Received: 31 October 2021 | Accepted: 21 April 2022

DOI: 10.1111/resp.14280

ORIGINAL ARTICLE

Official Journal of the Asian Pacific Society of Respirology
Respirology APSR WILEY

Examining the impact of multilevel upper airway surgery on the obstructive sleep apnoea endotypes and their utility in predicting surgical outcomes

Ai-Ming Wong[1,2] | Shane A. Landry[3,4] | Simon A. Joosten[1,2] | Luke D. J. Thomson[3,4] | Anthony Turton[1] | Jeremy Stonehouse[1] | Darren R. Mansfield[1,4] | Glen Burgess[5,6] | Andrew Hays[5] | Scott A. Sands[7,8] | Christopher Andara[3] | Caroline J. Beatty[3,4] | Garun S. Hamilton[1,2] | Bradley A. Edwards[3,4]

[1]Monash Lung, Sleep, Allergy & Immunology, Monash Health, Monash Medical Centre, Melbourne, Victoria, Australia

[2]School of Clinical Sciences, Monash University, Melbourne, Victoria, Australia

[3]Department of Physiology, Biomedicine Discovery Institute, Monash University, Melbourne, Victoria

[4]School of Psychological Sciences and Turner Institute for Brain and Mental Health, Monash University, Melbourne, Victoria

[5]Department of Ear, Nose and Throat, Monash Health, Melbourne, Australia

[6]Department of Surgery, School of Clinical Sciences, Monash University, Melbourne, Victoria, Australia

[7]Division of Sleep and Circadian Disorders, Department of Medicine and Neurology, Brigham & Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

[8]Department of Allergy, Immunology and Respiratory Medicine and Central Clinical School, The Alfred and Monash University, Melbourne, Victoria, Australia

Correspondence
Bradley A. Edwards
Email: bradley.edwards@monash.edu

Funding information
Heart Foundation of Australia Future Leader Fellowship, Grant/Award Number: 101167; NHMRC Early Career Fellowship, Grant/Award Number: 1139745; Monash University

Associate Editor: M. Safwan Badr; **Senior Editor:** Chris Grainge

Abstract

Background and objective: Upper airway surgery for obstructive sleep apnoea (OSA) is an alternative treatment for patients who are intolerant of continuous positive airway pressure (CPAP). However, upper airway surgery has variable treatment efficacy with no reliable predictors of response. While we now know that there are several endotypes contributing to OSA (i.e., upper airway collapsibility, airway muscle response/compensation, respiratory arousal threshold and loop gain), no study to date has examined: (i) how upper airway surgery affects all four OSA endotypes, (ii) whether knowledge of baseline OSA endotypes predicts response to surgery and (iii) whether there are any differences when OSA endotypes are measured using the CPAP dial-down or clinical polysomnographic (PSG) methods.

Methods: We prospectively studied 23 OSA patients before and ≥3 months after multilevel upper airway surgery. Participants underwent clinical and research PSG to measure OSA severity (apnoea–hypopnoea index [AHI]) and endotypes (measured in supine non-rapid eye movement [NREM]). Values are presented as mean ± SD or median (interquartile range).

Results: Surgery reduced the AHI_{Total} (38.7 [23.4 to 79.2] vs. 22.0 [13.3 to 53.5] events/h; $p = 0.009$). There were no significant changes in OSA endotypes, however, large but variable improvements in collapsibility were observed (CPAP dial-down method: Δ1.9 ± 4.9 L/min, $p = 0.09$, $n = 21$; PSG method: Δ3.4 [−2.8 to 49.0]%$V_{eupnoea}$, $p = 0.06$, $n = 20$). Improvement in collapsibility strongly correlated with improvement in AHI (%$\Delta AHI_{SupineNREM}$ vs. Δcollapsibility: $p < 0.005$; $R^2 = 0.46$–0.48). None of the baseline OSA endotypes predicted response to surgery.

Conclusion: Surgery unpredictably alters upper airway collapsibility but does not alter the non-anatomical endotypes. There are no baseline predictors of response to surgery.

KEYWORDS
obstructive sleep apnoea, OSA endotypes, predictor, upper airway surgery, ventilation

Garun S. Hamilton and Bradley A. Edwards contributed equally to this study.

This study was previously accepted as a conference abstract at the Annual Conference of American Thoracic Society (ATS) 2020.

INTRODUCTION

Upper airway surgery is a second-line treatment for patients with obstructive sleep apnoea (OSA) who are unable to tolerate continuous positive airway pressure (CPAP) and/or oral appliance therapy. While surgery may be curative, response to surgery is unpredictable and many patients have residual OSA post-surgery.[1–4] A key issue faced by clinicians is that there are no reliable clinical predictors to accurately identify patients who are suitable for surgery a priori, leading to unsuccessful and unnecessary surgery in many.

Recent works show that OSA is caused by multiple interactive physiological endotypes (anatomical and non-anatomical—i.e., airway muscle responsiveness/compensation, respiratory arousal threshold and loop gain [LG]).[5,6] Moreover, knowledge of the baseline OSA endotypes can improve prediction of the response to OSA treatments. For example, using the CPAP dial-down method to measure the OSA endotypes, Edwards et al.[7] reported that baseline upper airway collapsibility and LG were independent predictors of the reduction in apnoea–hypopnoea index (AHI) to oral appliance therapy. Similar findings have been observed when analysing the OSA endotypes measured from clinical polysomnography (PSG).[8,9] Furthermore, there is accumulating evidence that comprehensive knowledge of the factors contributing to OSA pathogenesis has strong potential for predicting and explaining responses to non-CPAP OSA treatments.[7,8,10,11]

Little is known about how upper airway surgery affects the OSA endotypes. Only one study[12] has measured upper airway collapsibility (using the pharyngeal critical closing pressure [P_{crit}] technique) in 13 patients undergoing uvulopalatopharyngoplasty (UPPP). This study demonstrated highly variable changes in upper airway collapsibility with surgery, and greater improvements in collapsibility were associated with therapeutic response. However, no baseline clinical, polysomnographic or physiological factors were able to predict response to surgery. No measurements of the non-anatomical endotypes were available for interpretation at the time, and the presence/severity of these non-anatomical factors may explain the variable responses to UPPP. More recently, work by our group and others have utilised the newer techniques using data extracted from clinical PSGs to measure an individual's LG before and after surgery.[13–15] Such studies have shown that an elevated LG was associated with a poorer surgical outcome. However, to date, no study has assessed: (i) how surgery impacts all *four* OSA endotypes simultaneously, (ii) whether knowledge of these endotypes can aid prediction of surgical success/failure, and (iii) whether the answers to (i) and (ii) vary if OSA endotypes are measured using either the CPAP dial-down or extracted from clinical PSG methods.

