Effect of Oral Appliance Therapy on Upper Airway Collapsibility in Obstructive Sleep Apnea

Andrew T Ng, Helen Gotsopoulos, Jin Qian, and Peter A Cistulli

Department of Respiratory and Sleep Medicine, St. George Hospital, University of New South Wales, Sydney, Australia

Oral appliance therapy is emerging as an alternative to continuous positive airway pressure for the treatment of obstructive sleep apnea (OSA). However, its precise mechanisms of action are yet to be defined. We examined the effect of a mandibular advancement splint (MAS) on upper airway collapsibility during sleep in OSA. Ten patients with proven OSA had a custom-made MAS incrementally adjusted during an acclimatization period until the maximum comfortable limit of mandibular advancement was reached. Polysomnography with the splint was then performed. After a 1-week washout period, upper airway closing pressures during sleep (with and without MAS) were determined. Significant improvements with MAS therapy were seen in the apnea/hypopnea index (25.0 ± 3.1 vs. 13.2 ± 4.5/hour, $p < 0.03$) and upper airway closing pressure in Stage 2 sleep (-1.6 ± 0.4 vs. -3.9 ± 0.6 cm H_2O, $p < 0.01$) and in slow wave sleep (-2.5 ± 0.7 vs. -4.7 ± 0.6 cm H_2O, $p < 0.02$) compared with no therapy. These preliminary data indicate that MAS therapy is associated with improved upper airway collapsibility during sleep. The mediators of this effect remain to be determined.

Keywords: mandibular advancement splint; obstructive sleep apnea; upper airway collapsibility

Obstructive sleep apnea (OSA) is a common disorder occurring in around 4% of men and 2% of women in the middle-aged workforce (1). It is characterized by recurrent obstruction of the upper airway during sleep (2). The current treatment of choice is continuous positive airway pressure delivered via a nasal mask to the upper airway during sleep (3). This is an extremely effective treatment, but its cumbersome nature often leads to reduced tolerance and compliance (4–6). An emerging treatment alternative is oral appliance therapy (7), which has potential advantages over continuous positive airway pressure because it is less obtrusive, does not make noise, and is more portable. Of the five randomized crossover trials comparing continuous positive airway pressure with oral appliances (8–12), all but one (12) demonstrated a patient preference in favor of oral appliances. However, although oral appliance therapy has been shown to be effective across all grades of OSA severity (13, 14), a key limitation is reduced effectiveness compared with continuous positive airway pressure (8–12).

Current understanding of the precise mechanisms of action of oral appliances in OSA is incomplete. A better understanding of these mechanisms could improve our ability to predict treatment outcome, a key unresolved issue. Intuitively, one would believe that mandibular advancement should improve the anteroposterior dimension of the oropharynx. However, recent studies suggest that increases in upper airway caliber occur in the lateral dimension at the level of the velopharynx (15, 16). Hence, the anatomic changes induced by mandibular advancement appear to be quite complex, presumably due to the intricate linkages between upper airway structures. Regardless of these anatomic changes, the ultimate determinant of upper airway closure is the degree of upper airway collapsibility during sleep. Abnormal upper airway collapsibility during sleep has been clearly documented in both snorers and patients with OSA compared with normals (17, 18). Furthermore, treatment of OSA by weight loss or surgery has been shown to improve upper airway collapsibility in responders (19, 20). We postulate that oral appliance therapy reduces upper airway collapsibility during sleep. Hence, our aim was to examine the effect of oral appliance therapy on upper airway collapsibility during sleep.

METHODS

Study Population

Adult patients were recruited from a multidisciplinary Sleep Disorders Clinic in a University Teaching Hospital. Inclusion criteria were the presence of at least two symptoms of OSA (snoring, fragmented sleep, witnessed apneas, daytime sleepiness) and evidence of OSA on polysomnography, with an apnea/hypopnea index (AHI) of 10/hour or more. Patients were excluded if there was evidence of periodontal disease, dental caries, edentulism, an exaggerated gag reflex, or predominant central sleep apnea on polysomnography. The study was approved by the institutional Ethics Committee, and written informed consent was obtained from all patients before commencement. We used a mandibular advancement splint (MAS) as described previously by our group (13, 14).

