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Changes in Obstructive Sleep Apnea Severity, Biomarkers, and Quality of Life After Multilevel Surgery

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Abstract

Objectives/Hypothesis—To evaluate the impact of multilevel obstructive sleep apnea surgical treatment on sleep-disordered breathing severity, health-related measures, and quality of life, and to examine the association between changes in sleep-disordered breathing severity and these other outcomes.

Study Design—Prospective cohort study.

Methods—Subjects with obstructive sleep apnea unable to tolerate positive airway pressure therapy and with evidence of multilevel (palate and hypopharynx) obstruction underwent uvulopalatopharyngoplasty, tonsillectomy, and genioglossus advancement, with or without hyoid suspension. All subjects had preoperative and postoperative study assessments, including blood draw for C-reactive protein, interleukin-6, homocysteine, homeostasis model of insulin resistance, and leptin, and evaluation with the Functional Outcomes of Sleep Questionnaire.

Results—Thirty subjects underwent multilevel surgical treatment. The mean apnea-hypopnea index decreased from 44.9 ± 28.1 to 27.8 ± 26.4 events/hour ($P = .008$). Thirteen (43%) subjects in this heterogeneous sample achieved a response to surgery (defined as an apnea-hypopnea index reduction of ≥50% to an absolute level <15 events/hour), and body mass index ≤32 kg/m^2 was associated with a higher likelihood (55%, 12/22) of response ($P = .04$). There was no overall change in C-reactive protein levels, but responders demonstrated a decrease (−1.02 ± 0.98 mg/L, $P = .003$) that was independent of changes in body weight. There were no significant changes in other health-related measures. Responders and nonresponders both demonstrated improvements in sleep-related quality of life.

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This trial was registered at ClinicalTrials.gov as NCT00518128. There are no off-label or investigational uses of drugs and devices to disclose.

Level of Evidence: 2b

Conclusions—This multilevel surgery was associated with a low likelihood of response in subjects with body mass index >32 kg/m^2. Responders had decreased C-reactive protein levels that were independent of changes in body weight.

Keywords

Sleep apnea; surgery; C-reactive protein; quality of life; palate; genioglossus advancement; uvulopalatopharyngoplasty

INTRODUCTION

Obstructive sleep apnea (OSA) is associated with substantial cardiovascular morbidity and mortality, endocrine disturbances, excessive daytime somnolence, quality of life and performance deficits, and motor vehicle crashes. Specific measures have been identified that may reflect these adverse health-related consequences, including biomarkers such as C-reactive protein (CRP).[1] Similarly, valid and reliable tools have been developed to assess the functional impacts of sleep disorders such as OSA.[2]

The goals of OSA treatment are twofold: 1) the elimination of disordered breathing events during sleep and 2) the prevention or reversal of the associated adverse health-related and functional consequences noted above. Positive airway pressure therapy (PAP) is recognized as the first-line treatment for most OSA patients because it eliminates disordered breathing events, but some patients do not tolerate this treatment modality and may consider other options, including surgery. All OSA treatments have the potential to improve breathing patterns during sleep, but the extent to which they treat its adverse consequences is equally important. For surgical OSA treatment, most studies have focused on reducing disordered breathing events during sleep, and the evidence related to these biomarkers and sleep-related quality of life is limited.

The objective of this study was to evaluate the impact of multilevel upper airway surgery (concurrent uvulopalatopharyngoplasty with possible tonsillectomy and genioglossus advancement with possible hyoid suspension) on sleep-disordered breathing severity as well as health-related and functional outcomes. We hypothesized that the changes in sleep-disordered breathing severity would be associated with changes in health-related and functional outcomes.

