

Oropharyngeal Collapse Predicts Treatment Response With Oral Appliance Therapy in Obstructive Sleep Apnea

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Study Objectives: To examine whether primary oropharyngeal collapse of the upper airway during sleep predicts treatment success with oral appliance therapy in patients with obstructive sleep apnea.

Design: Prospective physiologic study.

Setting: Multidisciplinary sleep disorders clinic in a university teaching hospital.

Patients: Twelve treatment-naïve adult patients with obstructive sleep apnea (apnea-hypopnea index ≥ 10 /h and at least 2 of the following symptoms: snoring, fragmented sleep, witnessed apneas, or daytime sleepiness).

Intervention: Custom-made mandibular advancement splint (MAS).

Measurements and Results: A baseline diagnostic polysomnogram confirmed AHI ≥ 10 per hour. During the following acclimatization period, a custom-made adjustable MAS was incrementally advanced until maximum comfortable mandibular protrusion was reached. A second polysomnogram with MAS in situ determined efficacy. Following a 1-week washout period, a final sleep study was performed using multisensor catheters (with and without MAS, in random order during the same night) to deter-

mine upper-airway closing pressures and the site or sites of upper-airway collapse. MAS resulted in significant improvements, mean \pm SEM, in AHI (22.0 ± 2.6 vs 9.2 ± 1.9 /h, $p < .01$) and upper-airway closing pressures during stage 2 non-rapid eye movement sleep (-1.1 ± 0.3 vs -2.8 ± 0.5 cm H₂O, $p < .01$). All 4 patients with primary oropharyngeal collapse achieved an AHI < 5 per hour. Only 1 of the 8 patients with primary velopharyngeal collapse achieved an AHI < 5 per hour. Oropharyngeal collapse, compared with velopharyngeal collapse, predicted treatment success with MAS ($p < .02$).

Conclusions: These preliminary data suggest that primary oropharyngeal collapse of the upper airway during sleep is an important predictor of treatment outcome with MAS therapy.

Keywords: Obstructive sleep apnea, orthodontic appliances, upper airway collapsibility

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INTRODUCTION

ORAL APPLIANCES ARE INCREASINGLY BEING RECOGNIZED AS A TREATMENT MODALITY FOR OBSTRUCTIVE SLEEP APNEA (OSA). THESE TYPICALLY INDUCE protrusion of the mandible by an appliance worn during sleep and are often referred to as mandibular advancement splints (MAS). Up to 50% of patients are complete treatment responders, and it is often the patient's preferred choice of treatment when compared with continuous positive airway pressure (CPAP) therapy.¹⁻⁵ In general, however, its efficacy is inferior to CPAP therapy, and a key unresolved issue is the inability to predict which patients will respond favorably to treatment.

A number of different predictive models have been reported in the literature and incorporate various physiologic and anthropomorphic measurements.⁶⁻⁸ However, most of these measurements involve awake variables, and no predictive model has been tested

prospectively to assess clinical utility. Current understanding of the mechanisms of action of MAS on upper-airway function remains incomplete, and a better knowledge is required to improve our ability to predict treatment outcome. We recently demonstrated that upper-airway collapsibility during sleep improved significantly with MAS therapy⁹ and found that patients with greater improvements in upper-airway closing pressures (UACP) also had greater improvements in apnea-hypopnea index (AHI). However, baseline UACP was not predictive of treatment outcome. This led us to hypothesize that the site of upper-airway collapse during sleep is an important determinant of MAS-treatment response. Such an approach has been shown to have some benefit in predicting treatment response to uvulopalatopharyngoplasty.¹⁰ Hence, our primary aim in this study was to evaluate whether the location of upper-airway collapse during sleep influences treatment outcome with MAS therapy in patients with OSA. Our secondary aims were to compare UACP changes induced by MAS by site of upper-airway collapse and to determine whether MAS alters the site of upper-airway collapse.