Accordingly, we aimed to use both gold standard (CPAP dial-down) and clinical (PSG) endotyping methods to systematically assess the effect of upper airway surgery on the endotypes causing OSA (Aim 1), determine if knowledge of baseline OSA endotypes can predict response to surgery (Aim 2) and whether there is any variation in results when using OSA endotypes measured via either method (Aim 3).

SUMMARY AT A GLANCE

This is the first study to measure how upper airway surgery affects all *four* obstructive sleep apnoea (OSA) endotypes using both the continuous positive airway pressure dial-down and clinical polysomnographic methods. Using either method, surgery unpredictably altered the upper airway anatomy/collapsibility and did not alter the non-anatomical endotypes. None of the baseline OSA endotypes were able to predict the response to surgery.

METHODS

Study participants

This was a prospective study of patients with documented OSA (AHI ≥ 15 events/h) who underwent multilevel upper airway surgery (majority received palate-based surgery) and at least one other type (nasal surgery, tonsillectomy, and/or tongue-based surgery); further details on the types of upper airway surgery received by each patient are provided in Appendix S1 in the Supporting Information. Patients unable to tolerate (or who refused) CPAP or oral appliance therapy were recruited from an Ear, Nose and Throat (ENT) clinic (Monash Health) between February 2017 and August 2018. Patient suitability and type of surgery were determined and performed by one of the three ENT surgeons. Patients were excluded if they had prior palate and/or tongue-based surgery.

Experimental design and setup

Participants underwent: (a) baseline clinical PSG to measure OSA severity and four OSA endotypes (i.e., extracted from clinical PSG)[16–18] and (b) research PSG to measure OSA endotypes (i.e., CPAP dial-down method).[19] Questionnaires including the Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ) were obtained, as well as baseline anthropomorphic and blood pressure measurements. All measurements were repeated ≥12 weeks after surgery.

Two trained sleep technicians (blinded to study intervention) scored and staged the PSGs according to standard criteria.[20] Hypopnoeas were defined as a ≥30% reduction in airflow from baseline, associated with a ≥3% oxygen desaturation and/or arousal (≥3 s).

Measuring the OSA endotypes

Detailed description of the methods for measuring the endotypes (via CPAP dial-downs and extracted from clinical PSG) are provided in Appendix S1 and Figures S1 and S2 in the Supporting Information. Briefly, the OSA endotypes (listed below) were measured using both techniques in supine non-rapid eye movement (NREM) sleep:

1. Upper airway collapsibility—$V_{passive}$ and V_{active}
2. Muscle compensation—V_{Comp}
3. Respiratory arousal threshold
4. LG

The CPAP dial-down method provided a measure of steady-state LG (Loop gain$_{_CPAP}$), whereas the clinical PSG method provided a measure of dynamic LG, reported here as LG at the natural cycling frequency (i.e., frequency of periodic breathing if breathing was unstable) (Loop gain$_{_PSG}$). We also measured LG at 1 cycle/min (LG_1) using the clinical PSG method (see Appendix S1 in the Supporting Information).

Statistical analysis

Statistical analysis was conducted using GraphPad Prism 8 (Dotmatics, Boston, MA) and STATA (Version 12, StataCorp, 2013, College Station, Texas) with $p < 0.05$ considered significant. All data were tested for normality using Shapiro–Wilk testing. Values are expressed as means ± SD or medians (interquartile range [IQR]) unless stated otherwise. Paired *t*-tests or Wilcoxon signed-rank tests were used to assess the effect of surgery on the OSA endotypes/PSG variables as appropriate.

Correlation analyses were performed to examine the relationships between: (a) the change in OSA endotypes vs. $\%\Delta AHI_{SupineNREM}$, and to compare (b) OSA endotypes measured using the CPAP dial-down and obtained from clinical PSG methods.

Participants were categorized as 'responders' if post-treatment AHI reduced by ≥50% from baseline with post-treatment AHI < 10 events/h using AHI_{Total} and $AHI_{SupineNREM}$, given the CPAP dial-down method measures endotypes in the supine position. As a secondary outcome, participants were defined as 'responders' if their post-treatment AHI reduced by ≥50% from its baseline value only. Due to lack of participants fulfilling the stricter responder definition to enable meaningful analysis, the secondary responder definition is reported—i.e., Criteria #1 (post-treatment AHI_{Total} reduced by ≥50% from baseline) and Criteria #2 (post-treatment $AHI_{SupineNREM}$ reduced by ≥50% from baseline).

Independent samples *t*-tests or Mann–Whitney *U*-tests were used to assess differences between responders and non-responders as appropriate.

Sample size and power calculations

The number of participants to be studied for Aim 1 was based on a power analysis to detect a difference in upper airway collapsibility following UPPP using the data of Schwartz et al.,[12] the only study known at the time to have examined the impact of upper airway surgery on any OSA endotype measured using the CPAP dial-down technique. A sample size of 18 OSA patients is required to detect a reduction of 3.3 ± 5.4 cm H_2O in upper airway collapsibility with 80% power and an alpha of 0.05. Additionally, only two studies[13,14] have examined how multilevel upper airway surgery impacts the non-anatomical endotypes measured from clinical PSG (i.e., LG and arousal threshold). Using data from these studies, a sample size of 7–21 patients is required to detect a significant difference in LG and arousal threshold with 80% power and an alpha of 0.05. Furthermore, based on the data of Joosten et al.,[13] a total of six responders and 12 non-responders are required to detect a significant difference in LG. Therefore, we aimed to recruit 30 participants in order to allow for participant attrition (∼20%).