MATERIALS AND METHODS

This prospective cohort study included subjects with OSA (apnea-hypopnea index >5 events/hour on preoperative diagnostic sleep study) who were unable to tolerate PAP. All subjects were seen by the primary author (E.J.K.) at the University of California San Francisco (UCSF), Department of Otolaryngology–Head and Neck Surgery. Inclusion criteria included age >18 years, inability to tolerate PAP, evidence of multilevel (palate/tonsillar and hypopharyngeal/retrolingual) upper airway obstruction, and the desire to proceed with surgical treatment. Inability to tolerate positive airway pressure therapy was defined as mean use of no more than 4 hours per night despite aggressive attempts to improve tolerance and adherence, with confirmation from referring sleep medicine physician

and the primary author that the subject had not achieved successful treatment. Evidence of multilevel obstruction was based on a number of factors: awake physical examination documenting Friedman stage II or III classification[3] and narrowing of the palatal and hypopharyngeal/retrolingual airway regions on awake fiberoptic endoscopy, lateral cephalogram x-ray, and/or drug-induced sleep endoscopy (showing multilevel obstruction if performed prior to procedure selection).[4,5] No specific inclusion or exclusion criteria were drawn from findings of any single evaluation technique other than those noted above. Exclusion criteria included pregnant women; acute illness or infection; coexisting untreated or unstable sleep disorder other than obstructive sleep apnea; inability to fast overnight; or known cardiac, hepatic, renal, or neurologic disorder. This study was approved by the UCSF institutional review board, and all subjects provided written informed consent.

Preoperative full-night diagnostic polysomnograms occurred prior to study enrollment and were performed according to standard clinical practice. They were repeated if not performed within 1 year of surgery or if there was a change in body weight of more than 5 kg. All subjects included in this analysis underwent a full-night postoperative polysomnogram at least 3 months following surgery at the same sleep testing facility as their preoperative study, in an attempt to enhance consistency in study interpretation.

Over one half (53%, 16/30) of the subjects underwent preoperative and postoperative polysomnograms at the UCSF Sleep Disorders Center. The recording montage at the UCSF Sleep Disorders Center consisted of C3/A2 and C4/A1 electroencephalograms, bilateral electrooculograms, a bipolar submental electromyogram, thoracic and abdominal respiratory inductance plethysmography, airflow (using nasal-oral thermocouple and nasal pressure cannula), finger pulse oximetry, electrocardiogram, body position (mercury switch sensor), and bilateral leg movements (piezoelectric sensors). Sleep stages and arousals were scored using standard criteria.[6] Apneas were defined as a complete or almost complete cessation of airflow (by thermocouple), and hypopneas were identified as a >30% reduction in airflow associated with a ≥4% oxygen desaturation, according to Medicare criteria.[7] Apneas associated with no evidence of effort on both thoracic and abdominal channels were considered to be central and otherwise as obstructive. The following polysomnogram results were recorded: apnea-hypopnea index (AHI) (apneas plus hypopneas per hour of sleep), apnea index (apneas per hour of sleep), hypopnea index (hypopneas per hour of sleep), lowest oxygen saturation, the percentage of sleep time with oxygen saturation below 90%, and the percentages of sleep time spent in stages N3 and rapid eye movement (REM) sleep. Of the subjects not undergoing preoperative and postoperative polysomnograms at the UCSF Sleep Disorders Center, the majority (40% of total, 12/30) underwent studies at a center using recent consensus-based recommendations from the American Academy of Sleep Medicine, with a similar definition of apneas and a hypopnea defined by a decrease in airflow of at least 50% for at least 10 seconds with an associated oxygen desaturation of at least 3% or a sleep arousal.[6]

Surgical decision making was based on preoperative evaluation and patient preferences and was independent of potential enrollment in this study. In a single procedure, subjects underwent uvulopalatopharyngoplasty, with tonsillectomy if tonsils had not been removed previously, genioglossus advancement,[8] and in certain cases, hyoid suspension using the

thyrohyoid suspension technique.[9] Genioglossus advancement was selected as the primary hypopharyngeal surgery in this study because it has been associated with favorable outcomes in combination with palate surgery for subjects with multilevel obstruction.[10] The decision whether to perform hyoid suspension was based on multiple factors, including cosmesis of the associated cervical scar and subject preferences.

