https://doi.org/10.5664/jcsm.8920

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

A randomized controlled trial of oxygen therapy for patients who do not respond to upper airway surgery for obstructive sleep apnea

Simon A. Joosten, MBBS, PhD[1,2,3,*]; Michael Tan, MBBS[1,*]; Ai-Ming Wong, MBBS, PhD [1,2]; Shane A. Landry, PhD[4,5]; Paul Leong, MBBS[1,2]; Scott A. Sands, PhD[6,7]; Caroline Beatty, BA[4,5]; Luke Thomson, RPSGT[4,5]; Jeremy Stonehouse, BSc[1]; Anthony Turton, BSc[1]; Garun S. Hamilton, MBBS PhD[1,2,3]; Bradley A. Edwards, PhD[4,5]

*[1]Monash Lung and Sleep, Monash Medical Centre, Clayton, Victoria, Australia; [2]School of Clinical Sciences, Monash University, Melbourne, Victoria, Australia; [3]Monash Partners–Epworth, Melbourne, Victoria, Australia; [4]Department of Physiology, School of Biomedical Sciences and Biomedical Discovery Institute, Monash University, Melbourne, Victoria, Australia; [5]Turner Institute for Brain and Mental Health, Monash University, Melbourne, Victoria, Australia; [6]Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham & Women's Hospital & Harvard Medical School, Boston, Massachusetts; [7]The Alfred and Monash University, Melbourne, Victoria, Australia; *Contributed equally.*

Study Objectives: We aimed to determine whether patients diagnosed with obstructive sleep apnea (OSA) who fail to respond to upper airway surgery may be successfully treated with supplemental oxygen and whether we could identify baseline physiologic endotypes (ie, collapsibility, loop gain, arousal threshold, and muscle compensation) that predict response to oxygen therapy.

Methods: We conducted a single night, randomized double-blinded cross over trial in which patients with OSA who failed to respond to upper airway surgery were treated on separate nights with oxygen therapy (4 L/min) or placebo (medical air). Effect of oxygen/air on OSA on key polysomnography outcomes were assessed: apnea-hypopnea index (AHI), AHI without desaturation (ie, flow-based AHI), arousal index, and morning blood pressure. OSA endotypes were estimated from the polysomnography signals to determine whether baseline OSA physiology could be used to predict response to oxygen therapy.

Results: There was a statistically significant reduction in AHI and flow-based AHI on oxygen vs placebo (flow-based AHI: 42.4 ± 21.5 vs 30.5 ± 17.1 events/h, P = .008). Arousal index was also reduced on oxygen vs placebo (41.1 ± 19.5 vs 33.0 ± 15.3 events/h, P = .006). There was no significant difference in morning blood pressure between oxygen and placebo. Although 7 of 20 individuals experienced a 50% reduction or greater in flow-based AHI on oxygen (responders), there was no difference in the baseline OSA endotypes (or clinical characteristics) between responders and nonresponders.

Conclusions: Our findings demonstrate that a proportion of patients who fail to respond to upper airway surgery for OSA respond acutely to treatment with supplemental oxygen.

Clinical Trial Registration: Registry: Australian New Zealand Clinical Trials Registry; Name: Oxygen therapy for treating patients with residual obstructive sleep apnea following upper airway surgery; URL: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373566; Identifier: ACTRN12617001361392.

Keywords: obstructive sleep apnea, sleep apnea syndromes, treatment, oxygen inhalation therapy

Citation: Joosten SA, Tan M, Wong A-M, et al. A randomized controlled trial of oxygen therapy for patients who do not respond to upper airway surgery for obstructive sleep apnea. *J Clin Sleep Med*. 2021;17(3):445–452.

BRIEF SUMMARY

Current Knowledge/Study Rationale: There is mounting evidence that patients may fail to respond to upper airway surgery for obstructive sleep apnea because of the presence of a number of nonanatomic endotypic traits, in particular an elevated loop gain. Treatments that target loop gain may be used to salvage treatment for patients who fail to respond to upper airway surgery.

Study Impact: This randomized controlled trial is the first to demonstrate that supplemental oxygen therapy can be used to acutely improve obstructive sleep apnea metrics after failure to respond to upper airway surgery. Predicting patient responses to treatments for obstructive sleep apnea remains an ongoing challenge for the field.

INTRODUCTION

Upper airway surgery is a frequently used second-line obstructive sleep apnea (OSA) treatment, and it has the potential to cure OSA without the need for ongoing device adherence. However, surgery often fails to completely resolve OSA, and more than one third of patients have ongoing respiratory events at a significant rate.[1,2] As such, there has been an intense focus on identifying factors that may predict surgery outcomes and salvage treatments that may be used subsequent to surgical failure. Importantly, there are currently no randomized controlled trials investigating treatment options specifically for patients who fail to respond to upper airway surgery.

OSA is known to be caused by a combination of anatomic and nonanatomic factors.[3] The main nonanatomic endotypes that are thought to contribute to OSA include the following: elevated loop gain (unstable respiratory control), low arousal threshold, and poor upper airway dilator muscle effectiveness. Importantly, upper airway surgery is an anatomic treatment that enlarges the retroglossal airway by reducing and/or tightening

soft tissue structures in the upper airway. For patients who do not respond to upper airway surgery, the treatment failure must be caused by 1 or more of the following: (1) the anatomical defect is too severe to be overcome by surgery or (2) surgery improves the anatomy, but the ongoing presence of nonanatomic pathophysiologic factors means that there is ongoing OSA.

