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

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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: \( \Delta 1.9 \pm 4.9 \ L/min, \ p = 0.09, \ n = 21 \); PSG method: \( \Delta 3.4 \ [2.8 to 49.0]\% V_{eupnoea}, \ p = 0.06, \ n = 20 \)). Improvement in collapsibility strongly correlated with improvement in AHI (%ΔAHI/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
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. 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]). 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. 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). 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.

Little is known about how upper airway surgery affects the OSA endotypes. Only one study has measured upper airway collapsibility (using the pharyngeal critical closing pressure [Pcrit] 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.

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 (Aim 2) and whether there is any variation in results when using OSA endotypes measured via either method (Aim 3).

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) and (b) research PSG to measure OSA endotypes (i.e., CPAP dial-down method). 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. 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—\( V_{\text{passive}} \) and \( V_{\text{active}} \)
2. Muscle compensation—\( V_{\text{Comp}} \)
3. Respiratory arousal threshold
4. LG

The CPAP dial-down method provided a measure of steady-state LG (Loop gain\(_{\text{CPAP}}\)), 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\(_{\text{PSG}}\)). 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. \( \% \Delta \text{AHISupineNREM} \), 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 \( \geq 50\% \) from baseline with post-treatment AHI \( < 10 \) events/h using AHI\(_{\text{Total}}\) and AHI\(_{\text{SupineNREM}}\), 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 \( \geq 50\% \) 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\(_{\text{Total}}\) reduced by \( \geq 50\% \) from baseline) and Criteria #2 (post-treatment AHI\(_{\text{SupineNREM}}\) reduced by \( \geq 50\% \) 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\(_2\)O in upper airway collapsibility with 80% power and an alpha of 0.05. Additionally, only two studies\(^{3,14}\) 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 (\( V_{\text{passive,CPAP}} \) [\( \Delta 1.9 \pm 4.9 \) L/min, \( p = 0.09 \]) and \( V_{\text{passive,PSG}} \) [\( \Delta 3.4 \pm 2.8 \) to \( 49.0\% \text{V_{apnoea},} \ 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%...
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 $\text{AHI}_{\text{Total}} \geq 50\%$ reduction from baseline (Criteria #1), seven of 23 (30.4\%) were responders. Using post-treatment $\text{AHI}_{\text{SupineNREM}} \geq 50\%$ 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 $\%\Delta\text{AHI}_{\text{SupineNREM}}$. Repeating the analyses using the OSA endotypes derived from the research PSG

![Flow diagram of enrolment, exclusion criteria and final cohort included in the analysis.](image-url)
Compared to Schwartz et al.’s study, another study 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 $\Delta P_{\text{crit}} = 221.7\%$ vs. Schwartz et al.’s COV for $\Delta P_{\text{crit}} = 122.9\%$), despite a similar average change in collapsibility (current study’s average $\Delta P_{\text{crit}} = -2.7\text{ cm H}_2\text{O}$ vs. Schwartz et al.’s average $\Delta P_{\text{crit}} = -3.3\text{ cm H}_2\text{O}$). The variable surgeries within the current study may have resulted in more variable outcomes. However, we also found that similar to Schwartz et al., 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, $\text{11/21(52.3\%)}$ 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 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 and lateral positioning). 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. 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. Patients in Li et al.’s study had higher LGs at baseline (potentially

### 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/m²                | 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 $\%\Delta AHI_{\text{SupineNREM}}$ was strongly correlated with the improvement in upper airway collapsibility (i.e., $\Delta V_{\text{passive}} [p < 0.005; R^2 = 0.46–0.48]$; see Figure S4 in the Supporting Information) and $\Delta V_{\text{active}} [CPAP: p = 0.007, R^2 = 0.42$; clinical PSG: $p = 0.01, R^2 = 0.31)]$ using both techniques. Furthermore, the $\%\Delta AHI_{\text{SupineNREM}}$ 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 $\%\Delta AHI_{\text{SupineNREM}}$.

### Comparison of OSA endotype estimates with both techniques

The anatomical OSA endotypes (i.e., $V_{\text{passive}}$ and $V_{\text{active}}$) measured with the CPAP dial-down technique correlated with values measured from the clinical PSG technique ($p < 0.001; R^2 = 0.32$ for $V_{\text{passive}}$ and $R^2 = 0.42$ for $V_{\text{active}}$). 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. Compared to Schwartz et al.’s study, 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 $\Delta P_{\text{crit}} = 221.7\%$ vs. Schwartz et al.’s COV for $\Delta P_{\text{crit}} = 122.9\%$), despite a similar average change in collapsibility (current study’s average $\Delta P_{\text{crit}} = -2.7\text{ cm H}_2\text{O}$ vs. Schwartz et al.’s average $\Delta P_{\text{crit}} = -3.3\text{ cm H}_2\text{O}$). The variable surgeries within the current study may have resulted in more variable outcomes. However, we also found that similar to Schwartz et al., 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, 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 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 and lateral positioning). 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. 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. Patients in Li et al.’s study had higher LGs at baseline (potentially...
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. The reasons for the discrepancies between studies are unclear.

Although our study has a lower sample size than earlier studies based on data from Schwartz et al., 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 $n = 7–21$). The
lower effect size \((d)\) observed in our study \((P_{\text{crit}}: d = 0.51\) 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 \((\text{required } n = 16)\). However, we observed a substantially lower effect size \((\text{Loop gain}_{\text{PSG}}: d = 0.14)\) 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 \((i.e., \text{CPAP dial-down vs. from clinical PSG})\) and the observation that the non-anatomical endotypes \((\text{obtained using})\)
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 preoperatively 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 Anda: 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).

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**CONFLICTS OF INTEREST**

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**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

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