Study Assessment

All subjects underwent study assessment on two occasions: preoperatively within 2 weeks prior to surgery but on a separate date from the procedure and postoperatively at least 3 months following surgery but within 6 weeks after the postoperative sleep study. Each study assessment included measurement of height and body weight, medical history, and morning (between 7–9 AM and within 2 hours of awakening) fasting (for at least 8 hours) blood draw. Blood samples were sent at the time of blood draw for the following tests: CRP (high sensitivity), homocysteine, and leptin. A subset of subjects had collection of stored, frozen serum samples that were sent in a delayed fashion for interleukin-6, insulin, and glucose testing. All biomarker assays were performed using the standard methods of the UCSF clinical laboratory. CRP (high sensitivity) was measured using the technique of rate turbidimetry. Homocysteine and insulin were measured using a chemiluminescent immunoassay technique. Leptin was measured using a radioimmunoassay technique. Interleukin-6 (high sensitivity) was measured with an enzyme immunoassay technique. Glucose was measured using an oxygen consumption method. The homeostasis model of insulin resistance (HOMA-IR) was calculated according to the standard method (fasting insulin [μU/mL] × fasting glucose [mmol/L] / 22.5), which has been shown to be valid when compared to the gold standard euglycemic clamp method.[11]

Sleep-related quality of life was evaluated with the Functional Outcome of Sleep Questionnaire (FOSQ), a 30-item instrument that measures the effect of excessive daytime sleepiness on activities of daily living.[2] Mean-weighted item scores are used to generate five subscales (general productivity, social outcome, activity level, vigilance, and intimacy and sexual relationships) that together produce a composite score. The total score ranges from 5 to 20, and lower scores indicate greater dysfunction. The FOSQ composite score was analyzed as a continuous variable.

Statistical Analysis

Descriptive statistics were calculated for baseline subject characteristics, including body mass index (defined as weight in kilograms divided by the square of height in meters). All continuous measures are reported with mean ± standard deviation. Preoperative and postoperative sleep study results were calculated, and paired *t* tests were used to evaluate changes after surgical treatment. Results are reported for the entire cohort and for subgroups defined by commonly used criteria for response to surgery or successful outcome. Two different definitions for surgical response developed by other authors were used in this study. One included the most common criteria in the literature, requiring ≥50% reduction in the apnea-hypopnea index to an absolute level <15 events/hour with no oxygen desaturation on the postoperative sleep study below 85% (with subjects hereafter classified as Response15 or NoResponse15). The second, also cited in the literature,[12] was similar except that it required

a postoperative AHI <5 events/hour (hereafter, Response5 and NoResponse5). The Response15/NoResponse15 criteria were used for the majority of the subgroup analyses.

Changes in body weight were calculated for the entire cohort and the Response15 and NoResponse15 subgroups, with paired *t* tests to evaluate possible changes after surgery. Linear regression tested the association between changes in AHI and body weight.

The potential association between performance of tonsillectomy or hyoid suspension and both the change in AHI (*t* tests) and surgical response (χ^2 testing) was examined. In addition, previously published studies of multilevel OSA surgery have identified specific subject factors that have been associated with outcomes after multilevel OSA surgery: AHI, body mass index >30 kg/m^2, body mass index >32 kg/m^2, mandibular insufficiency or retrognathia (defined by sella-nasion-point B [SNB] angle <78° on lateral cephalogram), and Friedman stage.[10] These were evaluated for their association with outcomes using two types of tests. First, a χ^2 test was used to examine the association between the Response15/NoResponse15 result and the appropriate categorical distribution (for AHI there were three categories: >5–15, >15–30, and >30 and two for all other potential risk factors, including only Friedman stage II vs. III, as none of the subjects were Friedman stages I or IV). Second, values of continuous measures (preoperative AHI, body mass index [BMI], and SNB angle) were compared in the Response15 and NoResponse15 subgroups using *t* tests.

Preoperative and postoperative biomarker values and FOSQ composite scores and their changes were calculated. Paired *t* tests examined changes in the entire cohort as well as the Response15 and NoResponse15 subgroups, evaluating the changes from baseline for each subgroup individually and comparing the changes between the subgroups. Linear regression was used to test for an association between changes in biomarkers or FOSQ composite score and changes in AHI, with additional adjustment for changes in body weight if the association was statistically significant.

The primary biomarker outcome in this study was the change in CRP. The sample size of 30 subjects was determined by the ability to detect a difference of 0.90 mg/L in CRP following surgical treatment, with 80% power at an $\alpha = .05$ level. *P* values <.05 were considered statistically significant. Statistical analyses were conducted using Stata version 10.0 (StataCorp LP, College Station, TX).