One of the most important nonanatomic contributors to OSA pathogenesis is an unstable ventilatory control system (ie, high loop gain). Loop gain is an engineering term that describes the inherent stability/instability of a feedback loop system. In a ventilatory control system that has a high loop gain, any respiratory disturbance will be amplified and perpetuated, leading to ventilatory instability. Conversely in a system with a low loop gain, any disturbance will be dampened out, and breathing will naturally stabilize. Up to 36% of patients with OSA have an elevated loop gain, and patients with OSA with more favorable upper airway collapsibility tend to have a higher loop gain.[4] In such individuals, interventions specifically targeted to lower loop gain (eg, oxygen[5] or acetazolamide[6]) may improve OSA severity. Furthermore, recent developments have allowed for the quantification of loop gain from clinical polysomnographic (PSG) recordings, opening the possibility for easily measuring loop gain in clinical populations: a critical key step in identifying candidates for such novel therapies.[7,8]

The effect of surgery on loop gain has been explored in 2 studies to date, with conflicting results.[9,10] We previously demonstrated that elevated loop gain at baseline is a predictor of surgical failure; however, in our study, surgery did not alter loop gain. Conversely, recent research by Li et al[10] (in a cohort of Asian patients with more severe OSA who had larger reductions in OSA severity after upper airway surgery) demonstrated that loop gain is reduced by upper airway surgery. The suggestion in the study of Li et al is that at least part of a patient's elevated loop gain is because of the intermittent hypoxia induced by OSA itself and that amelioration of the OSA from surgery can reduce this acquired portion of elevated loop gain. This raises the prospect that patients who fail to respond to upper airway surgery for OSA may have an elevated loop gain that could be targeted with treatments such as oxygen or acetazolamide.

To determine whether patients who fail to respond to upper airway surgery may be successfully treated with oxygen (a loop gain–lowering treatment), we conducted a single night, randomized double-blinded crossover trial in which patients with OSA who failed to respond to upper airway surgery were treated on separate nights with oxygen therapy or placebo (medical air). We also aimed to determine what factors could be used to predict patients who are likely to respond to oxygen therapy.

METHODS

Participants

Patients were recruited into the study if they were >18 years of age, had a previous diagnosis of OSA, had undergone upper airway surgery treatment for OSA (consisting of a combination of one or more of septal or turbinate surgery, palatal surgery, tongue surgery and adenoidectomy, and tonsillectomy) and had failed to have a complete surgical response, which was defined by a reduction in apnea-hypopnea index (AHI) to a level less than 10 events/h. As such, participants enrolled in the study all had a pre- and postsurgery PSG.

Patients were identified for this study in 2 ways: (1) patients enrolled in a previous study of surgery for OSA were contacted, and (2) patients were identified through interrogation of the hospital records for upper airway surgery, and this list was cross-referenced with a list of patients who had a diagnostic PSG to identify patients who have had surgery and a pre- and postsurgery PSG (**Figure 1**).

Patients gave written, informed consent before enrollment, and the study was approved by the Monash Health Human Research Ethics Committee (RES-17-0000-165A). The trial was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12617001361392).

Study design

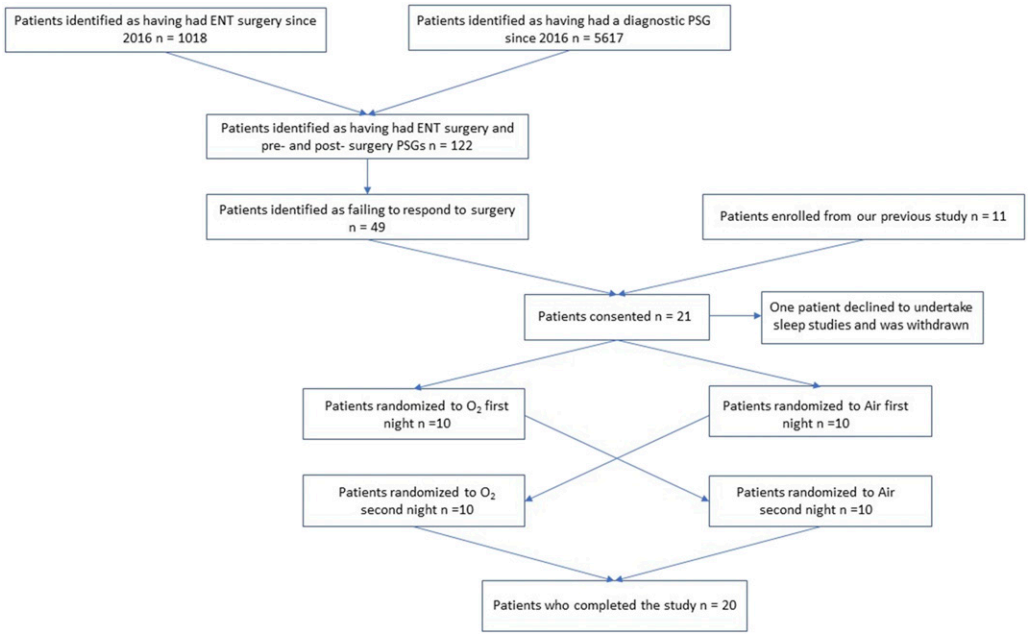
We used a single night intervention, placebo-controlled double-blinded crossover study design in which participants were randomized to first receiving active intervention (supplemental oxygen, 4 L/min) or placebo (medical air, 4 L/min). A member of the team not involved in participant enrollment and outcome assessment generated the allocation sequence using an online random number generator. Participants and outcomes assessors (sleep scoring) were blinded to treatment allocation. Patients underwent both interventions during clinical sleep studies, conducted at least 1 week apart. The primary outcome for the study was AHI (specifically, flow-based AHI [AHI_{fb}] without desaturation criteria) on oxygen vs the AHI_{fb} on air (placebo treatment); standard AHI, morning blood pressure, and arousal index were secondary outcomes. A single night of treatment was determined to be effective based on previous observations that oxygen administration has no additional beneficial effect beyond that of the first night and that improvements in OSA severity are lost immediately with treatment withdrawal.[11]

