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Effect of Mandibular Position on Upper Airway Collapsibility and Resistance

ABSTRACT

It has been proposed that advancement of the mandible is a useful method for decreasing upper airway collapsibility. We carried out this study to test the hypothesis that mandibular advancement induces changes in upper airway patency during midazolam sedation. To explore its effect, we examined upper airway pressure-flow relationships in each of 4 conditions of mouth position in normal, healthy subjects (n = 9). In the neutral position, Pcrit (*i.e.*, critical closing pressure, an index of upper airway collapsibility) was -4.2 cm H_2O, and upstream resistance (Rua) was 21.2 cm H_2O/L/sec. In the centric occlusal position, Pcrit was -7.1 cm H_2O, and Rua was 16.6 cm H_2O/L/sec. In the incisor position, Pcrit was significantly reduced to -10.7 cm H_2O, and Rua was significantly reduced to 14.0 cm H_2O/L/sec. Mandibular advancement significantly decreased Pcrit to -13.3 cm H_2O, but did not significantly influence Rua (22.1 cm H_2O/L/sec). We conclude that the mandibular incisors' position improved airway patency and decreased resistance during midazolam sedation.

KEY WORDS: critical closing pressure, sedation, upper airway, mandibular advancement, sleep apnea.

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INTRODUCTION

Obstructive sleep apnea (OSA) is caused by an obstruction of the upper airway during sleep, and the most effective treatment is continuous positive airway pressure (CPAP), delivered *via* a nasal mask. Unfortunately, CPAP is a cumbersome device that often leads to poor tolerance and compliance. Recently, oral appliances that produce mandibular advancement controlled both OSA and snoring (Clark *et al.*, 1993; Eveloff *et al.*, 1994; Ferguson *et al.*, 1997; Kato *et al.*, 2000). Although these devices are thought to increase upper airway caliber, activate upper airway dilator muscles, and decrease upper airway compliance, their precise mode and site of action are unknown. We believe that a systematic assessment of the dose-response effects of mandibular advancement on upper airway patency will provide an insight into their mode of action.

Two key factors control upper airway patency. Critical closing pressure, which represents nasal pressure at zero flow, is an index of upper airway collapsibility. Resistance reflects the degree of upper airway narrowing upstream to the site of collapse. Several studies used critical pressure to evaluate the effect of mandibular advancement on upper airway collapsibility. Kato and co-workers reported that mandibular advancement lowered closing pressure, in a dose-dependent fashion, in all pharyngeal segments; however, their study was performed on subjects under complete neuromuscular blockade (Kato *et al.*, 2000). Ng *et al.* (2003) also found reduced closing pressure with mandibular advancement during sleep in OSA patients; however, they used a nasal occlusion technique that precluded the estimation of airway resistance.

Recently, we reported that critical closing pressure (Pcrit) can be measured by analyzing pressure-flow relationships during midazolam sedation (Ayuse *et al.*, 2004). In our study, Pcrit during midazolam sedation was comparable with Pcrit during natural non-REM sleep. Therefore, the effects of mandibular appliances on upper airway function during normal sleep can be modeled with the use of midazolam sedation. The purpose of this study was to describe the effect of mandibular advancement on upper airway collapsibility and resistance during sedation. We also used these findings to model the effect of mandibular position on upper airway function during sleep.

METHODS

Subjects

Pcrit was measured in nine healthy males under sedation (21.6 ± 1.5 yrs; mean body weights, 64.5 ± 8.1 kg; mean height, 1.69 ± 0.5 m; and BMI, 20.8 ± 3.6 kg/m^2) and free of any obvious class 2 or retrognathia. All subjects provided informed written consent. The Human Investigation Committee of the Nagasaki University School of Dentistry approved all experimental protocols.