METHODS

Study Population

Treatment-naïve patients were recruited from a multidisciplinary sleep disorders clinic in a university teaching hospital. Inclusion criteria were the presence of at least 2 symptoms of OSA (snoring, fragmented sleep, witnessed apneas, daytime sleepiness) and evidence of OSA on polysomnography, with an AHI ≥ 10 per hour. Patients were excluded if there was evidence of periodontal disease, dental caries, edentulism, an exaggerated gag reflex, or predominant central sleep apnea. The study was approved by the

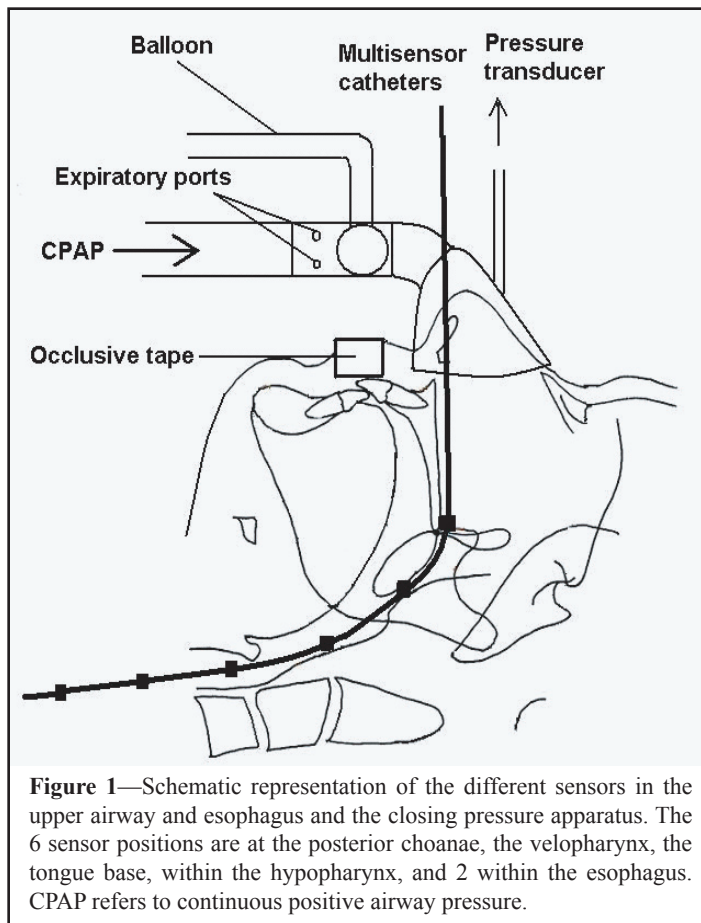
Disclosure Statement

This was not an industry supported study. Dr. Cistulli is on the Medical Advisory Board of SomnoMed Ltd, a company that is commercializing the oral appliance used in this study. He has received consulting fees and holds shares in the company. He has been a principal investigator in sponsored clinical trials for ResMed and Cephalon. Drs. Ng and Qian have indicated no financial conflicts of interest.

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institutional ethics committee, and written informed consent was obtained from all patients.

Oral Appliance

We used a commercially available custom-made 2-piece adjustable MAS (SomnoMed MAS™, SomnoMed Ltd, Australia), which has previously been described by our group.^{6,9,30}

Protocol

Patients underwent an acclimatization period of approximately 6 weeks, during which the MAS was incrementally advanced until the maximum comfortable limit was reached. Polysomnography was performed at the end of acclimatization with the MAS to determine efficacy. Patients then had no treatment during a 1-week period (a previously demonstrated effective washout period⁶). A subsequent sleep study, involving the use of multisensor catheters within the upper airway and esophagus, was performed to identify the primary and secondary site or sites of airway obstruction during sleep. This was performed with and without MAS in a single night, in random order to avoid an order effect.

Outcome Measures

Polysomnography

Standard nocturnal polysomnography was performed as previously described.^{6,9} Sleep recordings and respiration-measurement techniques were scored in a standard fashion^{12,13,29} by an experienced polysomnographer who was blinded to the patients' treatment. In brief, apnea was defined as cessation of airflow for at

least 10 seconds. Hypopnea was defined as a reduction in amplitude of airflow, measured as pressure change at the nares, or thoracoabdominal wall movement of greater than 50% of the baseline measurement for more than 10 seconds with an accompanying oxygen desaturation of at least 3% and/or associated with arousal. These events were considered obstructive if they occurred in association with continued diaphragm electromyogram activity and thoracoabdominal wall movement.