PSG

PSGs were performed in an in-patient setting at Monash Health, an academic sleep center in Melbourne, Australia, and were recorded using a Grael amplifier (Compumedics, Abbotsford, Victoria, Australia). The recording included a 6-channel electroencephalogram (F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1), bilateral electrooculogram, mentalis/submentalis electromyogram, anterior tibialis (left and right) electromyogram, and electrocardiogram. Respiration was assessed via nasal pressure cannula, oronasal thermistor, thoracic and abdominal respiratory inductance plethysmography bands, and fingertip pulse oximetry.

Sleep stages, arousal, and respiratory events were scored according to American Academy of Sleep Medicine 2012 recommended criteria[12] using Profusion PSG3 software (Compumedics, Abbotsford, Victoria, Australia). Specifically, hypopneas were scored when nasal pressure signal dropped by ≥ 30% from baseline for ≥ 10 seconds, and the event was associated with either a 3% or greater fall in oxygen and/or an arousal from sleep. Given that supplemental oxygen can attenuate oxygen desaturations and thereby mask the occurrence of hypopneas, our primary outcome assessment included

Figure 1—Consort diagram.



ENT = ear nose and throat, PSG = polysomnography.

additional flow-based hypopneas ($Hypopneas_{fb}$) to calculate an AHI_{fb}. Specifically, a single experienced sleep scientist scored $Hypopneas_{fb}$ during periods where there was a 30% reduction flow (regardless of coincident electroencephalogram arousal or desaturation). All respiratory events (apneas, hypopneas, and $Hypopneas_{fb}$) were summed and divided by total sleep time to calculate the AHI_{fb}.

Blood pressure

Blood pressure was taken on the right arm of supine participants on waking using an Omron Automatic Blood Pressure Monitor (model HEM-7320; Omron, Kyoto, Japan).

Oxygen delivery

Oxygen (100% O_2, 4 L/min) or placebo/medical air (21% O_2, 4 L/min) was entrained into the same nasal cannula (model 2021, Teleflex Medical Australia) used to measure airflow/nasal pressure. Specifically, a Y connector was used to simultaneously connect the cannula to the Grael amplifier and a wall-mounted oxygen/air flow regulator.

Measuring the OSA endotypes

PSG data were exported from Compumedics Profusion PSG3 (Version 3, Build 401, 2014, Compumedics) in European Data Format. European Data Format files were imported into Matlab (R2018a; Mathworks Inc., Natick, MA) and analyzed using previously described methods.[7,8] In brief, this method uses ventilation data contained within a PSG to model a patient's ventilatory drive (or intended ventilation). Ventilation data are obtained through a nasal pressure signal (linearized, integrated to yield breath-to-breath uncalibrated tidal volume × respiratory rate, mean normalized). A chemoreflex control model (delay, response time, and loop gain) is then best fit (least-squares) to the PSG ventilation signal during aliquots of unobstructed breaths (ie, when ventilation matches ventilatory drive). The ventilatory response to arousal is calculated via a separate factor that is also fit to the data.[7] The parameters that are calculated from these PSG data include the following:

- Vpassive (upper airway collapsibility): the median ventilation achieved at eupneic ventilatory drive.
- Vactive: the median ventilation achieved at maximum ventilatory drive (ie drive at the arousal threshold).
- Compensation: the amount of compensatory ventilation that can be achieved by activating the upper airway musculature. Calculated as the difference between Vpassive and Vactive.
- Loop gain: the ratio of response to disturbance of the chemoreflex control model measured at the natural frequency.
- Arousal threshold: the level of ventilatory drive at which respiratory arousal occurs.

PSG data were quality controlled at each time point (presurgery, postsurgery, air/placebo night, and oxygen night) to ensure adequate nasal pressure trace. For our endotyping methods, quality nasal pressure trace is critical in ensuring accurate data calculations. Traits were assessed using pre- and postsurgery data. Assessment of the traits on oxygen vs placebo was not a primary objective of the study (also simultaneous delivery of air or oxygen at 4 L/min rendered nasal pressure signals unsuitable for advanced analysis beyond clinical scoring).

Statistical analysis

Data were collated in Microsoft Excel (Version 1810; Microsoft Corporation, Redmond, WA) and analyzed using SPSS (version 25, 2017; New York, NY) and Prism 7 (7.02; GraphPad Software Inc., La Jolla, CA). Continuous variables

Table 1—Baseline participant characteristics before and after surgery (n = 20).

