logistic regression model.
Abbreviations: ArTH, arousal threshold; LG, loop gain; OR values represent the odds of response per 1-SD increase in each endotype or endotypic interaction.

between surgery responders and non-responders. Surgery altered both the anatomical and non-anatomical endotypes, specifically improving upper airway collapsibility, enhancing stability of the ventilation control system, and reducing the ArTH. Compared with that of non-responders, responders had lower baseline LG. A stable ventilation control system is a favorable determinant of surgical response. Endotypic interactions provide more specific interpretations. In patients with improved muscle compensation or a more collapsible airway (lower Vpassive), a lower LG was more predictive of success. However, in the presence of decreased muscle compensation or reduced collapsibility (higher Vpassive), a lower LG was less predictive of success. Furthermore, the sensitivity and specificity of this endotype-based model were 75% and 88%, respectively, with good accuracy in predicting the effects of upper airway surgery.

Our study observed that surgery substantially decreased LG and improved the stability of the ventilation control system. This is consistent with previous research conducted in the Chinese population, which showed that surgery significantly decreased LG [14]. High LG is induced, at least to some extent, in Chinese individuals with OSA and can be reduced by ameliorating hypoxemia and AHI [14]. However, Wong et al. [15] reported there was no significant reduction in LG before and after surgery. This inconsistency may be explained by the lower baseline AHI and the smaller reduction in AHI after treatment in the study by Wong et al. Moreover, different ethnic groups with OSA have distinct physiologic characteristics [25]. All participants involved in our study were ethnically Chinese, whereas Wong's study did not specify the participants' racial backgrounds, which may indicate differences in the racial composition between the two studies.

Upper airway surgery significantly decreased the ArTH in participants with OSA. Previous research has also indicated that the ArTH is significantly reduced by surgery [14, 26]. The severity of OSA has been strongly associated with the ArTH, which increases following discontinuation of CPAP and decreases immediately following the initiation of CPAP therapy, a trend that continues up until at least 3 months [27]. Upper airway surgery can significantly reduce the severity of OSA (as indicated by a lower AHI) [13] and subsequently decrease the ArTH [28–30]. Moreover, sleep fragmentation plays a major role in increasing the ArTH [28–30]. The ArI is the "gold standard" for detecting sleep fragmentation [31]. Our results indicated that surgery reduced ArI and improved sleep fragmentation, which may have decreased the ArTH. The combination of a decrease in AHI and ArI induced by surgery may explain the significant decrease in the ArTH post-surgery.

Multilevel upper airway surgery significantly improves upper airway collapsibility [13], as measured by increased Vpassive. However, surgery did not significantly alter the upper airway muscle compensation. These results indicated that although surgery induced tissue scarring and healing patterns while enlarging the upper airway [32], it did not disrupt upper airway muscle function or effectiveness.

Multilevel upper airway surgery cures only a subset of individuals with OSA, and predicting the treatment response remains challenging [33, 34]. Although surgical responders typically have specific anatomical features, the current criteria are not sufficiently accurate for clinical use [5]. Our results indicated that pathophysiological traits play a significant role in surgical response prediction, with promising implications for advanced patient selection and precision medicine. This study identified baseline endotypic traits, and their interactions were significantly associated with upper airway surgery response. A favorable response to surgery was independently associated with a lower LG. In patients with improved muscle compensation or a more collapsible airway (lower Vpassive), a lower LG was associated with a higher probability of surgical success. However, in the presence of decreased muscle compensation or reduced collapsibility (higher Vpassive), a lower LG was less predictive of success.

The current study indicated that the stability of the ventilation control system (lower LG) is independently associated with a favorable surgical response. Previous research has also indicated that higher LG is a significant determinant of residual OSA after upper airway surgery, which is more common in participants with mild OSA severity [26]. The surgery effect prediction model used in this study also included interactions between endotypic traits. The interaction between LG and upper airway collapsibility indicated that a higher LG and mild upper airway collapsibility were significant determinants of an unsuccessful surgical response. Studies have also indicated that higher LG is associated with unfavorable hypoglossal nerve stimulation or oral appliance response in patients with OSA [8, 9].

The current study highlights the importance of understanding endotypes in a clinical setting using baseline polysomnographic data, before proceeding with upper airway surgery. The selection of patients with OSA who receive surgical treatment is primarily based on Friedman, AHI, and DISE [35–41]; however, the long-term success rate of surgery is only 40%. This study constructed a predictive model for the effect of surgery based on baseline