RESULTS

Thirty subjects underwent multilevel OSA surgical treatment. Mean age was 44.6 ± 10.6 years (range, 19–66 years), and 7% (2/30) were female. Based on subject report, most (7%, 21/30) were non-Hispanic Caucasian, four (13%) Hispanic Caucasian, three (10%) Asian-American, and two (7%) African-American. Twenty (67%) subjects underwent tonsillectomy, and 19 (63%) underwent hyoid suspension. Preoperative BMI was 30.1 ± 4.2 kg/m^2.

Sleep-Disordered Breathing Severity

Sleep study results are shown in Table I. Preoperatively, the distribution across categories defined by commonly used AHI cut points was 7% (2/30) with >5 to 15 events/hour, 33% (10/30) with >15 to 30 events/hour, and 60% (18/20) with >30 events/hour. Postoperative sleep studies were performed 208 ± 67 days (range, 91–323 days) following surgery.

Thirteen (43%) subjects achieved a surgical response using the most common criteria (Response15), whereas seven (23%) achieved a surgical response using the more stringent criteria (Response5). In the cohort as a whole, there was a significant decline in AHI and an increase in the percentage of REM sleep. The Response15 and Response5 subgroups had statistically significant declines in the AHI, whereas the NoResponse15 and NoResponse5 subgroups did not. Overall, there was a decrease in body weight of 1.7 ± 4.2 kg ($P = .038$). There were no statistically significant changes in body weight in the Response15, NoResponse15, Response5, and NoResponse5 subgroups individually, and there were no differences in the changes in body weight between the appropriate subgroup pairs (all $P > .05$). There was no association between changes in AHI and body weight on linear regression ($P = .52$). There was no association between the likelihood of a surgical response and the criteria for scoring of respiratory events.

There was no association between the change in AHI and the performance of tonsillectomy ($P = .21$) or hyoid suspension ($P = .13$). There was also no association between the performance of these procedures and either the Response15/NoResponse15 or Response5/NoResponse5 outcome (P values .56–.70).

There was an association between Response15/NoResponse15 and the BMI cut point of 32 kg/m^2, with only 12% (1/8) of subjects with higher BMI achieving a response ($P = .04$). In these subjects with BMI >32 kg/m^2, there was also no association between the change in AHI and the performance of tonsillectomy ($P = .38$) or hyoid suspension ($P = .11$). There was no association between the likelihood of surgical response and the severity of sleep-disordered breathing (based on AHI categories described above, $P = .25$), BMI at a cut point of 30 kg/m^2 ($P = .31$), SNB angle <78° ($P = .56$), or Friedman stage ($P = .67$). There were no differences in preoperative AHI ($P = .39$), BMI ($P = .27$), or SNB angle ($P = .22$) between the Response15 and NoResponse15 subgroups.

Biomarkers and FOSQ

Results for biomarkers and FOSQ scores are shown in Table II. Postoperative study assessment was performed 28 ± 13 days (range, 12–60 days) following the postoperative sleep study and 236 ± 61 days (range, 103–398 days) following surgery. In the entire cohort, there was a modest increase in homocysteine levels, an increase in FOSQ scores, and a trend toward a decline in IL-6 levels. There were no changes in other biomarkers. Limiting the analysis to all subjects with preoperative BMI ≤32 kg/m^2 did not change these findings dramatically, including the lack of a statistically significant change in CRP (−0.30 ± 1.7, $P = .42$).

The Response15 subgroup showed a decrease in CRP and a modest increase in homocysteine levels, without changes in the NoResponse15 subgroup. FOSQ scores

decreased in both subgroups. Other biomarkers showed no statistically significant changes, although the Response15 subgroup demonstrated point estimates that were greater in magnitude. Comparing changes between the Response15 and NoResponse15 subgroups, only the changes in CRP were statistically different ($P = .04$). Other than CRP (discussed below), there was no association between the changes in biomarkers and the change in AHI on linear regression (data not shown).

CRP decreased in the Response5 subgroup (−1.16 ± 1.20, $P = .04$) as well as the subjects (n = 6) in the Response15 subgroup who did not have a postoperative AHI below 5 events/hour (−0.85 ± 0.73, $P = .04$). In an analysis of CRP changes in subjects with interleukin-6 data (n = 21), the changes were reduced in magnitude but similar for the cohort (no statistically significant change, $P = .60$) and for those within the Response15 subgroup (−0.89 ± 0.78, $P = .009$). Linear regression showed an association between the change in AHI and change in CRP, suggesting a decrease of 0.20 (95% confidence interval, 0.02–0.38) in CRP for every decrease in the AHI of 10 events/hour ($P = .035$). With adjustment for changes in body weight (which was not itself associated with the change in CRP, $P = .29$), this finding was largely unchanged (decrease in CRP of 0.19 for decrease in AHI of 10 events/hour, $P = .047$).