Variable	Before Surgery	After Surgery	*P*
BMI, kg/m^2	31.3 ± 4.2	30.6 ± 4.4	.180
Total AHI, events/h	40.5 ± 21.2	34.0 ± 22.0	.120
Supine AHI, events/h	55.8 ± 28.1	58.2 ± 26.8	.653
Total AHI$_{fb}$, events/h	47.8 ± 19.1	39.5 ± 21.5	.204
Supine AHI$_{fb}$, events/h	58.6 ± 26.7	60.7 ± 25.0	.692
Loop gain	0.450 ± 0.100	0.436 ± 0.090	.166
Arousal threshold, %Veupnea	132.9 (113, 162.2)	134.5 (108.1, 181.3)	.812*
Vpassive, %Veupnea	96.9 (89.4, 99.4)	98.3 (92.0, 99.1)	.294
Vactive, %Veupnea	101.3 (61.4, 106.6)	98.5 (35.8, 103.4)	.595
Compensation, %Veupnea	3.0 (−25.2, 7.6)	1.9 (−19.4, 4.7)	.169

Values are means ± standard deviation. AHI = apnea-hypopnea index, AHI$_{fb}$ = flow-based apnea-hypopnea index, BMI = body mass index, NREM = non–rapid eye movement, REM = rapid eye movement. *Wilcoxon test.

are reported as mean ± standard deviations for parametric data and as median and interquartile range (25th percentile, 75th percentile) for nonparametric data. Comparisons of primary and secondary end points for the effect of oxygen vs placebo were made with paired *t* tests for parametric data, Wilcoxon signed rank, or Mann–Whitney *U* tests for nonparametric data; χ^2 test for categorical data; and Fisher's exact test where expected cell counts were less than 5. Correlations of baseline characteristics with primary end points are reported using Pearson's correlation for parametric data and Spearman's ρ for nonparametric data. To determine the characteristics of patients that benefitted most from oxygen therapy, we categorized patients as responders if they demonstrated a > 50% reduction in AHI$_{fb}$.[13] Comparisons between responder and nonresponder characteristics were made using unpaired *t* tests. Significance was accepted at $P < .05$.

RESULTS

The demographics and baseline characteristics of patients enrolled before and after upper airway surgery are displayed in **Table 1**. The average age was 51.6 ± 13.6 years (presurgery), and 17 of 20 (85%) were male. The mean time between the presurgery and postsurgery studies was 51.5 ± 11.8 days. Additionally, AHI indices and body mass index were unchanged between postsurgery and placebo night (data not shown). In total, when classified as (1) nasal, (2) tonsillar, (3) palatal, or (4) tongue, the 20 patients received a total of 53 surgeries (when categorized as above). Three patients received surgery to 1 level (as defined above, 2 nasal surgeries for complete nasal occlusion, 1 tongue-only surgery), 4 patients received surgery to 2 levels, 10 patients received surgery to 3 levels, and 3 patients received surgery to 4 levels (details of individual patient surgeries are given in the supplemental material). Patients responded minimally to surgery (per patient selection), and no significant impact of surgery on the endotypic traits was observed (**Table 1**; of note, removing the 2 participants who had nasal-only surgery did not change any of the following results significantly).

Effect of oxygen vs placebo

Oxygen significantly reduced the AHI$_{fb}$ compared with placebo (42.4 ± 21.5 vs 30.5 ± 17.1 events/h, $P = .008$; **Figure 2**; **Table 2**). Similar reductions were observed in the standard AHI, as well as the supine and non–rapid eye movement–specific AHI measures.

Secondary outcomes

The arousal index was also reduced on oxygen vs placebo (41.1 ± 19.5 vs 33.0 ± 15.3 events/h, $P = .006$), supported by reduced stage 1 and greater stage 2 non–rapid eye movement sleep (**Table 2**). There was no significant difference in morning blood pressure between the air and oxygen nights.

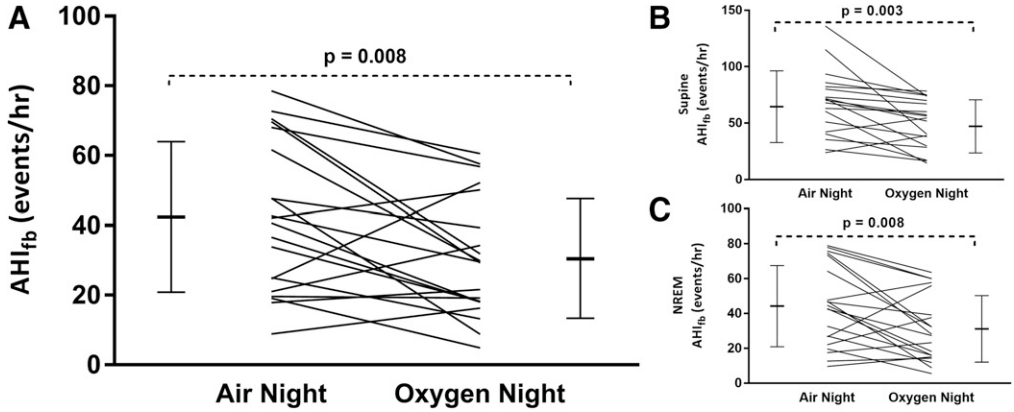
Responders/nonresponders to oxygen

There were 7 responders (ie, ≥ 50% reduction in AHI$_{fb}$, oxygen vs air) and 13 nonresponders. Examination of data at the postsurgery study (**Table 3**) revealed no significant differences between responders and nonresponders. Notably, AHI indices, loop gain, and collapsibility were greater in nonresponders vs responders by meaningful margins, but differences were nonsignificant. To determine whether there were any significant differences in the type or number of surgeries between responder and nonresponder groups, we classified surgery as (1) nasal, (2) tonsillar, (3) uvula, or (4) tongue. Using Fisher's exact test, there were no significant differences in the type of surgery between responder and nonresponder groups. A similar analysis of the number of surgeries performed on a patient (1, 2, 3, or 4 surgeries as classified above) using Fisher's exact test also demonstrated no significant differences between responder and nonresponder groups.