Upper Airway Closing Pressure

This technique provides a direct measurement of the pressure at which experimentally induced airway collapse occurs (Figure 1).^{27,28} It differs from pharyngeal critical pressure (Pcrit), which is thought to measure the pressure surrounding the locus of pharyngeal collapse and is an indirect measurement based on pressure-flow relationships.²⁶ In brief, a specially designed nose mask system that allowed for the provision of CPAP as well as complete external occlusion at the nose was used. This mask consisted of a modified silastic bubble mask that incorporated rigid nasal prongs to prevent nasal alae collapse. A perspex tube was connected to the manifold of the mask through which a rubber balloon catheter (Foley urinary catheter) was inserted. Using a syringe, complete occlusion was achieved by manually inflating the balloon with air. Patients slept supine with their head kept in the neutral position. During sleep, CPAP was titrated to prevent snoring and upper-airway obstruction. Following continuous stable sleep of at least 10 minutes, complete external nasal occlusion was applied at end expiration, causing each obstructed inspiratory effort to produce a progressive increase in suction pressure to a maximum value, followed by a rapid return to baseline. Each subsequent occluded inspiratory effort produced a larger (more subatmospheric) increase in nasal pressure until a critical pressure was reached, at which point the nasal pressure ceased to increase despite increasing inspiratory efforts, as evidenced by the esophageal pressure tracings. This critical pressure has been defined as the UACP (Figure 2). The more negative the UACP the less collapsible (i.e., more stable) the airway. Occlusive tape was applied to the patient's mouth to prevent mouth leaks. Multiple measurements were taken in each of the conditions. Average UACP in stage 2 non-rapid eye movement (NREM) sleep in patients with OSA has been shown to occur between -0.6 and -4.2 cm H₂O and in snorers between -3.7 and -8.2 cm H₂O. UACP was also shown to be more stable (i.e., more negative) during slow-wave sleep.^{27,28}

Sites of Upper Airway Collapse

For this study, upper-airway sites were defined as follows: velopharynx (from the level of the hard palate to the tip of the uvula), oropharynx (end of the uvula to the tip of the epiglottis), and hypopharynx (tip of the epiglottis to the vocal cords) (Figure 2). A calibrated multisensor solid-state catheter system (Gaeltec, Dunvegan, Scotland) was used to measure pressure at 5 predetermined sites within the upper airway in order to localize the collapsing segment (Figure 1). The catheters were passed through the patient's nose following preparation with 1 mL of lignocaine 1% spray, intubated into the upper airway and the esophagus, and secured firmly with tape to the tip of the patient's nose. Nasendoscopy with the patient supine was performed to verify sen-