Study Design

A prospective study design was used. Each patient underwent three sleep studies. The first diagnostic polysomnogram confirmed an AHI of more than 10/hour and was performed before study commencement. After an acclimatization period during which incremental anterior adjustments of the mandible were made until the maximum comfortable limit was reached, an additional polysomnogram was performed with the MAS to determine treatment efficacy. Patients then underwent no treatment during a 1-week washout period. A final sleep study was then performed, solely for the purpose of making upper airway closing pressure (UACP) measurements, with and without the MAS (treatment order was randomly assigned within this study night).

Outcome Measures

Polysomnography. Standard nocturnal polysomnography was performed as described previously (13, 14). Sleep recordings were scored in a standard fashion (21, 22) by an experienced polysomnographer who was blinded to the patients' treatment.

UACP. The technique used to measure UACP was first reported by Issa and Sullivan (17, 18). Patients slept in the supine position with the head and neck kept in the neutral position. A specially designed nose mask system was used, allowing for the provision of continuous positive airway pressure as well as complete external occlusion at the nose. Complete external nasal occlusion applied at end-expiration causes each 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 produces a larger (more subatmospheric) increase in nasal pressure until a critical pressure is

reached, at which point the nasal pressure ceases to increase despite increasing inspiratory efforts as evidenced by the increasing respitrace and diaphragm EMG activity. This critical pressure has been defined as the UACP. A typical recording from one of the study patients is shown in Figure 1. The more negative the UACP, the less collapsible the airway. Two qualitatively different patterns of response to nasal occlusion have been identified (17). In the most commonly seen type 1 response, the airway closure occurs only during the inspiratory phase. In the type 2 response, the critical pressure reached during inspiration is also maintained during expiration, indicating complete obstruction during both phases of the respiratory cycle. Multiple measurements were taken in each of the conditions and were highly reproducible. The validity of this technique has been verified by concurrent measurement of esophageal and tracheal pressures (17).

Treatment Outcome

Complete response was defined as a resolution of symptoms and reduction in AHI to less than 5/hour. Partial response was defined as improved symptoms plus a 50% reduction or more in AHI but remaining 5/hour or more. Failure was defined as less than 50% reduction in AHI.

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 treatment. Correlation analysis was performed using Spearman's rank correlation coefficient for nonparametric data. The Mann–Whitney U test was used to compare UACP measurements between treatment outcome groups. All descriptive statistics are presented as mean ± SD. Estimated means are presented as mean ± SEM.

RESULTS

Study Population

The study sample consisted of 10 patients (nine males and one female), all of whom completed the protocol. Patient characteristics at baseline are presented in Table 1. There was no significant difference between baseline and treatment regarding weight. The mean mandibular advancement with the MAS was 4.6 ± 1.4 mm (range, 3.0–8.0) from centric occlusion.

Outcomes

The MAS was well tolerated. Only mild 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 are summarized in Table 2. MAS treatment resulted in a significant reduction in AHI and a significant increase in minimum Sa_{O_2}. The MAS resulted in complete response in five patients (50%), partial response in two patients (20%), and treatment failure in three patients (30%). Six patients (60%) achieved an AHI of less than 10/hour.

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS

Variable	Mean ± SD ($n = 10$)	Range
Sex, male/female	9/1	
Age, yr	44 ± 12	28–58
BMI, kg/m^2	30.8 ± 6.2	24.6–46.8
Neck circumference, cm	40.3 ± 0.5	38.0–42.5
AHI, h^{-1}	25.0 ± 9.8	14.6–44.6
MinSa$_{O_2}$, %	86 ± 4	79–93

Definition of abbreviations: AHI = apnea/hypopnea index; BMI = body mass index; MinSa$_{O_2}$ = minimum Sa$_{O_2}$.

MAS treatment resulted in significant improvements in UACP during Stage 2 non-REM sleep and slow wave sleep (Table 2). Improvement was noted in all subjects, albeit to different degrees. Nine patients had the type 1 response with and without MAS. One patient had the type 2 response without MAS, converting to a type 1 response with MAS.