Predicting response to oxygen therapy

Previous work in predicting response to oxygen therapy using sleep apnea endotypes has been successful in identifying responders to oxygen therapy.[13] We applied the predictive equation published by Sands et al[13] to our postsurgery endotypes data to determine predicted vs actual responders to oxygen therapy. The predictive equation successfully predicted responder status in 7 of 7 cases in the postsurgery data (sensitivity, 100%; specificity, 23.1%), although with a low specificity, in that 10 cases were predicted to

Figure 2—Effect of oxygen vs air on the AHI_{fb}.



(A) Individual patient data for change in AHI_{fb} from air night to oxygen night. **(B)** Individual patient data for change in supine AHI_{fb} from air night to oxygen night. **(C)** Individual patient data for change in NREM AHI_{fb} from air night to oxygen night. Individual patient data for change in AHI_{fb} from air night to oxygen night. AHI_{fb} = flow-based apnea-hypopnea index, NREM = non–rapid eye movement.

Table 2—Effect of oxygen on sleep-disordered breathing (n = 20).

Variable	Air	Oxygen	*P*
AHI, without desaturation criteria*			
Total, events/h	42.4 ± 21.5	30.5 ± 17.1	.008
Supine, events/h	64.5 ± 31.7	47.1 ± 23.0	.003
NREM, events/h	44.3 ± 23.3	31.2 ± 19.1	.008
AHI, with desaturation criteria			
Total, events/h	37.0 ± 22.2	24.1 ± 15.7	.002
Supine, events/h	62.3 ± 32.4	43.6 ± 23.7	.001
NREM, events/h	37.6 ± 23.5	24.5 ± 17.1	.008
TST, min	363.2 ± 54.8	356.3 ± 60.8	.454
Percent time supine	27.8 (17.8, 53.8)	30.5 (8.5, 64.8)	.879
Total AI, events/h	41.1 ± 19.5	33.0 ± 15.3	.006
Sleep efficiency, %	78.2 ± 10.4	79.3 ± 12.4	.492
N1%	29.9 ± 15.0	24.1 ± 15.6	<.0001
N2%	44.4 ± 10.5	49.2 ± 6.7	.006
N3%	11.7 ± 9.7	14.2 ± 10.1	.160
REM%	14.0 ± 4.6	12.5 ± 5.0	.251
Systolic blood pressure, mm Hg	135.9 ± 12.8	128.0 ± 32.1	.425†
Diastolic blood pressure, mm Hg	83.5 ± 11.1	84.1 ± 9.9	.785†
Epworth Sleepiness Scale score	6.6 ± 3.5	6.5 ± 4.3	0.869

Values are means ± standard deviation. AHI = apnea-hypopnea index, N1% = percent of total sleep time in non-rapid eye movement sleep stage 1, N2% = percent of total sleep time in non-rapid eye movement sleep stage 2, N3% = percent of total sleep time in non-rapid eye movement sleep stage 3, NREM = non–rapid eye movement, REM = rapid eye movement, TST = total sleep time. *Based on flow-based apnea-hypopnea index. †Only 18 patients included in this analysis because morning blood pressures were not collected for 2 participants on their air night.

respond to oxygen and did not. Importantly, the model successfully predicted 3 cases of nonresponse with 100% sensitivity.

Exploratory analysis of loop gain reduction with surgery and response to oxygen therapy

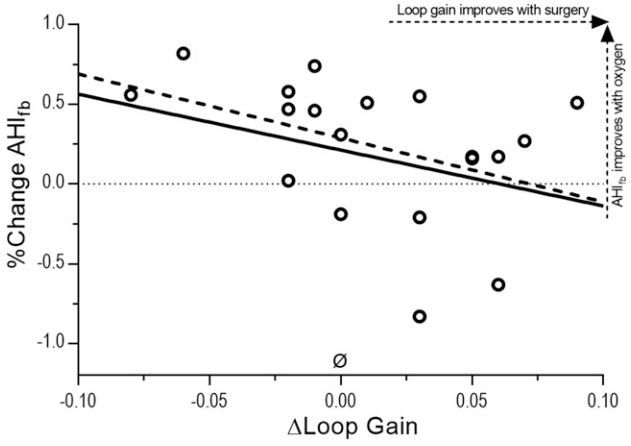
That a component of elevated loop gain may be acquired and subsequent to the development of OSA raises the possibility that any reduction in loop gain with initial treatment may reduce the effectiveness of any additional/subsequent loop gain–lowering therapies. Because of the noted change in loop gain with surgery observed by Li et al,[10] we were interested in analyzing the relationship between the change in loop gain with surgery and the reduction in AHI_{fb} to oxygen therapy after surgery. We conducted an analysis to determine whether change (improvement, ie, presurgery loop gain minus postsurgery loop gain) in loop gain with surgery was correlated with percent change in AHI (improvement, ie, [air night AHI_{fb} – oxygen night AHI_{fb}]/air night AHI_{fb}) with oxygen therapy (**Figure 3**). We found a

Table 3—Baseline (postsurgery) participant characteristics by oxygen response status (n = 20).