RESULTS

Participant demographics

Twenty-three participants were included in the final analysis (Figure 1). All participants received a minimum of two surgical procedures simultaneously, with only two participants having had prior nasal surgery (Tables S1 and S2 in the Supporting Information describe nasoendoscopy findings and provide a list of surgical procedures undertaken).

Effect of surgery on sleep, patient-reported outcomes and OSA endotypes

Baseline patient demographics are presented in Table 1. The effects of surgery on sleep architecture, sleep-disordered breathing and OSA endotypes are summarized in Tables 2 and 3.

As a group, surgery was associated with a reduction in overall AHI ($p = 0.009$) (Figure 2A) and improvement in patient-reported symptom scores (ESS improved by a median of 5.0 [IQR −6.0 to −2.0, $p < 0.001$]; FOSQ [total score] by a median of 9.3 [IQR 0.75 to 22.1, $p = 0.001$]) (see Figure S3 in the Supporting Information).

Assessing endotypes measured using both CPAP dial-down and extracted from clinical PSG methods, there was a trend towards an improvement in upper airway collapsibility ($V_{passive\_CPAP}$ [Δ1.9 ± 4.9 L/min, $p = 0.09$] and $V_{passive\_PSG}$ [Δ3.4 −2.8 to 49.0%$V_{eupnoea}$, $p = 0.06$]; Figure 2B), however, the effect was highly variable between individuals. In particular, 10 of 21 (47.6%) participants had an improvement in upper airway collapsibility, two of 21 (9.5%) participants had no significant change (i.e., <10%

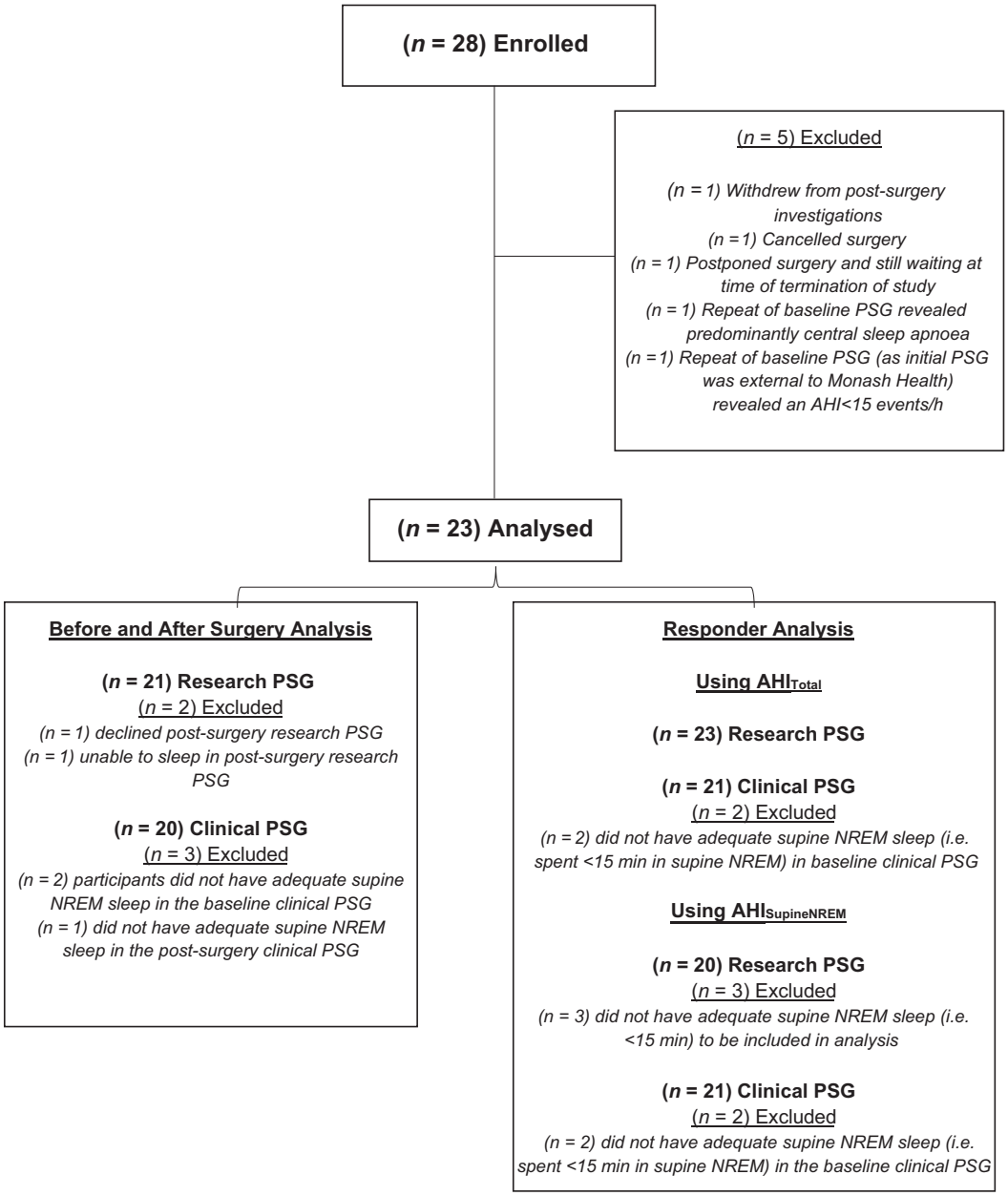

FIGURE 1 Flow diagram of enrolment, exclusion criteria and final cohort included in the analysis. Initially, 28 participants were enrolled; however, only 23 had adequate data to be included in the final analysis. AHI, apnoea–hypopnoea index; NREM, non-rapid eye movement; PSG, polysomnography

difference from baseline) and nine of 21 (42.9%) participants experienced a significant decline in upper airway collapsibility. There were no significant differences between baseline and post-surgery values for the non-anatomical endotypes using either measurement (Table 3).

Predictors of response to surgery

Using post-treatment AHI_{Total} ≥ 50% reduction from baseline (Criteria #1), seven of 23 (30.4%) were responders. Using post-treatment $AHI_{SupineNREM}$ ≥ 50% reduction from baseline (Criteria #2), seven of 20 (35.0%) were classified as responders. None of the individual baseline OSA endotypes were predictive of surgical success using either Criteria #1 or #2 (see Tables 4 and S3–S5 in the Supporting Information for further details).