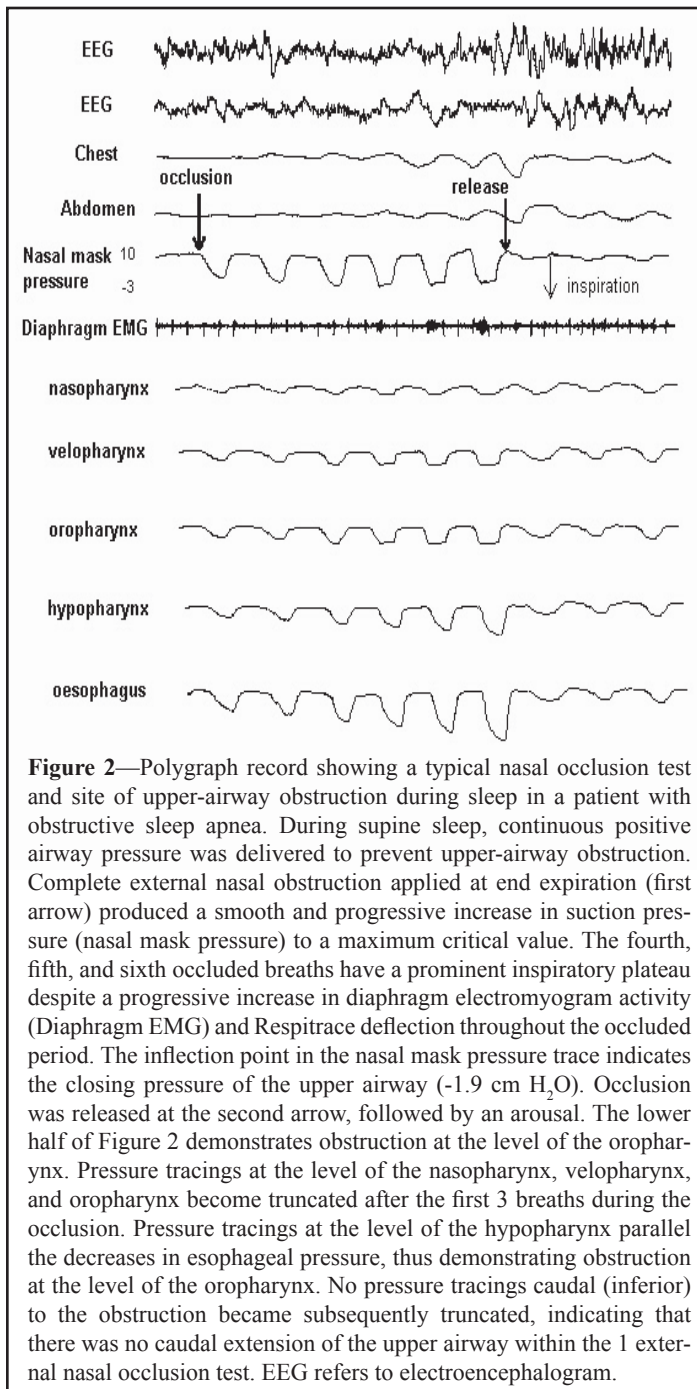


Figure 2—Polygraph record showing a typical nasal occlusion test and site of upper-airway obstruction during sleep in a patient with obstructive sleep apnea. During supine sleep, continuous positive airway pressure was delivered to prevent upper-airway obstruction. Complete external nasal obstruction applied at end expiration (first arrow) produced a smooth and progressive increase in suction pressure (nasal mask pressure) to a maximum critical value. The fourth, fifth, and sixth occluded breaths have a prominent inspiratory plateau despite a progressive increase in diaphragm electromyogram activity (Diaphragm EMG) and Respiration deflection throughout the occluded period. The inflection point in the nasal mask pressure trace indicates the closing pressure of the upper airway (-1.9 cm H₂O). Occlusion was released at the second arrow, followed by an arousal. The lower half of Figure 2 demonstrates obstruction at the level of the oropharynx. Pressure tracings at the level of the nasopharynx, velopharynx, and oropharynx become truncated after the first 3 breaths during the occlusion. Pressure tracings at the level of the hypopharynx parallel the decreases in esophageal pressure, thus demonstrating obstruction at the level of the oropharynx. No pressure tracings caudal (inferior) to the obstruction became subsequently truncated, indicating that there was no caudal extension of the upper airway within the 1 external nasal occlusion test. EEG refers to electroencephalogram.

sor placement. The sensors were spaced at 2-cm intervals, and 2 sensors lay within the esophagus. All signals were amplified, observed, and recorded on a Macintosh computer (Apple, Cupertino, CA) using GastroMac software (Neomedix Systems, Sydney, NSW, Australia). Supine radiographs taken in the morning following the sleep study confirmed that placement of the sensors had not changed.

Treatment Outcome

Complete response was defined as resolution of symptoms and AHI of less than 5/hour. Partial response was defined as improved symptoms plus at least a 50% reduction in AHI but remaining at 5 or more per hour. Failure was defined as a less than 50% reduction in AHI. Treatment outcomes were also expressed in terms of percentage reduction in AHI.

Table 1—Characteristics of the Study Sample at Baseline

Variable	Mean ± SD	Range
Sex, men/women, no.	11/1	
Age, y	51 ± 9	38-66
BMI, kg/m ²	27.5 ± 3.9	19.2-34.0
Neck circumference, cm	41.5 ± 3.0	35.0-45.5
AHI, no./h		
Total	22.0 ± 8.9	10.1-36.9
Supine	38.4 ± 16.4	17.8 - 67.4
Lateral	5.9 ± 8.4	0.3 - 16.2
MinSaO ₂ , %	84 ± 4	78-89

BMI refers to body mass index; AHI, apnea-hypopnea index; MinSaO₂ = minimum arterial oxygen saturation.