Variable	Responder (n = 7)	Nonresponder (n = 13)	*P*
Age, yr	49.9 ± 7.9	54.2 ± 13.5	.455
Sex, male %	86% (6/7)	85% (11/13)	.948*
BMI, kg/m^2	31.9 ± 4.9	29.9 ± 4.1	.351
Total AHI, events/h	25.7 ± 16.8	38.5 ± 23.7	.223
Supine AHI, events/h	56.0 ± 24.4	59.4 ± 28.9	.799
Total AHI_{fb}, events/h	29.0 ± 17.2	45.2 ± 22.0	.111
Supine AHI_{fb}, events/h	57.3 ± 23.6	62.5 ± 26.5	.669
Loop gain	0.392 ± 0.118	0.460 ± 0.065	.112
Arousal threshold, %Veupnea	133.3 ± 60.4	164.4 ± 68.6	.328
Vpassive, %Veupnea	98.3 ± 1.8	84.9 ± 28.0	.229
Vactive, %Veupnea	84.4 ± 38.4	68.6 ± 45.2	.443
Compensation, %Veupnea	−13.8 ± 38.3	−16.3 ± 31.1	.878

Values are means ± standard deviation. AHI = apnea-hypopnea index, AHI_{fb} = flow-based apnea-hypopnea index, BMI = body mass index. *χ^2 test.

Figure 3—Correlation of change in loop gain with surgery and percent improvement in AHI_{fb} with oxygen.



AHI_{fb} = flow-based apnea-hypopnea index, dashed line = regression with outlier excluded, solid line = regression line with outlier included, Δ = change, Ø = statistical outlier.

negative correlation between change in loop gain with surgery and percent change in AHI_{fb} with oxygen therapy ($r = -0.475$, $P = .040$; outlier excluded, n = 19). This suggests that the more loop gain is altered by surgery, the less the subsequent reduction in $\%AHI_{fb}$ will be with oxygen treatment.

DISCUSSION

Our study is the first randomized controlled trial of oxygen therapy for the treatment of OSA in patients who have failed to respond to upper airway surgery. The major findings of our study are that the AHI and arousal index were significantly reduced with oxygen therapy (albeit the overall AHI improvement on oxygen is modest), whereas morning blood pressure and Epworth Sleepiness Scale scores were not. Seven of 20 patients (35%) responded to oxygen therapy (>50% reduction in AHI_{fb}). These findings demonstrate that OSA treatment failure with upper airway surgery may be improved with the administration of oxygen in a proportion of patients. Current predictive models were able to accurately predict (sensitivity, 100%) who is unlikely to respond to oxygen therapy, but further refinement is required to improve the specificity in identifying true responders.

Salvaging upper airway surgical failure

Upper airway surgery is a well-established treatment for OSA. However, there are many factors that make application of surgical treatment difficult to standardize and study, including patient assessment and selection, procedure selection and execution, and how successful treatment is defined. Some of the most reliable surgical data comes from small randomized controlled trials that suggest that more than one third of patients who undergo upper airway surgery still have significant residual OSA.[1,2]

Despite the significant population of patients who undergo upper airway surgery for OSA and who continue to experience frequent respiratory events, very few studies have explored salvage treatment options. In one of the only salvage treatment studies performed to date, Benoist et al[14] recruited patients who had undergone surgical treatment with a median residual AHI of 18.3 events/h and applied a positional modification technique to avoid supine sleep. The avoidance of supine sleep in this group resulted in a 50% reduction in AHI in approximately one third of patients,[14] a similar proportion of responders to our study. Given that changing body position from supine to lateral markedly improves airway anatomy/collapsibility,[15–17] the positive effect on the AHI observed by Benoist et al[14] suggests that approximately one third of patients in that study population who failed to respond to upper airway surgery (but subsequently responded to supine sleep avoidance) did so because of an ongoing anatomical deficit that is amenable to further anatomic treatment.

A subpopulation of surgical nonresponders who have favorable upper airway anatomy

It is reasonable to postulate that surgery fails to resolve OSA in a proportion of patients because either the anatomical deficit is

too great to overcome or that the surgery was inadequately performed/planned/executed. However, there is mounting evidence that a proportion of patients who fail to respond to upper airway surgery for OSA do so because of the presence of additional nonanatomic factors.

Many patients with OSA have multiple pathophysiologic processes (ie, endotypes) that contribute to their respiratory events, including respiratory control instability (high loop gain), low arousal threshold, and poor upper airway dilator muscle effectiveness. The important causal role of these nonanatomic endotypes has been emphasized over the last decade with the development of simplified,[18] and subsequently, noninvasive[8] techniques for measuring them. Notably, a key finding in one of the largest cohort of patients with OSA was that approximately 20% of patients with OSA have mild airway collapsibility and elevated loop gain.[4]

The finding in our present study that oxygen can improve OSA after surgery supports previous work identifying a subpopulation of patients with OSA who have more favorable anatomy and elevated loop gain. For example, in the study by Sands et al,[13] 25% of patients with OSA demonstrated a fall in AHI of more than 50% with oxygen administration. Interestingly, the smaller proportion of responders in that study compared with ours may be because the study of Sands et al[13] recruited all comers with OSA, whereas our study selected a population likely to be enriched with nonanatomic OSA factors. We feel there are 2 possible explanations for why oxygen therapy might work after surgery in our group of patients: (1) they did not have a major anatomic deficit in the first place and surgery has had little impact on their physiology and b) anatomy has been improved to a degree by surgery, and the patient has ongoing loop gain elevation that is amenable to oxygen therapy.