A significant positive correlation was found between the change in AHI and change in UACP in Stage 2 non-REM sleep ($r = 0.64$, p < 0.05). A median improvement in UACP (Stage 2 non-REM sleep) of 2.8 cm H_2O (25th, 75th percentiles 1.9, 5.7) was observed in the complete responders, and this was significantly greater than the median of 1.1 cm H_2O (25th, 75th percentiles: 0.6, 1.2) seen in the combined group of partial responders and treatment failures (Mann–Whitney U: z = −2.41, p < 0.01).

No significant correlation was found between baseline UACP and AHI or between the degree of mandibular advancement and change in UACP.

DISCUSSION

Despite the increasing use of oral appliances in the treatment of OSA, considerable uncertainty about their precise mechanisms of action exists. This is the first study to examine the influence of an oral appliance on UACP during sleep. We found that the MAS improved upper airway collapsibility and suggest that this is one mechanism through which OSA is improved.

Upper airway patency is complex and involves a number of interrelated factors. A balance exists between its tendency to collapse, induced by the subatmospheric intraluminal pressure during inspiration, and upper airway dilator muscle activity, which is influenced by upper airway dimensions and complex neuromuscular reflex interactions (2). Upper airway collapsibility measured by the UACP is likely to reflect the net effect of all these factors. Our patients had a baseline average UACP of –1.6 ± 0.4 cm H_2O in Stage 2 sleep and –2.5 ± 0.7 cm H_2O in slow wave sleep during supine sleep. These results are consistent with previous findings in patients with OSA by Issa and Sullivan (17).
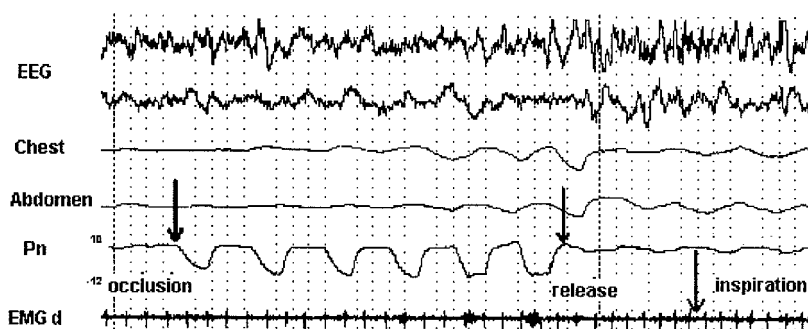

Figure 1. Polygraph record showing a typical type 1 nasal occlusion test during Stage 2 non–rapid eye movement sleep in a patient with obstructive sleep apnea (OSA). Complete external nasal airway occlusion was applied at end-expiration (*first arrow*). Note that at a critical nasal pressure (Pn = −6.1 cm H_2O) the fifth and sixth occluded breaths have a prominent inspiratory plateau despite a progressive increase in diaphragm EMG (EMG d) activity and respitrace (chest and abdomen) deflection throughout the occluded period. The inflection point in the nasal pressure trace indicates the closing pressure of the upper airway. Occlusion was released at the *second arrow*, followed by an arousal. Inspiration is downward.

TABLE 2. OUTCOME MEASUREMENTS

Variable	No MAS	MAS	p Value
BMI, kg/m^2	30.8 ± 6.2*	30.9 ± 6.1†	0.4
Neck circumference, cm	40.3 ± 0.5*	40.4 ± 0.5†	0.6
AHI, h^{-1}	25.0 ± 3.1*	13.2 ± 4.5†	0.03
MinSa$_{O_2}$, %	86 ± 6*	90 ± 3†	0.01
UACP Stage 2 NREM, cm H$_2$O	−1.6 ± 1.4‡	−3.9 ± 1.9‡	< 0.01
UACP SWS, cm H$_2$O	−2.5 ± 1.9‡	−4.7 ± 1.7‡	< 0.02

Definition of abbreviations: AHI = apnea/hypopnea index; BMI = body mass index; MAS = mandibular advancement splint; MinSa$_{O_2}$ = minimum Sa$_{O_2}$; UACP Stage 2 NREM = upper airway closing pressure during Stage 2 non–rapid eye movement sleep; UACP SWS = upper airway closing pressure during slow wave sleep.