Relationship between the changes in OSA endotype and OSA severity

Twenty participants (87%) achieved adequate supine NREM sleep (≥15 min) during their pre- and post-surgery clinical (i.e., diagnostic) PSGs to be utilised in the analysis comparing the change in OSA endotypes (derived from the clinical PSG) versus $\%\Delta AHI_{SupineNREM}$. Repeating the analyses using the OSA endotypes derived from the research PSG

TABLE 1 Baseline patient characteristics

Variable	Value	$n = 23$	%
Age, years	46.5 ± 14.1		
Tried CPAP prior to surgery		14	60.9
Using CPAP prior to surgery		8	34.8
Modified Mallampati position, score, *n*, %	1	1	4.3
	2	6	26.1
	3	13	56.5
	4	3	13.1
Friedman tonsil size, grade, *n*, %	0	1	4.3
	1	6	26.1
	2	7	30.4
	3	7	30.4
	4	2	8.7
Gender, male %		18	78.3
BMI, kg/m^2	31.3 ± 5.2		
ASA, category, *n* (%)	1	2	8.7
	2	20	87.0
	3	1	3.3
	4	0	0.0

Note: Values are provided as mean ± SD.
Abbreviations: ASA, American Society of Anesthesiologists physical status classification; BMI, body mass index; CPAP, continuous positive airway pressure.

was limited to 18 participants (78.3%), as two participants did not have a complete set of measurements pre- and post-surgery. The $\%\Delta AHI_{SupineNREM}$ was strongly correlated with the improvement in upper airway collapsibility (i.e., $\Delta V_{passive}$ [$p < 0.005$; $R^2 = 0.46$–0.48; see Figure S4 in the Supporting Information] and ΔV_{active} [CPAP: $p = 0.007$, $R^2 = 0.42$; clinical PSG: $p = 0.01$, $R^2 = 0.31$]) using both techniques. Furthermore, the $\%\Delta AHI_{SupineNREM}$ was correlated with the reduction in arousal threshold (CPAP: $p = 0.03$, $R^2 = 0.28$; clinical PSG: $p = 0.01$, $R^2 = 0.31$). There were no other statistically significant correlations seen between the change in the other OSA endotypes and $\%\Delta AHI_{SupineNREM}$.

Comparison of OSA endotype estimates with both techniques

The anatomical OSA endotypes (i.e., $V_{passive}$ and V_{active}) measured with the CPAP dial-down technique correlated with values measured from the clinical PSG technique ($p < 0.001$; $R^2 = 0.32$ for $V_{passive}$ and $R^2 = 0.42$ for V_{active}). However, no significant relationships were observed between the non-anatomical endotypes.

DISCUSSION

This is the first study to measure the effect of upper airway surgery on OSA endotypes using two different techniques. Using either measurement, large changes in upper airway collapsibility were observed in either direction. There was a trend towards overall improvement; however, this did not reach statistical significance due to large inter-individual variability. Notably, the degree of improvement in collapsibility was strongly related to the improvement in OSA severity. Furthermore, surgery did not systematically alter the non-anatomical endotypes and there were no baseline endotypic predictors of surgical response.

Upper airway collapsibility: Upper airway collapsibility is the key determinant in the development of OSA.[5] Compared to Schwartz et al.'s study[12] that examined one type of upper airway surgery (i.e., UPPP), multilevel surgery (our study) had a more variable response on collapsibility (current study's coefficient of variation [COV] for $\Delta P_{crit} = 221.7\%$ vs. Schwartz et al.'s COV for $\Delta P_{crit} = 122.9\%$), despite a similar average change in collapsibility (current study's average $\Delta P_{crit} = -2.7$ cm H_2O vs. Schwartz et al.'s average $\Delta P_{crit} = -3.3$ cm H_2O). The variable surgeries within the current study may have resulted in more variable outcomes. However, we also found that similar to Schwartz et al.,[12] the response to surgery was determined by the magnitude of improvement in upper airway collapsibility rather than by the degree of collapsibility at baseline. Therefore, despite the increased variability seen, both studies arrived at the same conclusions, whereby upper airway surgery has a large but variable effect on collapsibility, and the response to surgery was determined by the magnitude of improvement in collapsibility.

The variability in upper airway collapsibility following surgery appears to be greater than what is observed with oral appliance therapy, another OSA treatment known to improve OSA by decreasing upper airway collapsibility. Unlike oral appliance therapy whereby mandibular advancement improved collapsibility in all patients,[21] 11 of 21(52.3%) participants in the current study experienced a worsening in collapsibility following surgery. Thus, surgery appears to have a heterogenous effect on upper airway collapsibility which may explain why it is difficult in our study to predict the response to surgery a priori using baseline physiological or clinical measures.

Loop gain: Our study confirms previous findings[13] that surgery does not alter LG (assessed using either technique). Furthermore, our findings are consistent with previous studies that have examined the impact that other common OSA therapies have on OSA endotypes (oral appliance[7] and lateral positioning[10]). Specifically, such interventions are known to alter the degree of anatomical compromise but have no impact on the non-anatomical endotypes.

However, there is also evidence to the contrary. Li et al.[14] reported a significant decrease in LG following surgery (i.e., Han-UPPP). These patients had more severe OSA and had a greater reduction in AHI post-surgery relative to the current study. Hypoxia is known to increase LG.[22] Patients in Li et al.'s study[14] had higher LGs at baseline (potentially

TABLE 2 Clinical characteristics of all patients ($n = 23$) before and after upper airway surgery