In favor of point 1, it is possible that unfavorable anatomy only partly contributes to OSA in these patients in the first place, and it is the nonanatomic factors that are the effect modifiers. Notably, there is a subpopulation of patients with OSA with a high loop gain and more favorable anatomy, and we demonstrated previously that elevated loop gain predicts failure to respond to 2 anatomic treatments: upper airway surgery[9] and mandibular advancement device treatment.[19] The implication here is that, in some patients, there is only a minor anatomic deficit for an anatomic treatment to work on. In support of this, it is important to note that oxygen therapy reduces loop gain without altering the other pathophysiologic contributors to OSA.[5] In this way, we understand the response of patients to oxygen in our study reflects a reduction in loop gain without a change in anatomy or any of the other pathophysiologic factors.

In favor of point 2, surgery may improve upper airway anatomy without resolving OSA, thus rendering the patient amenable to treatment directed at nonanatomic factors. Importantly, available evidence suggests that (1) surgery improves upper airway functional anatomy as measured by pharyngeal critical closing pressure,[20] and (2) 36% of patients with OSA have an elevated loop gain.[4] Additionally, the concept of effect modification of anatomy on the nonanatomic traits raises the possibility that as anatomy improves, the effect of nonanatomic traits on OSA pathogenesis is amplified.[21,22] By contrast, in our study, cohort upper airway anatomical measurements (Vpassive, Vactive, Vcomp) were not significantly altered by surgery, suggesting that (by our measurement) the anatomic component of OSA was not significantly altered by surgery in these patients.

If surgery fails to reduce the AHI, there may be a degree of acquired elevation in loop gain that is amenable to oxygen therapy. Elevated loop gain may be both a direct pathophysiologic cause of OSA and also become elevated as a direct consequence of intermittent hypoxia associated with OSA.[23] Certainly, in a recent study, Li et al[14] demonstrated that large reductions in AHI after upper airway surgery were associated with a reduction in loop gain in the order of 24%, suggesting that the elevated loop gain was at least in part acquired. In this way, patients who fail to respond to upper airway surgery may have ongoing elevations of loop gain that are amenable to oxygen therapy. That the change in loop gain with surgery negatively correlated with percent change in AHI with oxygen therapy in our study supports the possibility that failure of surgery to reduce the AHI (and therefore the acquired component of elevated loop gain) indicates that the patient will be amenable to loop gain lowering treatment such as oxygen.

Limitations

The major limitation of our study is a failure to be able to determine the effect of oxygen and air treatment delivery on the endotypes. The strategy we used for nasal pressure delivered inconsistent quality recordings that resulted in insufficient data to accurately report on these parameters. In this way, it is impossible to say if AHI_{fb} or AHI was reduced on oxygen because of a reduction in loop gain. We feel that previous studies support this assumption,[5,13] but we are unable to definitively report that finding here. With regard to the use of baseline (postsurgery) trait measurements to predict responder status, we feel that it is reasonable given previous literature demonstrating suggesting repeatability of trait measurement,[18] supporting the idea that baseline measurements are likely to remain stable in the absence of treatments that affect that measurement; in our study, this means that the baseline postsurgical measurement of loop gain is likely to represent a reasonable measurement of loop gain on placebo. Additionally, given that the PSG characteristics were similar between postsurgery PSG and the air/placebo treatment PSG, we expect that the physiology underlying the OSA in these situations to also be the same.

Because our study was powered to detect differences in AHI, it may be that our sample size is too small to determine predictors of response to oxygen, noting that previous studies that were able to find predictors of response to other non–continuous positive airway pressure treatments had larger included numbers.[9,13] Future studies with larger numbers of recruited patients may be able to confirm our current findings and further explore predictors of response.

Last, we were unable to accurately and continuously monitor route of breathing (nasal vs oral) in this study because patients were instrumented as per standard clinical PSG setup, which enhances the generalizability of the results. To accurately and continuously monitor route of breathing, additional instrumentation would have been required, which we feel would have limited the generalizability of the study methodology and results.

CONCLUSIONS

In conclusion, we demonstrated for the first time that a proportion of patients who fail to respond to upper airway surgery for OSA respond acutely to treatment with oxygen. Determining which patients will respond to the various non–continuous positive airway pressure treatments for OSA remains an ongoing challenge for clinicians and researchers.