Comparison made using paired *t* test.

Data are presented as mean ± SEM.

* Data obtained from baseline polysomnogram (without MAS).

† Data obtained from polysomnogram with MAS.

‡ Data obtained from closing pressure determination sleep study.

This study demonstrated a relationship between the magnitude of improvement in UACP during Stage 2 sleep and the improvement in AHI. In addition, the improvement in UACP during Stage 2 sleep in the group of complete responders was significantly greater than that found in the other two groups combined. However, an interesting finding in our study was that UACP improved after MAS treatment even in the failures, albeit to a lesser extent. This suggests that it is the magnitude of improvement in UACP that determines treatment outcome. How mandibular advancement improves upper airway collapsibility, however, remains unclear. Anatomic improvements in the anteroposterior dimension of the oropharynx have been postulated, although recent studies (15, 16) suggest that it is the *lateral* dimensions of the velopharynx that improve. Another mechanism proposed by Isono and coworkers (23) is that mandibular advancement stretches the soft palate, thus stiffening the velopharynx because of the connection of the lateral wall of the soft palate to the base of the tongue through the palatoglossal arch.

Improved upper airway collapsibility has been seen when other treatment alternatives have been successful. Schwartz and coworkers (19, 20) have demonstrated improvements in upper airway collapsibility after treatment success with weight loss and also with uvulopalatopharyngoplasty using a technique called the pharyngeal critical pressure. This technique, which is different from the closing pressure technique used in our study, examines pressure–flow relationships during sleep using the Starling resistor model (flow through a collapsible conduit) of the upper airway. Pharyngeal critical pressure is the pressure below which occlusion and cessation of airflow occurs. This pressure is found by measuring maximal airflow at different nasal mask pressures and then extrapolating to the pressure at which no airflow occurs (24). Therefore, pharyngeal critical pressure is a derived value and is believed to represent the pressure surrounding the locus of pharyngeal collapse. This model predicts that when pharyngeal critical pressure is positive relative to atmospheric nasal pressure, the upper airway should close. The closing pressure technique that we used measures the airway suction pressure at which pharyngeal closure occurs in response to complete external nasal occlusion, which is fundamentally different from the pharyngeal critical pressure technique. We chose the closing pressure technique because it provides a direct measure of the pressure at which airway collapse occurs.

In our study, the average mandibular protrusion of 4.6 mm is less than that seen in other studies (13, 14). This was the maximum comfortable limit tolerated by our study patients and was 65% of the maximum possible protrusion on average.

One potential limitation of our study was treatment order bias because UACP measurements were made with and without MAS during a single night. This was reduced by randomizing the treatment order during the closing pressure determination study. As a result of the unpredictability of achieving REM sleep during the overnight protocol, only two patients had reliable UACP determinations in this sleep stage. Another limitation was the inability of the technique to localize the site(s) of obstruction within the upper airway. This could be overcome in future studies by using a catheter measuring pressure at different levels in the upper airway during a closing pressure determination study. Although the sample studied was small, there was uniformity of the direction of effect in all patients.

In conclusion, we have demonstrated that oral appliance therapy improves upper airway collapsibility during sleep in patients with OSA. The magnitude of improvement in UACP was greater in patients who achieved a complete response to treatment. Given that treatment success with MAS is not achievable in every patient, further research is needed to determine whether UACP can be used as a predictor of treatment outcome.