Experimental Techniques

Polysomnographic Measurements

All subjects underwent routine hemodynamic monitoring (systolic and diastolic blood pressure and pulse rate), polysomnographic monitoring of sleep, electroencephalograms (EEG), and submental electromyograms (EMG). To determine the depth of sedation, we processed EEG signals with a BIS monitor (Aspect Medical Systems Inc., Natick, MA, USA). Oxygen saturation (SpO_2) was measured by pulse oximetry. A four-sensor pressure transducer catheter (Gaeltec CTO-4, Dunvegan, Isle of Skye, Scotland) was passed *via* the nares into the upper airway and esophagus, so that esophageal (Peso), hypopharyngeal (Phypo), oropharyngeal (Poro), and nasopharyngeal pressure (Pnaso) could be measured simultaneously. The distance between the end of the catheter (Peso)—the surface of which was covered with a silicone membrane—and each sensor was 18 cm, 21 cm, and 24 cm, respectively.

Airflow and nasal pressure (Pn) were monitored with a pneumotachometer (model 3830, Hans Rudolph, Inc., Kansas City, MO, USA) and differential pressure transducer (model 1100, Hans Rudolph, Inc., USA). All the measurements were displayed and stored simultaneously on a desktop computer equipped with Power lab data acquisition software (model 8sp, ADInstruments, Sydney, Australia) and recorded on an 8-channel thermal recorder.

Experimental Apparatus

Pressure was controlled at the nose (P_N) over the range -15 to +15 cm H_2O. We used a device which produced both pressures (Modified CPAP device, MAP GmbH, Martinsried, Germany). The outflow from this valve was then connected, in series, to the pneumotachometer and nasal mask (Fig. 1).

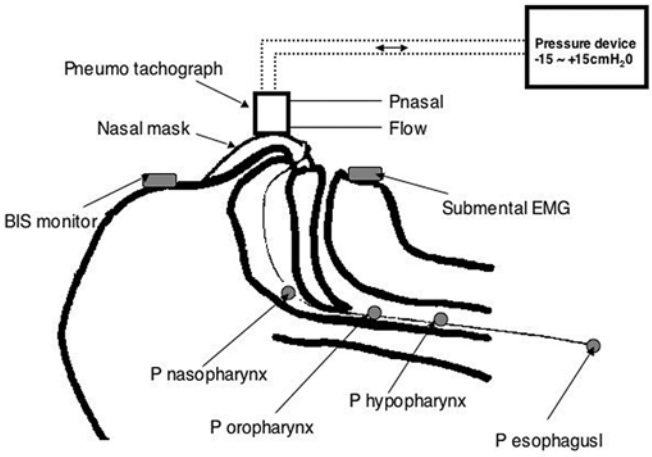

Figure 1. Diagram of experimental techniques.

Experimental Protocols

Sedation

No pre-medication was given. Midazolam sedation was maintained by an infusion method (Litman *et al.*, 2002a). Initially, the subjects were sedated by the injection of midazolam at a rate of 0.5 mg *per* min. When adequate sedation was obtained, continuous midazolam infusion (0.25 μg/kg/min) was begun. The subject's BIS values had to be less than 80, as previously described (Litman *et al.*, 2002a; Ayuse *et al.*, 2004), for adequate levels of conscious sedation to be obtained. At the conclusion of the experimental protocol, all subjects remained supine until they recovered.

Measurement of Upper Airway Collapsibility

After an adequate level of sedation was attained, the subjects were initially allowed to breathe under atmospheric pressure, while Pn was gradually increased to a holding pressure until inspiratory airflow limitation was abolished, as previously described (Schwartz *et al.*, 1998b; Boudewyns *et al.*, 2000). Thereafter, the nasal pressure was rapidly changed from the holding pressure to a lower pressure for 5 successive breaths before being changed to the holding pressure.

Protocols for Mandibular Advancement

Prior to the study, we made 3 rigid-type custom mandibular appliances—with 'centric occlusion', 'incisors aligned', and 'mandibular advancement' (75% of the subject's maximum possible protrusion)—constructed of clear acrylic resin and 1-mm polyethylene plate (Erkodur; Erkodent Inc., Pfalzgrafenweiler, Germany) for each subject. When we adjusted the level of maximum mandibular advancement, we were careful to avoid excessive discomfort and pain during the data acquisition period in each condition (5-10 min).