Statistical Analysis

Data were analyzed using a statistical package (SPSS Version 8.0; SPSS Inc, Chicago IL). Paired t-tests were used to compare clinical and physiologic variables before and after MAS therapy. UACP measurements before and after MAS therapy were compared using repeated-measures analysis of variance. The relationship between the site of upper-airway collapse and treatment outcome was assessed using a contingency table and Fisher exact test for small expected frequencies. All descriptive statistics are presented as mean ± SD. Estimated means are presented as mean ± SEM.

RESULTS

Study Population

The study sample consisted of 12 patients (11 men, 1 woman), all of whom completed the protocol. Patient characteristics at baseline are presented in Table 1. The majority of patients had supine-related OSA. There were no significant differences between baseline and treatment measurements with regard to body mass index or neck circumference. The mean mandibular advancement with the MAS was 4.5 ± 1.9 mm (range 3.0-9.0 mm), representing 71% of maximal protrusion on average.

Outcomes

The MAS was well tolerated by all patients. Only mild and transient side effects were experienced, which included excessive salivation, gum irritation, mouth dryness, and jaw discomfort. These did not preclude use of the MAS.

Polysomnographic outcomes, including change in AHI and supine and lateral AHI are summarized in Table 2. MAS therapy resulted in a significant reduction in AHI of 54% and a significant increase in minimum SaO₂. Complete response (AHI < 5/h) was achieved in 5 patients (42%), partial response in 2 patients (16%), and treatment failure in 5 patients (42%). Seven patients (58%) achieved an AHI < 10/hour. The 2 partial responders improved from a baseline AHI of 23.4/hour and 36.9/hour down to 8/hour and 11.1/hour, respectively. One treatment-failure patient had a baseline AHI of 14.7/hour, which improved to 9.4/hour.

During the repeated external nasal-occlusion tests, the site of primary upper-airway closure in all 12 patients remained the same throughout the night, with and without MAS. Two sites of upper-airway obstruction were seen: (1) velopharyngeal and (2)

Table 2—Outcome Measurements

Variable	No MAS	MAS	p Value
BMI, kg/m ²	27.5 ± 3.9	27.4 ± 3.9	.3
Neck circumference, cm	40.5 ± 3.0	40.4 ± 2.9	.6
AHI, no./h			
Total	22.0 ± 2.6	9.2 ± 1.9	.01
Supine	38.4 ± 4.9	13.0 ± 3.9	< .01
Lateral	5.9 ± 2.8	3.7 ± 1.2	.5
MinSaO ₂ (%)	84 ± 4	88 ± 3	.03
UACP, cm H ₂ O	-1.1 ± 0.3	-2.8 ± 0.5	< .02

Comparison made using paired t-test. Data for the upper-airway closing pressure in stage 2 non-rapid eye movement sleep (UACP) are compared using repeated-measures analysis of variance. Data are presented as mean ± SEM. MAS refers to mandibular advancement splint; BMI, body mass index; AHI, apnea-hypopnea index; MinSaO₂, minimum arterial oxygen saturation.

oropharyngeal obstruction. Neither multiple sites of upper-airway closure within the 1 patient nor caudal extension of the upper-airway obstruction were seen. The site of occlusion occurring in response to spontaneous apneas was also recorded and did not differ to that occurring in response to experimentally induced airway occlusion.

Eight patients had primary velopharyngeal closure (Table 3). Of these, 1 had a complete response, 2 had partial responses, and 5 had treatment failures. Four patients had primary oropharyngeal closure, and all had complete responses. Patients with oropharyngeal closure were significantly more likely to have complete responses with MAS therapy than were patients with velopharyngeal closure ($p < .02$). Mean change in UACP (stage 2 NREM sleep) in oropharyngeal collapsers was significantly greater than for velopharyngeal collapsers (-3.6 ± 0.8 cm H₂O vs -0.72 ± 0.2 cm H₂O, $p < .05$). Mean reduction in AHI in oropharyngeal collapsers was significantly greater than in velopharyngeal collapsers ($85\% \pm 8\%$ vs $35\% \pm 14\%$, $p < .05$). There was, however, no difference in mandibular protrusion between oropharyngeal collapsers (4.5 mm) and velopharyngeal collapsers (4.6 mm), and there was no correlation between the amount of advancement and treatment outcome.