Parameter	Before surgery ($n = 23$)	After surgery ($n = 23$)	p-value
Sleep characteristics			
Time in bed (min)	449.9 ± 44.7	443.9 ± 46.9	0.59
Total sleep time (min)	364.3 ± 66.1	373.0 ± 57.1	0.52
Sleep efficiency (%)	83.2 (73.9–90.3)	87.4 (80.0–92.1)	0.16
N1 duration (min)	52.0 (33.0–97.5)	49.0 (28.5–88.5)	0.07
N2 duration (min)	191.8 ± 62.4	198.3 ± 45.6	0.53
N3 duration (min)	50.8 ± 35.3	51.7 ± 36.6	0.85
REM duration (min)	52.4 ± 21.7	60.4 ± 18.5	0.12
Supine NREM duration (min)	142.3 ± 108.4	162.2 ± 99.4	0.40
Lowest SpO_2 (%)	82 (76–87)	87 (84–89)	**0.002**
ODI 3% (events/h)	26.70 (16.9–70.3)	16.9 (6.3–33.4)	**0.002**
Obstructive apnoea index (events/h)	4.5 (1.1–19.7)	0.8 (0.0–27.2)	0.16
Hypopnoea index (events/h)	20.5 (15.3–32.7)	14.9 (8.6–24.1)	**0.03**
Respiratory arousal index (events/h)	40.4 (23.7–79.8)	22.0 (13.3–53.5)	**0.01**
Total AHI (events/h)	38.7 (23.4–79.2)	22.0 (13.3–53.5)	**0.009**
AHI REM (events/h)	37.1 (21.1–68.1)	20.7 (9.9–41.9)	**0.01**
AHI NREM (events/h)	44.5 (22.3–81.5)	22.2 (12.9–53.8)	**0.01**
Supine NREM AHI (events/h)	85.7 (55.3–100.6)	45.7 (24.2–83.5)	**0.0006**
Patient-reported symptom scores			
ESS	10.0 (7.0–15.0)	6.0 (2.0–10.0)	**<0.001**
FOSQ (total score)	75.2 (55.6–87.4)	87.9 (75.6–95.7)	**0.001**
HADS (depression)	6.0 (3.0–10.0)	3.0 (0.0–7.0)	**0.01**
HADS (anxiety)	6.0 (3.0–11.0)	4.0 (2.0–8.0)	0.11
Variables and anthropomorphic measurements			
BMI (kg/m^2)	31.3 ± 5.2	30.8 ± 5.4	0.18
Weight (kg)	94.5 ± 15.2	93.5 ± 15.2	0.33
Neck circumference (cm)	40.1 ± 2.6	38.6 ± 2.1	**0.002**
Hip circumference (cm)	109.5 ± 10.7	106.6 ± 9.2	0.06
Waist circumference (cm)	105.2 ± 11.9	106.0 ± 13.1	0.66
Average SBP measured on the night of clinical PSG (mm Hg)	125 ± 13	124 ± 12	0.80
Average DBP measured on the night of clinical PSG (mm Hg)	79 ± 8	76 ± 11	0.36

Note: Values are provided as mean ± SD or median (IQR). Significant comparisons at $p < 0.05$ before versus after surgery. Paired t-tests were used for parametric data and Wilcoxon matched-pairs signed-rank test for non-parametric paired data.

Abbreviations: AHI, apnoea–hypopnoea index; BMI, body mass index; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; N1, Stage 1 sleep; N2, Stage 2 sleep; N3, Stage 3 sleep; NREM, non-REM; ODI, oxygen desaturation index; PSG, polysomnography; REM, rapid eye movement; SBP, systolic blood pressure; SpO_2, peripheral capillary oxygen saturation.

driven by greater hypoxia, median $LG_{\_PSG}$ 0.70 [0.58–0.80]) and thus had greater capacity for change in LG. The majority of our participants had a relatively low LG at baseline (mean $LG_{\_PSG}$ 0.45 ± 0.13). It is therefore possible that an absence of change post-operatively was due to a 'floor effect'.

Overall, there was no significant difference before and after surgery for the majority of the non-anatomical endotypes, and majority of the observed effect sizes for the non-anatomical endotypes were quite small (see Table 3, Cohen's d column). Thus, it is unlikely that insufficient power or sample size explain the non-significant statistical findings.

The current work did not identify any physiological predictors of treatment success. The lack of identifiable predictors of surgical response is in contrast with prior studies which have demonstrated that the presence of high LG is a predictor of poor surgical response.[13,15] The reasons for the discrepancies between studies are unclear.

Although our study has a lower sample size than earlier studies,[13–15] based on data from Schwartz et al.,[12] our study was adequately powered (required $n = 18$) to detect an improvement in upper airway collapsibility, as well as for LG and arousal threshold (required $n = 7$–21).[13,14] The

TABLE 3 Physiological characteristics of all patients ($n = 23$) before and after upper airway surgery

Parameter	Before surgery	After surgery	*p*-value	Cohen's *d*
Physiological characteristics (CPAP dial-down technique) $n = 23$				
$V_{eupnoea\_CPAP}$ (L/min)	6.7 ± 1.3	6.7 ± 1.4, $n = 21$	0.92	0
$V_{passive\_CPAP}$ (L/min)	−1.7 ± 3.8	0.2 ± 4.6, $n = 21$	0.09	0.45
V_{active_CPAP} (L/min)	1.5 ± 2.4, $n = 22$	1.9 ± 3.4, $n = 18$	0.59	0.13
Muscle compensation, V_{Comp_CPAP} (L/min)	2.7 (0.9 to 4.0), $n = 22$	2.5 (0.6 to 3.6), $n = 18$	0.67	0.01
Arousal threshold$_{_CPAP}$ (L/min)	10.4 (7.6 to 13.7), $n = 22$	11.9 (9.5 to 17.1), $n = 18$	0.15	0.31
Loop gain$_{_CPAP}$	2.9 (1.8 to 4.2), $n = 22$	4.2 (3.2 to 5.4), $n = 18$	0.14	0.30
Physiological characteristics (derived from the clinical PSG), $n = 20$				
$V_{passive\_PSG}$ (%$V_{eupnoea}$)	33.8 (0 to 75.4)	74.0 (2.9 to 83.8)	0.058	0.69
V_{active_PSG} (%$V_{eupnoea}$)	32.0 (0 to 92.4)	93.2 (0 to 103.6)	**0.048**	0.84
Muscle compensation, V_{Comp_PSG} (%$V_{eupnoea}$)	0.0 (−5.5 to 6.7)	0.0 (−2.5 to 4.3)	0.78	0
Arousal threshold$_{_PSG}$ (%$V_{eupnoea}$)	186.1 (135.8 to 224.9), $n = 19$	156.4 (133.6 to 195.0)	0.20	0.48
Loop gain$_{_PSG}$	0.45 ± 0.13, $n = 19$	0.45 ± 0.12	0.99	0

Note: Values are provided as mean ± SD or median (IQR). Significant comparisons at $p < 0.05$ before versus after surgery within responders and non-responders. Independent samples *t*-tests were used for parametric data and Mann–Whitney *U*-tests for non-parametric data.
Abbreviations: CPAP, continuous positive airway pressure; IQR, interquartile range; PSG, polysomnography.