All subjects were fitted with nasal masks that were affixed to their faces with a sealing compound. The pressure-flow data were acquired in different conditions in random order. In condition 1, the pressure-flow relationship was obtained for the neutral (resting) position with surgical tape occluding the subject's mouth. In condition 2, the pressure-flow relationship was obtained for centric occlusion with a custom-made splint and surgical tape as in condition 1. We used a custom-made mandibular advancement device to acquire data in the 'incisors aligned' position and with the mandible advanced 75% of the individual maximum advancement limit.

Data Analysis

Upper Airway Pressure Relationship

At each level of nasal pressure, breaths were evaluated for the presence of inspiratory airflow limitation, as previously described (Schwartz *et al.*, 1988, 1989; Boudewyns *et al.*, 2000; Ayuse *et al.*, 2004). As reported previously (Gold and Schwartz, 1996), the pressure-flow relationship was analyzed by least-squares linear regression and fitted by the following equation: VImax = (Pn - Pcrit) / Rua, where Pcrit is the critical closing pressure (nasal pressure at zero flow), and Rua is the resistance of the portion of the tube upstream to the site of collapse.

The effective site of upper airway collapse (nasopharyngeal, oropharyngeal, or hypopharyngeal) in 4 different mandibular positions was determined from the transmission of respiratory-related pressure fluctuations along the upper airway under given atmospheric pressure (zero cm H_2O), as determined from the 4 sensor pressure transducer catheter signals.

We also evaluated the upper airway opening pressure (minimally effective CPAP = eCPAP), defined as the minimal level of nasal continuous positive airway pressure required to prevent inspiratory airflow limitation (Issa and Sullivan, 1984; Condos *et al.*, 1994; Hosselet *et al.*, 2001).

Statistical Analysis

Effects of mouth opening for each outcome variable (Pcrit, Rua, eCPAP) were studied by an ANOVA for repeated measures, with a *post hoc* protected Fisher's test (Stat View 5.0, SAS Institute,

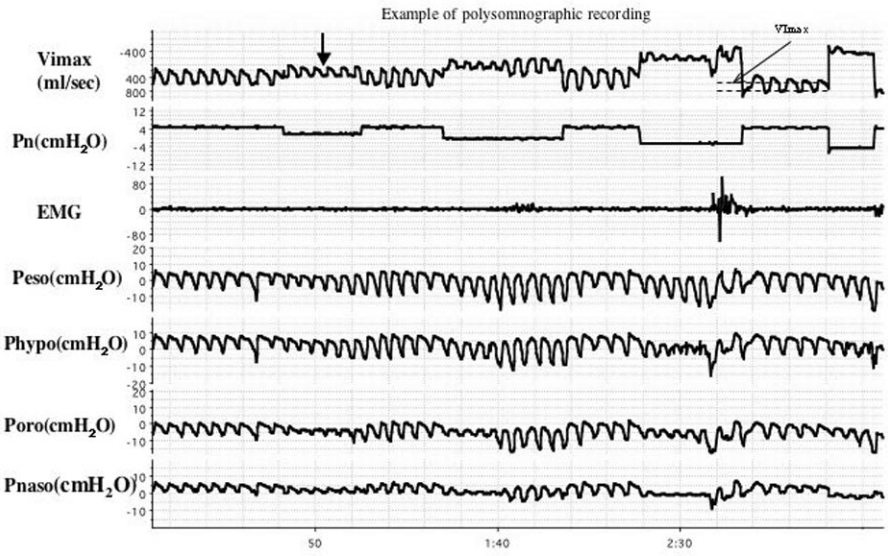

Figure 2. A representative polysomnographic recording is illustrated, showing the change in upper inspiratory airflow (VI) (top channel) and nasal pressure (Pn) (second channel from top). As shown, progressively sub-atmospheric levels of nasal pressure (Pn) were applied in stepwise manner (left to right) and kept constant at each pressure level for 5 or 6 breaths. At Pn values below 3 cm H_2O, inspiratory flow limitation ensued, as indicated by a flattening of the inspiratory airflow contour (see downward arrow from left), while the esophageal pressure (Peso) continued to become increasingly more negative. We obtained maximal inspiratory flow (VImax) by taking the difference between zero inspiratory flow and maximal inspiratory flow, as illustrated by the dotted lines. A period of zero flow was accompanied by similar changes in esophageal pressure (Peso), hypopharyngeal pressure (Phypo), and oropharyngeal pressure (Poro) during inspiratory efforts, together with failure of these pressure changes to be transmitted to the nasopharynx. Similar findings were observed in all subjects.