References

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230–1235.
2. Cistulli P, Sullivan CE. Pathophysiology of sleep apnea. In: Sullivan CE, Saunders NA, editors. Sleep and breathing, 2nd ed. New York: Marcel Dekker; 1994. p. 405–488.
3. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnea by continuous positive pressure applied through the nares. *Lancet* 1981;1:862–865.
4. Kribbs NB, Pack AI, Kline LR, Smith PL, Schwartz AR, Schubert NM, Redline S, Henry JN, Getsy JE, Dinges DF. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Respir Dis* 1993;147:887–895.
5. Engelman HM, Asgari-Jirhandeh N, McLeod AL, Ramsay CF, Dreary IJ, Douglas NJ. Self-reported use of CPAP and benefits of CPAP therapy: a patient survey. *Chest* 1996;109:1470–1476.
6. Weaver TE, Kribbs NB, Pack AI, Kline LR, Chugh DK, Maislin G, Smith PL, Schwartz AR, Schubert NM, Gillen KA, *et al.* Night to night variability in CPAP use over the first three months of treatment. *Sleep* 1997;20:278–283.
7. Schmidt-Nowara W, Lowe A, Weigand L, Cartwright R, Perez-Guerra F, Menn S. Oral appliances for the treatment of snoring and obstructive sleep apnea: a review. *Sleep* 1995;18:501–510.
8. Tan YK, L'Estrange PR, Luo YM, Smith C, Grant HR, Simonds AK, Spiro SG, Battagel JM. Mandibular advancement splints and continuous positive airway pressure in patients with obstructive sleep apnoea: a randomized cross-over trial. *Eur J Orthod* 2002;24:239–249.
9. Randerath WJ, Heise M, Hinz R, Ruehle KH. An individually adjustable oral appliance vs continuous positive airway pressure in mild to moderate obstructive sleep apnea syndrome. *Chest* 2002;122:569–575.
10. Ferguson KA, Ono T, Lowe AA, Keenan SP, Fleetham JA. A randomized crossover study of an oral appliance vs nasal-continuous positive airway pressure in the treatment of mild-moderate obstructive sleep apnea. *Chest* 1996;109:1269–1275.
11. Ferguson KA, Ono T, Lowe AA, al-Majed S, Love LL, Fleetham JA. A short-term controlled trial of an adjustable oral appliance for the treatment of mild-moderate obstructive sleep apnea. *Thorax* 1997;52:362–368.
12. Engleman HM, McDonald JP, Graham D, Lello GE, Kingshott RN, Coleman EL, Mackay TW, Douglas NJ. Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome: continuous positive pressure and mandibular repositioning splint. *Am J Respir Crit Care Med* 2002;166:855–859.
13. Mehta A, Qian J, Petocz P, Darendeliler MA, Cistulli PA. A randomized, controlled study of a mandibular advancement splint for obstructive sleep apnea. *Am J Respir Crit Care Med* 2001;163:1457–1461.
14. Gotsopoulos H, Chen C, Qian J, Cistulli PA. Oral appliance therapy

improves symptoms in obstructive sleep apnea. *Am J Respir Crit Care Med* 2002;166:743–748.

15. Ryan CF, Love LL, Peat D, Fleetham JA, Lowe AA. Mandibular advancement oral appliance therapy for obstructive sleep apnea: effect on awake caliber of the velopharynx. *Thorax* 1999;54:972–977.

16. Ishida M, Inoue Y, Suto Y, Okatamoto K, Ryoke K, Higami S, Suzuki T, Kawahara R. Mechanisms of action and therapeutic indication of prosthetic mandibular advancement in obstructive sleep apnea syndrome. *Psychiatry Clin Neurosci* 1998;52:227–229.

17. Issa FG, Sullivan CE. Upper airway closing pressures in obstructive sleep apnea. *J Appl Physiol* 1984;57:520–527.

18. Issa FG, Sullivan CE. Upper airway closing pressures in snorers. *J Appl Physiol* 1984;57:528–535.

19. Schwartz AR, Gold AR, Schubert N, Stryzak A, Wise RA, Permutt S, Smith PL. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1991;144:494–498.

20. Schwartz AR, Schubert N, Rothman W, Godley F, Marsh B, Eisele D, Nadeau J, Permutt L, Gleadhill I, Smith PL. Effect of uvulopalatopharyngoplasty on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1992;145:527–532.

21. Rechschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles, CA: Brain Information Service/Brain Research Institute; 1968.

22. American Sleep Disorders Association. EEG arousals: scoring rules and examples. *Sleep* 1992;15:173–184.

23. Isono S, Tanaka A, Tagaito Y, Sho Y, Nishino T. Pharyngeal patency in response to advancement of the mandible in obese anesthetized persons. *Anesthesiology* 1997;87:1055–1062.

24. Gold AR, Schwartz AR. The pharyngeal critical pressure: the whys and hows of using nasal continuous positive airway pressure diagnostically. *Chest* 1996;110:1077–1088.