ABBREVIATIONS

AHI, apnea-hypopnea index
AHI_{fb}, flow-based apnea-hypopnea index
OSA, obstructive sleep apnea
PSG, polysomnography

REFERENCES

1. 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):846–853.
2. Sommer UJ, Heiser C, Gahleitner C, et al. Tonsillectomy with uvulopalatopharyngoplasty in obstructive sleep apnea. *Dtsch Arztebl Int.* 2016;113(1-02):1–8.
3. Wellman A, Eckert DJ, Jordan AS, et al. A method for measuring and modeling the physiological traits causing obstructive sleep apnea. *J Appl Physiol 1985.* 2011;110(6):1627–1637.
4. 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.
5. Edwards BA, Sands SA, Owens RL, et al. Effects of hyperoxia and hypoxia on the physiological traits responsible for obstructive sleep apnoea. *J Physiol.* 2014;592(20):4523–4535.
6. Edwards BA, Connolly JG, Campana LM, et al. Acetazolamide attenuates the ventilatory response to arousal in patients with obstructive sleep apnea. *Sleep.* 2013;36(2):281–285.
7. Terrill PI, Edwards BA, Nemati S, et al. Quantifying the ventilatory control contribution to sleep apnoea using polysomnography. *Eur Respir J.* 2015;45(2):408–418.
8. Sands SA, Edwards BA, Terrill PI, et al. Phenotyping pharyngeal pathophysiology using polysomnography in patients with obstructive sleep apnea. *Am J Respir Crit Care Med.* 2018;197(9):1187–1197.
9. Joosten SA, Leong P, Landry SA, et al. Loop gain predicts the response to upper airway surgery in patients with obstructive sleep apnea. *Sleep.* 2017;40(7):zsx094.
10. Li Y, Ye J, Han D, et al. The effect of upper airway surgery on loop gain in obstructive sleep apnea. *J Clin Sleep Med.* 2019;15(6):907–913.
11. Gold AR, Schwartz AR, Bleecker ER, Smith PL. The effect of chronic nocturnal oxygen administration upon sleep apnea. *Am Rev Respir Dis.* 1986;134(5):925–929.
12. Berry RB, Brooks R, Gamaldo CE, et al; for the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events. Rules, Terminology and Technical Specifications.* Version 2.0. Darien, IL: American Academy of Sleep Medicine; 2012.
13. Sands SA, Edwards BA, Terrill PI, et al. Identifying obstructive sleep apnoea patients responsive to supplemental oxygen therapy. *Eur Respir J.* 2018;52(3):1800674.
14. Benoist LBL, Verhagen M, Torensma B, van Maanen JP, de Vries N. Positional therapy in patients with residual positional obstructive sleep apnea after upper airway surgery. *Sleep Breath.* 2017;21(2):279–288.
15. Joosten SA, Edwards BA, Wellman A, et al. The effect of body position on physiological factors that contribute to obstructive sleep apnea. *Sleep.* 2015;38(9):1469–1478.
16. Joosten SA, Landry SA, Sands SA, et al. Dynamic loop gain increases upon adopting the supine body position during sleep in patients with obstructive sleep apnoea. *Respirology.* 2017;22(8):1662–1669.
17. Joosten SA, Sands SA, Edwards BA, et al. Evaluation of the role of lung volume and airway size and shape in supine-predominant obstructive sleep apnoea patients. *Respirology.* 2015;20(5):819–827.
18. Wellman A, Edwards BA, Sands SA, et al. A simplified method for determining phenotypic traits in patients with obstructive sleep apnea. *J Appl Physiol 1985.* 2013;114(7):911–922.
19. Edwards BA, Andara C, Landry S, et al. Upper-airway collapsibility and loop gain predict the response to oral appliance therapy in obstructive sleep apnea patients. *Am J Respir Crit Care Med.* 2016;194(11):1413–1422.
20. Schwartz AR, Schubert N, Rothman W, et al. Effect of uvulopalatopharyngoplasty on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis.* 1992;145(3):527–532.
21. Owens RL, Edwards BA, Eckert DJ, et al. an integrative model of physiological traits can be used to predict obstructive sleep apnea and response to non positive airway pressure therapy. *Sleep.* 2015;38(6):961–970.
22. Li Y, Ye J, Han D, et al. Physiology-based modeling may predict surgical treatment outcome for obstructive sleep apnea. *J Clin Sleep Med.* 2017;13(9):1029–1037.
23. Orr JE, Edwards BA, Malhotra A. Rebuttal from J. E. Orr, B. A. Edwards and A. Malhotra. *J Physiol.* 2014;592(14):2909.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication July 9, 2020
Submitted in final revised form October 7, 2020
Accepted for publication October 7, 2020
Address correspondence to: Simon A. Joosten, MBBS, PhD, Monash Medical Centre, Monash Lung and Sleep, 246 Clayton Road, Clayton, 3168, Victoria, Australia; Tel: +613 9594 2900; Email: drjoosten@hotmail.com

DISCLOSURE STATEMENT

All authors have seen and approved this manuscript. S.A.J. is supported by a National Health and Medical Research Council Early Career Fellow (1139745). B.A.E. is supported by a Heart Foundation of Australia Future Leader Fellowship (101167). A.-M.W. received an Research Training Program stipend by Monash University for graduate research studies. P.L. received a postgraduate scholarship from the Royal Australasian College of Physicians and the National Health and Medical Research Council. S.A.S. was supported by the American Heart Association (Grant 15SDG25890059), the American Thoracic Society Foundation, and National Heart Lung and Blood Institute Grant R35HL135818. GSH and SAJ received equipment to support research from ResMed, Philips Respironics, and Air Liquide Healthcare unrelated to this research. SAS reports income from Nox Medical (consulting), Merck (consulting), Inspire (consulting), Apnimed (grant support), and Prosomnus (grant support), all unrelated to this research. BAE reports income from Signifier Medical (consulting) and Apnimed (grant support), both unrelated to this research. All other authors report no conflicts of interest.