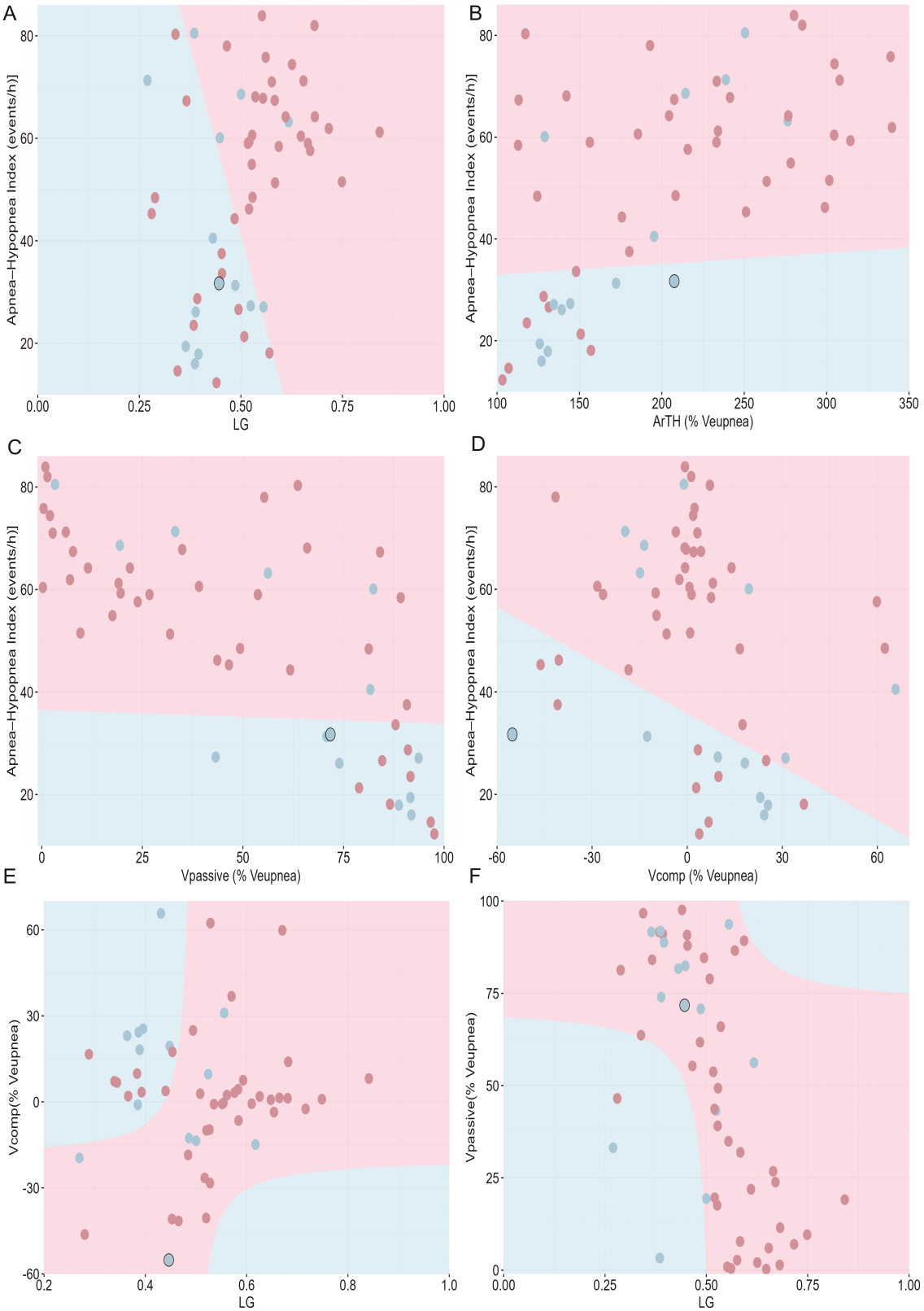


Figure 5. Two-trait cross-sectional "slices" of the five-dimensional multivariable logistic regression model. Each slice is a simplification of the full five-dimensional model; traits that are hidden from view are set to their mean value to facilitate presentation. Responders are indicated by blue circle dots and non-responders by pink circle dots. Open circles denote patients for whom the model simplification does not apply. For these patients, the two-dimensional prediction differs from the overall five-dimensional model prediction. Modeled response status is shown by the colored background (blue for predicted responders and pink for predicted non-responders). A–D represent the relationship of LG (A), ArTH (B), Vpassive (C), and Vcomp (D) respectively, with multilevel upper airway surgery response, independent of AHI; E and F represent the interaction between LG and Vcomp and their combined effect on the response to multilevel upper airway surgery, respectively. AHI, apnea hypopnea index; ArTH, arousal threshold; LG, loop gain.

Table 6. Changes in sleep and endotypic characteristics in predicted non-responders and predicted responders.