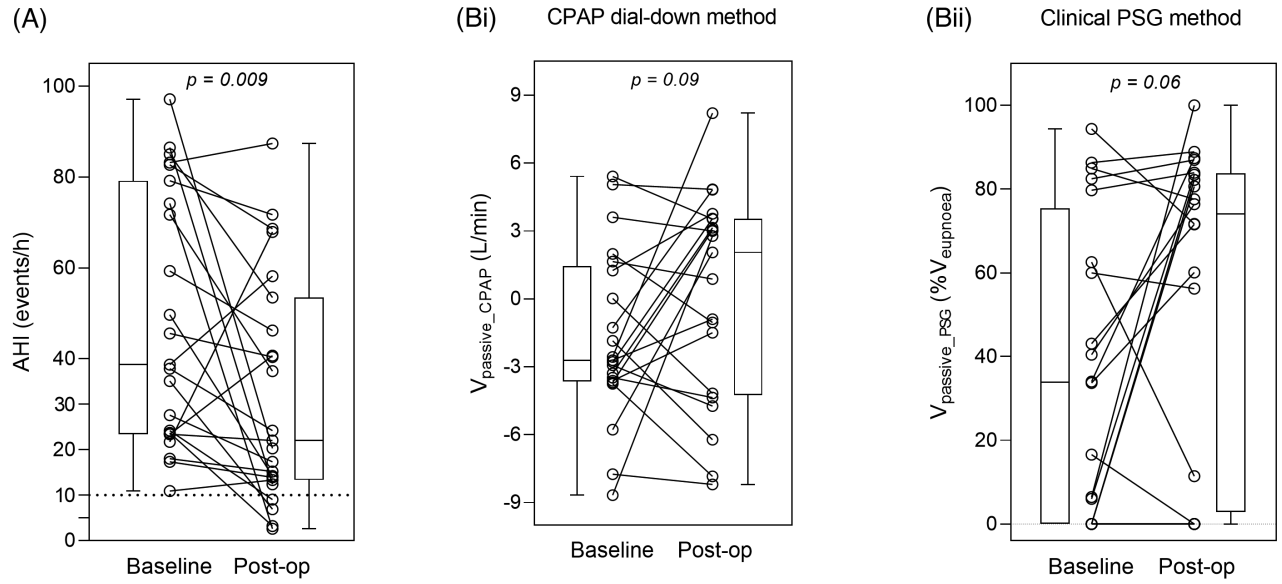

FIGURE 2 The effects of upper airway surgery on sleep and physiological variables. (A) Upper airway surgery significantly reduced the AHI; however, the effect was variable between individuals (Wilcoxon matched-pairs signed-rank test, $p = 0.009$). (B) There was a trend towards an improvement in upper airway collapsibility with upper airway surgery using either measurement (CPAP dial-down [$V_{passive\_CPAP}$, L/min] or extracted from clinical PSG [$V_{passive\_PSG}$, %$V_{eupnoea}$] methods); however, the effect was variable between individuals (paired *t*-test, $p = 0.09$ and Wilcoxon test, $p = 0.06$ in (i) and (ii), respectively). Note, a higher value on either *y*-axis indicates a less collapsible airway. AHI, apnoea–hypopnoea index; CPAP, continuous positive airway pressure; PSG, polysomnography; $V_{passive}$, upper airway collapsibility

lower effect size (*d*) observed in our study (P_{crit}: $d = 0.51$ vs. Schwartz et al.,[12] $d = 0.70$) appears to be due to greater inter-individual variability in the improvement of upper airway collapsibility, rather than by the lesser mean changes observed pre- and post-surgery. Furthermore, based on Joosten et al.,[13] our study was adequately powered to detect a difference in LG between responders and non-responders (required $n = 16$). However, we observed a substantially lower effect size (Loop gain$_{_PSG}$: $d = 0.14$) than Joosten et al.[13] ($d = 1.53$). It is therefore possible that the previous studies overestimated the true effect sizes for any effect of surgery.

A core strength of the current work is that the OSA endotypes were extracted and compared using two established methodologies, with similar results. Although the way in which all the OSA endotypes are measured is different (i.e., CPAP dial-down vs. from clinical PSG) and the observation that the non-anatomical endotypes (obtained using

TABLE 4 Physiological characteristics of surgical responders and non-responders before upper airway surgery (responder definition: Criteria #1: post-treatment AHI_{Total} ≥ 50% reduction from baseline)

Physiological characteristics (derived by the CPAP dial-down technique), $n = 23$			
Parameter	**Responders ($n = 7$)**	**Non-responders ($n = 16$)**	***p*-value**
$V_{eupnoea\_CPAP}$ (L/min)	7.01 (5.0–7.4)	6.2 (5.8–7.7)	0.67
$V_{passive\_CPAP}$ (L/min)	−0.7 ± 3.6	−2.2 ± 3.9	0.41
V_{active_CPAP} (L/min)	1.6 ± 1.6	1.5 ± 2.7	0.93
Muscle compensation, V_{Comp_CPAP} (L/min)	2.2 (0.4–6.9)	2.7 (1.0–4.1), $n = 15$	0.37
Arousal threshold$_{_CPAP}$ (L/min)	13.3 (9.7–15.9)	9.5 (7.1–12.2), $n = 15$	0.19
Loop gain$_{_CPAP}$	2.5 (1.9–4.9)	3.1 (1.6–4.1), $n = 15$	0.84
Physiological characteristics (derived from the clinical PSG), $n = 21$			
Parameter	**Responders ($n = 7$)**	**Non-responders ($n = 14$)**	***p*-value**
$V_{passive\_PSG}$ (%$V_{eupnoea}$)	34.0 (6.0–79.7)	37.0 (0–67.5)	0.81
V_{active_PSG} (%$V_{eupnoea}$)	38.4 (19.1–97.6)	24.4 (0–86.9)	0.48
Muscle compensation, V_{Comp_PSG} (%$V_{eupnoea}$)	2.6 ± 14.0	−4.6 ± 27.1	0.52
Arousal threshold$_{_PSG}$ (%$V_{eupnoea}$)	186.5 ± 39.5	183.8 ± 48.3, $n = 13$	0.90
Loop gain$_{_PSG}$	0.43 (0.40–0.56)	0.44 ± 0.14, $n = 13$	0.99