Linear regression analysis showed that the increase in homocysteine and FOSQ scores was not related to the change in AHI (data not shown), with or without adjustment for change in body weight (which was not itself associated with change in either measure).

Three subjects experienced notable postoperative complications. Two subjects had post-tonsillectomy bleeding; one resolved spontaneously without intervention, and one required a secondary procedure to control the bleeding as well as a blood transfusion. One subject experienced dental injury, likely related to genioglossus advancement, that required a root canal procedure.

DISCUSSION

This multilevel surgical treatment was associated with a decrease in OSA severity, but the degree of improvement for individual subjects varied widely. This finding is not new. Surgical treatment of obstructive sleep apnea includes a wide range of procedures, and this study adds to a growing body of literature indicating the need to identify factors associated with a favorable response. Over one half of the subjects with BMI ≤32 kg/m^2 achieved a substantial reduction in OSA severity (defined as a >50% reduction in the apnea-hypopnea index to an absolute level <15 events/hour with no oxygen desaturation on the postoperative sleep study below 85%) with this procedure combination; the proportion was notably lower with BMI >32 kg/m^2. Although comparison of figures across studies is fraught with peril, the response rates in this study are consistent with the literature for similar procedure combinations.[10] Compared to results reported for isolated palate surgery in subjects with presumed multilevel obstruction, our response rates in those with a BMI ≤32 kg/m^2 are higher than those reported that are as low as 5% to 8%,[3,13] but the response rate for those with higher BMI is not substantially higher. This study did not examine the association

between outcomes and other specific preoperative evaluation technique findings due to small sample size.

There was no association between outcomes and performance of tonsillectomy or hyoid suspension. For hyoid suspension in particular, it remains unclear as to which patient subgroups benefit most from this procedure.

OSA treatment must not only eliminate disordered breathing events during sleep but also prevent or reverse the disorder's associated health-related and functional consequences. Based on the hypothesis that effective (but not ineffective) treatment would be associated with improvements in these measures, we evaluated changes in selected biomarkers and FOSQ score and compared them to the change in OSA severity. Biomarkers are intermediate outcomes with their inherent limitations, but they may prove valuable in a disorder like OSA, for which some treatments, such as PAP, have high efficacy but effectiveness limited by compliance, and other treatments, such as surgery, have variable efficacy, albeit equal to effectiveness because there are no issues of compliance.[14] Biomarkers may ultimately have a role in monitoring the effectiveness of OSA treatment, similar to the use of hemoglobin A1c in monitoring glucose control in diabetes management based on its association with diabetic complications.[15] This is particularly true if the risks of OSA-related complications are more closely related to biomarker levels than OSA severity.

Subjects who had a substantial reduction in OSA severity also had a reduction in CRP, independent of changes in body weight. This reduction in CRP levels was seen in both subgroups of responders (Response15 and Response5), and interestingly, for the group of subjects who were considered responders by one definition (Response15) but not the other (Response5). There is substantial controversy as to the most appropriate definition of surgical response,[12] but the linear association between the reduction in AHI and CRP suggests that although greater reductions in AHI are more beneficial, smaller reductions may not be meaningless.

Two studies have examined surgical treatment and CRP. One showed a reduction in CRP 3 months after uvulopalatopharyngoplasty with tonsillectomy, with the reduction associated with the change in AHI.[16] Another incorporated a variety of multilevel procedures and showed a decline in CRP in the entire cohort as well as both subgroups defined similarly to the Response15 and NoResponse15 groups; there was no evaluation of the association between changes in OSA severity and CRP.[17]

Multiple studies have shown that elevated or high normal CRP predict the development of cardiovascular disease and its complications, independent of other risk factors.[1] A number of cross-sectional studies have examined the association between CRP and OSA severity. Some have suggested that CRP levels are more closely associated with BMI than OSA severity,[18–22] but others have shown an association independent either of BMI[23] or more detailed measures of adiposity[24,25] and in the nonobese.[26]