Characteristics	Predicted non-responders (n = 42)	Predicted responders (n = 12)	p value
$AHI_{Post\text{-}surgery}$ (events/h)	33.4 (18.2–53.2)[b]	6.6 (2.9–27.8)[b]	.003
$AHI_{Baseline}$ (events/h)	59.7 (45.1–67.9)[b]	27.0 (19.9–44.8)[b]	.008
AHI_{Change} (events/h)	20.9 (7.3–35.5)	18.9 (3.9–31.6)	.860
Age (y)	37.0 (33.0–49.3)[b]	34.5 (21.8–40.5)[b]	.042
Gender (M:F)	39:3	9:3	.224
BMI (kg/m^2)	27.4 (26.3–28.4)[a]	26.5 (25.4–27.6)[a]	.430
$MSaO_2$ (%)	93.0 (91.0–95.0)[b]	95.0 (94.0–96.0)[b]	.020
CT90 (%)	17.3 (6.4–35.5)[b]	3.2 (0.7–12.1)[b]	.008
LG	0.5 (0.5–0.6)[a]	0.4 (0.4–0.5)[a]	.07
ArTH (%Veupnea)	208.0 (140.2–277.1)[b]	147.6 (131.0–227.9)[b]	.176
Vcomp (%Veupnea)	1.3 (– 9.8–7.7)[b]	13.9 (– 9.7–24.8)[b]	.145
Vpassive (%Veupnea)	42.8 (11.0–82.8)[b]	76.4 (43.3–87.7)[b]	.096
ΔAHI ≥ 50% and treatment AHI < 10 events/h, Y:N	5:37	9:3	<.001
ΔAHI ≥ 50%, Y:N	16:26	9:3	.024

Abbreviations: AHI, apnea hypopnea index; $AHI_{Baseline}$, baseline apnea hypopnea index; AHI_{Change}, apnea hypopnea index difference between baseline and post-surgery; $AHI_{Post\text{-}surgery}$, post-surgery apnea hypopnea index; ArTH, arousal threshold; BMI, body mass index; CT90, the cumulative time spent at oxygen saturation below 90% in total sleep time; LG, loop gain; $MSaO_2$, mean oxygen saturation.
[a]Data are presented as mean and 95%CI.
[b]Indicates data presented as median and first to third quartiles.

endotypic characteristics. Predicted responders had significantly decreased postoperative AHI compared with that of predicted non-responders. The sensitivity and specificity of this model were 75% and 88 %, respectively. This study indicated that endotypes can be a useful approach for predicting surgical efficacy, thereby providing a theoretical foundation for precision medicine.

Limitations

Despite the novelty of our findings, several limitations of this study should be considered. First, the enrolled participants were all Chinese and predominantly male. Previous studies have indicated that physiological characteristics differ between races and sex [25, 42, 43], and our results should be interpreted with caution. Second, because craniomaxillofacial anatomical factors play a critical role in the pathogenesis of OSA in Chinese individuals, contributing to the difficulty in identifying those who may benefit from surgery. As a result, the overall success rate of upper airway surgery in our study was 26%, which is lower than that reported in other studies [5]. However, this real-world variability makes differences in patient characteristics more relevant in clinical practice. Third, the study participants were recruited over 9 years, but the results have not been cross-validated or externally validated on another dataset. Therefore, the results should be carefully interpreted, and validation in various research centers and larger samples is urgently needed. Fourth, the participants in this study appear to be relatively young, which may be another factor contributing to the differing results compared to previous studies. Fifth, this study did not include patients' self-reported symptoms, which remain fundamentally important in the context of clinical treatments. Future studies should consider the clinical symptoms. Moreover, the endotypic traits used in this study were derived from PSG data rather than gold standards; thus, the physiological insights drawn from this work should be interpreted with caution. However, PSG-derived endotypes have significant clinical potential, as they can be easily obtained and used to inform treatment decisions.

Conclusion

Our study demonstrated that multilevel upper airway surgery changed both anatomical and non-anatomical endotypic traits in the Chinese OSA population. A stable ventilation control system is a favorable determinant of surgical response. Moreover, endotypic interactions provide more specific interpretations. In patients with improved muscle compensation or a more collapsible airway (lower Vpassive), a lower LG was associated with a higher probability of surgical success. However, in the presence of decreased muscle compensation or reduced collapsibility (higher Vpassive), a lower LG was less predictive of success. Thus, our results provide a theoretical foundation for precision medicine.

Supplementary material

Supplementary material is available at *SLEEP* online.

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Author contributions

The corresponding authors are responsible for the authenticity of the data. All authors made a significant contribution to the work reported. X.T.W., S.Y.Y., W.J.H., J.G., H.L.Y., and S.K.Y. contributed to the study design, manuscript drafting, revision, and critical review of the article. T.J.Z., J.Y.Z., E.H.Z., H.M.Z., and W.J.H. contributed to data collection. X.T.W., W.J.H., S.L., H.M.Z., S.Y.Y., S.K.Y., and H.L.Y. contributed to the statistical analyses. All authors approved the final version of the manuscript to be published; they agreed on submission to this journal. All authors have agreed to be accountable for all aspects of the work.

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Disclosure Statements

Financial disclosure: All authors declared no conflict of interest. *Non-financial disclosure:* None.

Conflict of Interests

The authors declare that they have no competing interests.

Ethical Approval and Consent to Participate

This study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. (Approval No: 2019-KY-050[K]) and was registered at the Chinese Clinical Trial Registry (No. ChiCTR1900025714).

Consent for Publication

We obtained informed consent from all subjects.

Data Availability

The data include medical records and personal information and therefore the data can only be shared within the confinements of the China legislation and ethical conventions. Reasonable requests considering data sharing will be individually assessed.

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