Note: Values are provided as mean ± SD or median (IQR). Significant comparisons at $p < 0.05$ before versus after surgery within responders and non-responders. Independent samples *t*-tests were used for parametric data and Mann–Whitney *U*-tests for non-parametric data.
Abbreviations: AHI, apnoea–hypopnoea index; CPAP, continuous positive airway pressure; IQR, interquartile range; PSG, polysomnography.

either method) may not correlate in a linear fashion, the conclusions yielded are similar; specifically, (1) there was a trend to improvement in the anatomical OSA endotypes with surgery, but there was no change in the non-anatomical endotypes before and after surgery; and (2) baseline OSA endotypes by either method did not predict response to multilevel upper airway surgery.

Interestingly, while the anatomical OSA endotypes measured using either method were correlated, the non-anatomical endotypes were not. These findings are contrary to what has been shown in the validation studies.[17,18] Reasons for this disparity are not entirely clear but may be due to methodological differences: steady-state LG and dynamic LG are conceptually different variables[18] and arousal threshold values were previously validated against oesophageal data.[17] Nevertheless, despite the lack of correlation between the methods for non-anatomical endotypes, the key conclusions drawn from these measures are similar. The consistent findings across methods provide some support for the use of the simpler PSG methods to detect group-level changes in OSA endotypes in future research, but the absence of associations between methods means that our results do not provide clear support for the use of non-anatomical PSG endotypes as a replacement for CPAP dial-down methods at this time.

In conclusion, the current study is the first to examine how upper airway surgery altered all four OSA endotypes using both the CPAP dial-down and clinical PSG methods. Using either method, the results demonstrated that surgery has no effect on the non-anatomical endotypes causing OSA, and that patients who benefit the most from surgery are the ones who gained the greatest improvement in upper airway collapsibility—improvements in OSA and upper airway collapsibility were strongly correlated. However, surgery can potentially worsen upper airway collapsibility and thus OSA, and knowledge of the OSA endotypes pre-operatively did not predict the response to surgery in this cohort.

AUTHOR CONTRIBUTION

Ai-Ming Wong: Conceptualisation (supporting); formal analysis (lead); investigation (lead); methodology (equal); project administration (lead); writing – original draft (lead); writing – review and editing (lead). **Shane A. Landry:** Conceptualisation (supporting); formal analysis (equal); investigation (supporting); methodology (equal); software (supporting); supervision (supporting); writing – review and editing (equal). **Simon A. Joosten:** Conceptualisation (equal); methodology (equal); supervision (supporting); writing – review and editing (equal). **Luke D. J. Thomson:** Formal analysis (supporting); writing – review and editing (supporting). **Anthony Turton:** Formal analysis (supporting); writing – review and editing (supporting). **Jeremy Stonehouse:** Formal analysis (supporting); writing – review and editing (supporting). **Darren R. Mansfield:** Conceptualisation (supporting); methodology (supporting); supervision (supporting); writing – review and editing (supporting). **Glen Burgess:** Resources (supporting); writing – review and editing (supporting). **Andrew Hays:** Resources (supporting); writing – review and editing (supporting). **Scott A. Sands:** Software (supporting); writing – review and editing (supporting). **Christopher Andara:** Formal analysis (supporting); writing – review and editing (supporting). **Caroline J. Beatty:** Formal analysis (supporting); writing – review and editing (supporting). **Garun S. Hamilton:**

Conceptualisation (equal); methodology (lead); resources (lead); supervision (lead); writing – review and editing (equal). **Bradley A. Edwards:** Conceptualisation (lead); formal analysis (equal); investigation (supporting); methodology (lead); resources (lead); software (lead); supervision (lead); writing – review and editing (equal).

ACKNOWLEDGEMENTS

The authors wish to thank the participants for contributing to the current study.

Research funding: Dr Ai-Ming Wong was supported by an RTP Stipend by Monash University for graduate research studies. Dr Simon A. Joosten is supported by an NHMRC Early Career Fellowship (1139745). Associate Professor Bradley A. Edwards was supported by a Heart Foundation of Australia Future Leader Fellowship (101167). Open access publishing facilitated by Monash University, as part of the Wiley – Monash University agreement via the Council of Australian University Librarians.

CONFLICTS OF INTEREST

Associate Professor Garun S. Hamilton and Dr Simon A. Joosten have received equipment to support research from ResMed, Phillips Respironics and Air Liquide Healthcare. Associate Professor Bradley A. Edwards was supported by a Heart Foundation Future Leader Fellowship (101167) and has received grant funding from Apnimed and personal fees from Signifier Medical outside the current work. Dr Joosten is supported by an NHMRC Early Career Fellowship (1139745). Dr Scott A. Sands has consulted for Apnimed, Nox Medical and Merck; has received grant support from Apnimed, Prosomnus and Dynaflex; and may receive royalties from intellectual property relating to medications for sleep apnoea licenced by his Institution to Apnimed; and his industry interactions are managed by Brigham and Women's Hospital. All other authors have no financial or non-financial conflicts to disclose and do not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

DATA AVAILABILITY STATEMENT

Individual de-identified participant data can be shared on reasonable request following personal communication.

HUMAN ETHICS APPROVAL DECLARATION

The study was approved by the Monash Health Human Research Ethics Committee (16207A) and participants gave written informed consent prior to enrolment.