There are two groups of PAP studies. The first show no reduction in CRP,[18,19,21,27] but they suffer from two methodological weaknesses. They largely ignore treatment adherence or compliance, indicating in some cases that they asked subjects to use treatment[18] or chose not

to incorporate compliance data into their analyses.[27] In addition, the statistical analyses compare group means rather than changes in individual subjects.[19,21,27] Four studies of PAP have demonstrated improvements. One showed an association between the decrease in AHI on PAP and the reduction in CRP but did not report compliance data.[28] A randomized trial showed that 4 months of compliant PAP (range, 5–6.6 hours of mean nightly use) decreased CRP,[29] and two studies specifically showed that CRP decreased in compliant but not noncompliant users.[30,31]

This study's results are consistent with previous publications. Initiating OSA treatment does not guarantee a decrease in CRP; these changes are seen only in those subjects who have achieved effective treatment (true for both compliant PAP and substantial reductions in OSA severity after surgery). The one exception is the surgical study that did report a reduction in CRP for subjects who did not achieve a substantial reduction in OSA severity.[17]

The present study was designed with adequate statistical power to consider changes in CRP. We also considered other biomarkers and FOSQ scores. Although other surgical studies did suggest adequate power to analyze FOSQ scores, data to make accurate sample size estimates for other biomarkers were limited, as this is the first study of OSA surgical treatment to examine these other biomarkers. Overall, the results for other biomarkers demonstrate a consistent pattern: no changes in the entire cohort and point estimates suggesting possible greater changes in the Response15 than the NoResponse15 subgroup, albeit without statistical significance.

Interleukin-6 is a proinflammatory cytokine that stimulates production of CRP. In this study, in spite of the findings related to CRP, there were no statistically significant changes for interleukin-6. The difference may be related to the smaller sample size for interleukin-6, as the CRP findings in the subgroup with interleukin-6 results had similar findings as for interleukin-6.

Otherwise healthy OSA subjects have normal levels of homocysteine, but those with OSA and a history of ischemic heart disease have demonstrated elevated levels.[32] In the studies of otherwise healthy OSA subjects, PAP use lowered homocysteine levels within the high normal range[31] but had no effect in another.[21] In our study, surgical treatment was associated with a small increase in homocysteine levels, but the clinical significance of this increase with normal homocysteine levels (in all subjects from this study) is unclear.

Large clinic- and population-based studies have shown that insulin resistance (based on abnormal HOMA-IR values) is associated with OSA severity, even after adjustment for measures of obesity such as body mass index and percent body fat.[33] This study showed no statistically significant changes in the HOMA-IR, but this may be due to inadequate sample size and low statistical power.

The present study to our knowledge is the first to examine changes in leptin levels after OSA surgical treatment, although there was no difference in leptin levels after surgery. Leptin levels have been shown to be elevated in subjects with OSA, whereas effective PAP treatment reduces leptin levels to normal.[34] Using the standard deviation estimates of Table II, this sample size enables detection of a difference of 4.2 ng/mL in the entire cohort and

7.4 ng/mL in the Response15 subgroup with 80% power at an $\alpha = .05$ level. Both of these detectable differences are within the ranges reported after effective PAP, but a larger sample size would be able to detect smaller potential differences.

In spite of the large volume of evidence describing the adverse health-related consequences of OSA, many patients seek treatment only because of the decrement in quality of life associated with the disorder. Improvements in FOSQ scores have been shown with surgical treatment.[35–39] The present study showed substantial improvements in FOSQ scores, with improvements in both responder and nonresponder subgroups that were not statistically different from each other. The improvement in both subgroups and the lack of an association between changes in FOSQ scores and AHI raises one of two possibilities: that the potential benefits of OSA surgical treatment on surgical treatment are not captured entirely by AHI or other aspects of the Response15 definition, or that at least some of the FOSQ score changes are due to a placebo effect (possible given this is a subjective outcome in an unblinded study). It is notable that the magnitude of the FOSQ score changes in the published surgical literature is loosely correlated with the invasiveness of the procedure, ranging from means of 1.2 to 1.8 for tongue radiofrequency (in a randomized, placebo-controlled trial)[35,37] and 1.4 for the Pillar Procedure,[39] to 2.0 for tongue base suspension,[36] to 2.9 in this study, and to 4.5 for maxillomandibular advancement.[38]