While there was no significant difference between the body mass index, age, or baseline AHI in the oropharyngeal collapsers versus the velopharyngeal collapsers, the 1 patient with primary velopharyngeal collapse who had a complete response was also the thinnest (body mass index 19.2 kg/m²). The 1 woman in the study had oropharyngeal collapse and had a complete response.

UACP measurements were taken during all stages of sleep with the patient in the supine position. However, complete data sets were only attained during stage 2 NREM sleep due to the variability of attaining REM and slow-wave sleep during both parts of the night. Each patient underwent a minimum of 10 UACP measurements both with and without MAS, and these were highly reproducible within each condition. MAS therapy resulted in significant improvements in UACP during stage 2 NREM sleep (Table 2). A significant correlation was found between the change in AHI and change in UACP in stage 2 NREM sleep ($r = 0.67$, $p < .05$). Baseline UACP was not predictive of OSA severity, nor of treatment outcome. Treatment-order effects were found to be nonsignificant ($p = .7$). The critical CPAP pressure required to

Table 3—Site of Obstruction Versus Outcome Variables

	Site of Obstruction	
	Velopharynx	Oropharynx
Complete responder	1	4
Partial responder	2	0
Failure	5	0
AHI < 10/h with MAS	3	4
Baseline AHI, no./h	19.2 ± 3.0	27.7 ± 3.7
Baseline UACP, cm H ₂ O	-1.2 ± 0.4	-0.93 ± 0.4
UACP improvement	-0.72 ± 0.2	-3.6 ± 0.8 ^a

Complete responder refers to resolution of symptoms and reduction in apnea-hypopnea index (AHI) to <5/h; partial responder, improved symptoms plus $\geq 50\%$ reduction in AHI but remaining ≥ 5 /hour; failure, < 50% reduction in AHI; UACP, upper airway closing pressure in stage 2 non-rapid eye movement sleep.

Within the one patient, the site of upper airway obstruction did not change, nor did it change when the MAS was in situ.

^a $p < .05$

prevent upper-airway obstruction during the UACP determination was lower with MAS (10%-20%).

DISCUSSION

Our data indicate that the site of UA collapse during sleep in OSA has an important influence on oral appliance treatment outcome, with primary oropharyngeal collapse being strongly predictive of success. To date, a key barrier to the more widespread use of oral appliances in the treatment of OSA has been the difficulty of predicting treatment outcome, and our findings go some way toward resolving this problem.

The primary finding of this study, ie, the influence of oropharyngeal collapse during sleep on treatment outcome with oral appliances, could potentially be used to predict treatment response with MAS therapy. Other studies on prediction have focused on incorporating physiologic and anthropomorphic measurements into prediction equations,⁶⁻⁸ most of which involve awake variables, with none having been tested prospectively for clinical utility. A study by Sanner and coworkers¹⁴ has suggested that magnetic resonance imaging scans could predict treatment outcome. They studied awake patients performing the Mueller maneuver and suggested that MAS has a favorable effect on awake oropharyngeal collapse. In a subgroup analysis of the 7 treatment responders (defined as AHI < 10), 2 were found to have velopharyngeal collapse, 3 had oropharyngeal collapse, and 2 had combined velopharyngeal and oropharyngeal collapse without the MAS. When the MAS was worn, the Mueller maneuver caused upper-airway collapse only in the 2 velopharyngeal collapsers, and, in the rest of the patients, the upper airway remained patent. Another study by Henke et al¹¹ examined 12 patients using an oral appliance during sleep and used an upper-airway pressure transducer to determine the site of closure. During posthoc subgroup analysis, far greater reductions in AHI were seen in the 3 patients who had upper-airway closure below the velopharynx compared with the 9 patients who had upper-airway closure at the velopharynx, but no statistical significance was demonstrated. These studies suggest that oropharyngeal collapsers respond more favorably to MAS therapy, and our present study is the first to demonstrate that primary oropharyngeal collapse strongly predicts treatment

success.

Most of our patients were found to have upper-airway collapse at the velopharynx. This is in agreement with other authors who have studied patients with OSA using multisensor catheters during sleep.¹⁵⁻¹⁸ In a different study using anesthetized rather than sleeping subjects, Isono¹⁹ examined 40 patients and 17 controls using endoscopy and also found a predominance of velopharyngeal closure (49 subjects) versus oropharyngeal closure (8 subjects).