Clinical trial registration: ACTRN12616001514493 at the Australia New Zealand Clinical Trials Registry (ANZCTR) www.anzctr.org.au

ORCID

Ai-Ming Wong https://orcid.org/0000-0002-8325-705X
Shane A. Landry https://orcid.org/0000-0002-9041-3655
Simon A. Joosten https://orcid.org/0000-0002-7909-8025
Luke D. J. Thomson https://orcid.org/0000-0001-5568-775X
Darren R. Mansfield https://orcid.org/0000-0002-0565-9846
Caroline J. Beatty https://orcid.org/0000-0002-0808-1429
Garun S. Hamilton https://orcid.org/0000-0002-1744-2839
Bradley A. Edwards https://orcid.org/0000-0001-9383-1644

REFERENCES

1. Sundaram S, Lim J, Lasserson TJ. Surgery for obstructive sleep apnoea in adults. Cochrane Database of Systematic Reviews. 2005. https://doi.org/10.1002/14651858.cd001004.pub2
2. Browaldh N, Nerfeldt P, Lysdahl M, Bring J, Friberg D. SKUP3 randomised controlled trial: polysomnographic results after uvulopalatopharyngoplasty in selected patients with obstructive sleep apnoea. Thorax. 2013;68(9):846–53.
3. Stuck BA, Ravesloot MJL, Eschenhagen T, de Vet HCW, Sommer JU. Uvulopalatopharyngoplasty with or without tonsillectomy in the treatment of adult obstructive sleep apnea – a systematic review. Sleep Med. 2018;50:152–65.
4. MacKay S, Carney AS, Catcheside PG, Chai-Coetzer CL, Chia M, Cistulli PA, et al. Effect of multilevel upper airway surgery vs medical management on the apnea-hypopnea index and patient-reported daytime sleepiness among patients with moderate or severe obstructive sleep apnea: the SAMS randomized clinical trial. JAMA. 2020;324(12):1168–79.
5. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. Am J Respir Crit Care Med. 2013;188(8):996–1004.
6. Eckert DJ, Malhotra A. Pathophysiology of adult obstructive sleep apnea. Proc Am Thorac Soc. 2008;5(2):144–53.
7. Edwards BA, Andara C, Landry SA, Sands SA, Joosten SA, Owens RL, et al. Upper-airway collapsibility and loop gain predict the response to oral appliance therapy in patients with obstructive sleep apnea. Am J Respir Crit Care Med. 2016;194(11):1413–22.
8. Bamagoos A, Cistulli P, Sutherland K, Madronio M, Eckert D, Hess L, et al. Polysomnographic endotyping to select obstructive sleep apnea patients for oral appliances. Ann Am Thorac Soc. 2019;16:1422–31.
9. Op de Beeck S, Dieltjens M, Azarbarzin A, Willemen M, Verbraecken J, Braem MJ, et al. Mandibular advancement device treatment efficacy is associated with polysomnographic endotypes. Ann Am Thorac Soc. 2020;18:511–8.
10. Joosten SA, Edwards BA, Wellman A, Turton A, Skuza EM, Berger PJ, et al. The effect of body position on physiological factors that contribute to obstructive sleep apnea. Sleep. 2015;38(9):1469–78.
11. Sands SA, Edwards BA, Terrill PI, Butler JP, Owens RL, Taranto-Montemurro L, et al. Identifying obstructive sleep apnoea patients responsive to supplemental oxygen therapy. Eur Respir J. 2018;52(3):1800674.
12. Schwartz AR, Schubert N, Rothman W, Godley F, Marsh B, Eisele D, et al. Effect of uvulopalatopharyngoplasty on upper airway collapsibility in obstructive sleep apnea. Am Rev Respir Dis. 1992;145(3):527–32.
13. Joosten SA, Leong P, Landry SA, Sands SA, Terrill PI, Mann D, et al. Loop gain predicts the response to upper airway surgery in patients with obstructive sleep apnea. Sleep. 2017;40(7). https://doi.org/10.1093/sleep/zsx094
14. Li Y, Ye J, Han D, Zhao D, Cao X, Orr J, et al. The effect of upper airway surgery on loop gain in obstructive sleep apnea. J Clin Sleep Med. 2019;15(6):907–13.
15. Li Y, Ye J, Han D, Cao X, Ding X, Zhang Y, et al. Physiology-based modeling may predict surgical treatment outcome for obstructive sleep apnea. J Clin Sleep Med. 2017;13(9):1029–37.

16. Sands S, Edwards B, Terrill P, Taranto Montemurro L, Azarbarzin A, Marques M, et al. Phenotyping pharyngeal pathophysiology using polysomnography in patients with obstructive sleep apnea. Am J Respir Crit Care Med. 2018;197(9):1187–97.
17. Sands SA, Terrill PI, Edwards BA, Taranto Montemurro L, Azarbarzin A, Marques M, et al. Quantifying the arousal threshold using polysomnography in obstructive sleep apnea. Sleep. 2018;41(1):zsx183.
18. Terrill PI, Edwards BA, Nemati S, Butler JP, Owens RL, Eckert DJ, et al. Quantifying the ventilatory control contribution to sleep apnoea using polysomnography. Eur Respir J. 2015;45(2):408–18.
19. Wellman A, Edwards BA, Sands SA, Owens RL, Nemati S, Butler J, et al. A simplified method for determining phenotypic traits in patients with obstructive sleep apnea. J Appl Physiol (1985). 2013;114(7):911–22.
20. Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, et al. AASM scoring manual updates for 2017 (version 2.4). J Clin Sleep Med. 2017;13(5):665–6.
21. Bamagoos AA, Cistulli PA, Sutherland K, Ngiam J, Burke PGR, Bilston LE, et al. Dose-dependent effects of mandibular advancement on upper airway collapsibility and muscle function in obstructive sleep apnea. Sleep. 2019;42(6):zsz049.
22. Edwards BA, Sands SA, Owens RL, White DP, Genta PR, Butler JP, et al. Effects of hyperoxia and hypoxia on the physiological traits responsible for obstructive sleep apnoea. J Physiol. 2014;592(20):4523–35.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Wong A-M, Landry SA, Joosten SA, Thomson LDJ, Turton A, Stonehouse J, et al. Examining the impact of multilevel upper airway surgery on the obstructive sleep apnoea endotypes and their utility in predicting surgical outcomes. Respirology. 2022;27(10):890–9. https://doi.org/10.1111/resp.14280