Potential limitations of this study include the lack of a single sleep testing center for all sleep studies and the lack of blinding in the interpretation of sleep studies. Although these would enhance standardization in polysomnogram technique and interpretation, the present study was designed to reflect standard clinical practice, in which patients obtain sleep studies from multiple testing facilities and undergo trials of PAP prior to consideration of surgery. We attempted to maximize consistency in testing methods and interpretation by having subjects return to the same center for their postoperative study. We did evaluate the influence of scoring criteria for respiratory events centers and showed that there was no association between the likelihood of surgical response and the two different criteria used most commonly for the polysomnograms in the present study.[6,40]

Another potential weakness is that the multilevel surgical intervention shared certain features but was not uniform, as not every subject underwent tonsillectomy and/or hyoid suspension. We did evaluate this heterogeneity specifically and showed that the performance of these procedures was not clearly associated with outcomes. The lack of randomization raises issues as well, because we used subjects as their own controls rather than having an untreated control group or one receiving treatment by another method. Within-subject comparisons are useful for identifying biological effects, but raise issues such as regression to the mean and possible changes in biomarkers based on natural history or longitudinal changes. We doubt important changes would have occurred spontaneously based on both the literature and our experience, but controlled studies will be required in the future.

Finally, the sample size was sufficient only to detect large differences in biomarker changes, other than CRP and leptin. A larger study may have demonstrated that the patterns we observed, with point estimates showing greater changes in responders than nonresponders,

were statistically significant. Future research may utilize these results as preliminary data for a study to detect clinically meaningful changes in these biomarkers.

CONCLUSION

This multilevel surgical treatment was associated with a low likelihood of response in subjects with body mass index >32 kg/m^2. Responders had decreases in CRP levels that were independent of changes in body weight. Homocysteine levels increased slightly in the entire cohort and responders. There was an increase in FOSQ scores in the entire cohort that was also seen both in responders and nonresponders.

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TABLE I

Sleep Study Results.

	Entire Cohort (N = 30)				Response15 (n = 13)				NoResponse15 (n = 17)				Response5 (n = 7)				NoResponse5 (n = 23)			
	Pre	Post	Difference	p*	Pre	Post	Difference	p*	Pre	Post	Difference	p*	Pre	Post	Difference	p*	Pre	Post	Difference	p*
AHI	44.9 ± 28.1	27.8 ± 26.4	−17.1 ± 32.7	.008	39.8 ± 25.8	4.8 ± 3.4	−35.0 ± 25.4	.0003	48.9 ± 29.9	45.4 ± 22.2	−3.5 ± 31.6	.66	34.5 ± 11.2	3.1 ± 0.7	−31.4 ± 11.2	.03	48.1 ± 5.8	36.6 ± 5.1	−11.6 ± 33.0	.11
Al	18.1 ± 18.2	15.4 ± 25.4	−2.8 ± 18.5	.44	13.2 ± 11.9	1.8 ± 2.6	−11.4 ± 10.9	.003	18.6 ± 22.4	23. 3 ± 6.8	4.7 ± 20.7	.39	10.4 ± 4.7	0.6 ± 1.2	−9.8 ± 4.8	.12	18.3 ± 4.2	18.1 ± 5.2	−0.1 ± 4.3	.97
HI	26.7 ± 23.6	11.3 ± 13.5	−15.4 ± 26.3	.004	26.6 ± 19.8	3.0 ± 1.9	−23.6 ± 19.6	.001	26.7 ± 27.2	18.3 ± 15.6	−8.4 ± 29.8	.29	25.2 ± 7.9	2.5 ± 1.1	−22.7 ± 8.5	.04	27.2 ± 5.4	14.8 ± 3.1	−12.4 ± 6.1	.06
LSAT	82.4 ± 7.7	80.7 ± 7.6	−2.5 ± 10.7	.21	77.6 ± 11.8	89.8 ± 4.2	12.1 ± 10.1	.01	82.4 ± 7.6	80.6 ± 7.6	−1.8 ± 9.2	.44	81.3 ± 3.8	87.9 ± 1.7	6.5 ± 3.8	.13	80.1 ± 2.1	81.4 ± 1.1	1.3 ± 2.3	.57
% Time below 90% saturation	13.2 ± 15.6	9.1 ± 13.9	−4.1 ± 20.4	.40	10.4 ± 14.0	1.5 ± 2.0	8.9 ± 12.8	.09	14.4 ± 16.5	14.4 ± 15.7	0.0 ± 23.7	.99	1.4 ± 0.7	0.7 ± 0.4	−0.6 ± 0.4	.17	15.6 ± 3.9	11.5 ± 3.5	−4.0 ± 5.5	.48
Stage 3/4 sleep (%)	7.8 ± 9.8	9.6 ± 14.8	1.9 ± 16.6	.56	3.9 ± 7.0	6.3 ± 6.5	2.3 ± 7.7	.39	10.4 ± 10.7	12.1 ± 17.9	1.7 ± 20.2	.74	1.5 ± 1.0	7.0 ± 3.3	5.5 ± 3.2	.16	9.7 ± 2.3	10.7 ± 3.7	1.0 ± 4.1	.80
REM sleep (%)	7.4 ± 7.2	11.9 ± 9.4	4.5 ± 9.1	.01	11.1 ± 6.9	17.6 ± 5.5	6.5 ± 8.0	.04	4.8 ± 6.3	8.8 ± 9.8	4.0 ± 9.8	.11	7.4 ± 1.7	16.2 ± 1.2	8.8 ± 1.2	.002	6.9 ± 1.7	10.9 ± 2.2	3.9 ± 2.2	.08