Another observation from our present study was that the site of obstruction (taken during NREM sleep) remained fixed during repeated measurements. This is consistent with findings by Hudgel et al.²⁰ Two other studies by Katsounis et al¹⁷ and Shepard et al¹⁶ also found that upper-airway collapse remained fixed during NREM sleep but could extend caudally during REM sleep. Woodson et al¹⁸ found that the majority of their 12 patients also had a fixed site of upper-airway collapse, although 3 patients had extension of their initial retropalatal collapse. However, other authors have found more variability in the site of upper-airway collapse within the individual patient.^{15,21,22} While these discrepancies are likely to be real, interpretations of studies can be difficult because of different definitions and methodologies for upper-airway collapse,²¹ different nomenclature for the same anatomic structures, generally small numbers of patients, and many older studies having used only 3 sensors.¹⁵

Our study is also the first to examine the site of upper-airway collapse with and without MAS during sleep. Our findings demonstrate that the site of upper-airway collapse remained consistent within the same patient with or without the MAS in situ. This suggests that, while MAS improves overall upper-airway collapsibility (and significantly more so in oropharyngeal collapsers than in velopharyngeal collapsers), it does not alter the location of collapse. Our study suggests that the greatest physiologic impact of MAS occurs at the level of the oropharynx, and, therefore, patients with primary oropharyngeal collapse are more likely to respond favorably. Patients with oropharyngeal collapse were found to have greater improvements in UACP than those with velopharyngeal collapse. Patients who failed treatment with MAS also had smaller improvements in UACP, and it could be postulated that this is the reason for their nonresponsiveness to MAS therapy. The 1 patient with velopharyngeal collapse (body mass index 19.2) had only a moderate improvement in UACP with MAS, but was a treatment success. Perhaps being thin and a velopharyngeal collapse leads to a more favorable outcome, whereas, for oropharyngeal collapsers, weight does not appear to be so important. No doubt there are multiple factors that interact to produce the therapeutic effect in MAS treatment, and perhaps being thin, female, having supine-dependent OSA, certain craniofacial characteristics, and level of upper-airway obstruction are just the currently identified factors.³¹

The average mandibular protrusion of 4.5 mm is less than in previous studies²⁹ but nevertheless resulted in a 42% complete response rate, a rate that is comparable with other studies. This was, however, our patients' maximal comfortable mandibular protrusion amount and was 71% of maximum protrusion. This "dose" of advancement has been recommended in other studies. In addition, small advancements have also been known to result in treatment success.³¹

The major limitation to this study was the small sample size. This was due to the labor intensiveness and complex physiologic

measurements involved. Nevertheless, we believe that our study sample is a fair representation of the general OSA population. Most patients were middle-aged men, the severity of OSA covered the whole spectrum from mild to severe, the proportion of velopharyngeal and oropharyngeal collapsers was similar to other studies,¹⁵⁻¹⁸ the number of patients with positional OSA was 58% (similar to the 56% found by Oskenberg and colleagues³² in their study of positional OSA), and the treatment outcomes were similar to previous studies using the same appliance.^{6,9,29} One major difference, however, was the proportion of obese patients (25% in our study compared with 50% shown by Mortimore and colleagues³³ in their study examining obesity in OSA). Lower weight has been suggested as a possible predictor for treatment success in MAS therapy.^{7,34,35}

Other limitations included the shorter sleep times available to the patient during the UACP/collapsing-site studies leading to a paucity of REM sleep, which would have given additional information, and the local anesthesia applied to the nasal cavity. However, local anesthesia appears to have little influence on upper-airway resistance,^{23,24} and its effects would have disappeared after 30 minutes, long before any measurements were made.

In conclusion, prediction of treatment outcome with oral appliance therapy in OSA remains a key unresolved issue. Various algorithms have been postulated, but none have established any utility in clinical practice. While the upper-airway catheterization technique used in this study is unlikely to have a role in routine clinical practice, this study has demonstrated that the site of upper-airway closure is an important determinant of treatment outcome. Further studies are needed in order to develop a simple and clinically useful method of predicting oropharyngeal collapse and, hence, treatment success.

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