*P values are for paired t tests of differences.

Pre = preoperative; Post = postoperative; LSAT = lowest oxygen saturation; AHI = apnea-hypopnea index; AI = apnea index; HI = hypopnea index; REM = rapid eye movement.

TABLE II

Biomarker and Functional Outcome of Sleep Questionnaire Results.

	Entire Cohort (N = 30)					Response15 (n = 13)					NoResponse15 (n = 17)				
	No.	Pre	Post	Difference	*P**	No.	Pre	Post	Difference	*P**	No.	Pre	Post	Difference	*P**
C-reactive protein (mg/L)	30	2.71 ± 2.28	2.42 ± 2.19	−0.30 ± 1.68	.34	13	2.95 ± 3.06	1.93 ± 2.49	−1.02 ± 0.98	.003	17	2.54 ± 1.54	2.79 ± 1.92	0.25 ± 1.92	.59
lnterleukin-6 (pg/mL)	21	2.96 ± 2.74	2.00 ± 1.30	−0.96 ± 2.27	.07	9	3.39 ± 3.93	1.99 ± 1.37	−1.40 ± 3.32	.24	12	2.64 ± 1.45	2.02 ± 1.30	−0.63 ± 1.05	.06
Homocysteine (μmol/L)	30	8.0 ± 2.1	8.5 ± 2.3	0.6 ± 1.3	.02	13	7.8 ± 2,4	8.6 ± 3.0	0.8 ± 1.1	.02	17	8.1 ± 1.9	8.5 ± 1.7	0.4 ± 1.4	.29
HOMA-IR	21	4.19 ± 3.26	3.69 ± 2.09	−0.50 ± 2.29	.33	9	4.70 ± 4.00	3.47 ± 1.66	−1.23 ± 3.04	.23	12	3.74 ± 2.53	3.89 ± 2.48	0.15 ± 1.09	.65
Leptin (ng/mL)	30	12.5 ± 10.7	10.5 ± 6.8	−2.0 ± 8.0	.19	13	12.3 ± 12.5	9.1 ± 6.4	−3.3 ± 8.8	.20	17	12.6 ± 9.4	11.6 ± 7.1	−1.0 ± 7.5	.60
FOSQ composite score	30	14.6 ± 3.1	17.5 ± 2.7	2.9 ± 3.3	.0003	13	14.8 ± 2.9	18.5 ± 2.5	3.7 ± 3.4	.005	17	14.3 ± 3.1	16.5 ± 2.9	2.2 ± 3.1	.03

** P* values are for paired *t* tests of differences.

Pre = preoperative; Post = postoperative; HOMA-IR = homeostasis model of insulin resistance; FOSQ = Functional Outcome of Sleep Questionnaire.