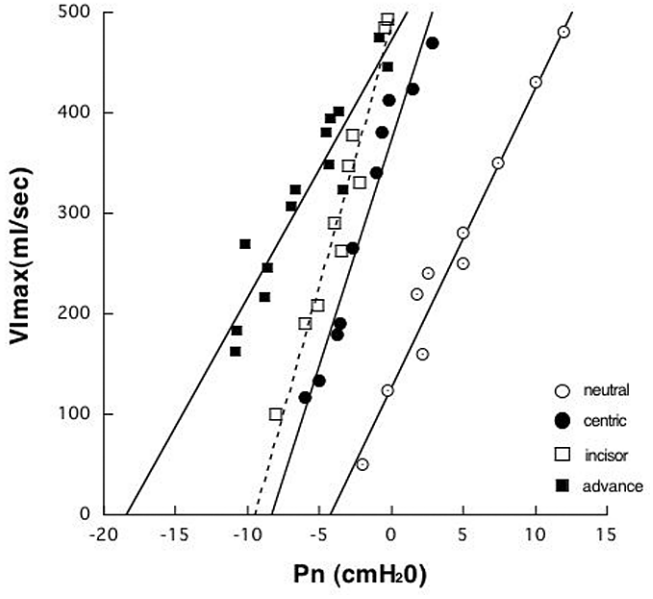

Figure 3. A representative example of the nasal pressure (Pn) *vs.* inspiratory flow (VImax) relationship in one subject. Nasal resistance (Rua) was defined as the reciprocal of the slope of the relationship between VImax and Pn, and Pcrit as the x intercept of the regression line, as illustrated. In the neutral position (open circle), Pcrit was -4.2 cm H_2O and Rua was 23.3 cm H_2O/L/sec. In centric occlusion (filled circle), Pcrit was -8.0 cm H_2O, and Rua was 15.0 cm H_2O/L/sec, while in the 'incisor aligned' position (open square), Pcrit was -9.3 cm H_2O and Rua was 14.3 cm H_2O/L/sec. In the mandibular advancement position (filled square), Pcrit was -18.5 cm H_2O, and Rua was 27.3 cm H_2O/L/sec.

Tokyo, Japan). A value of $p < 0.05$ was considered significant. Pcrit and Rua values are reported as mean ± SD, with 95% confidence intervals.

RESULTS

Moderate Sedation

After sedation, the average values from the BIS monitor decreased from 92.1 ± 1.9 to 72.5 ± 5.4, and there was no evidence of hypoxia or abnormal hemodynamic changes. Mandibular advancement in the incisor position was 2.9 ± 0.9 mm from centric occlusion (normal overjet) and 43.9 ± 9.7% of the maximum possible protrusion. The average 75% maximum protrusion was 5.6 ± 1.4 mm from centric occlusion.

Upper Airway Function during Sedation

A typical response to decreasing Pn (second channel from top) during sedation (Fig. 2) showed progressive sub-atmospheric levels of nasal pressure (Pn) applied in a stepwise manner (left to right) and held constant at each pressure level for 5 or 6 breaths. In all subjects, inspiratory flow limitations were apparent when Pn was reduced sufficiently below the holding pressure. When Pn values were below 3 cm H_2O, the inspiratory airflow signal shape changed from round to plateau, as indicated by the first downward arrow from the left. During the plateau in inspiratory airflow, Pes became more negative, which indicated that inspiratory airflow limitations were becoming apparent.

The velopharynx was the site of obstruction at the neutral position during sedation in all subjects. Fig. 2 shows an example of retro-palatal airway (velopharynx) obstruction. This refers to a period when zero flow was accompanied by similar changes in esophageal pressure (Peso), hypopharyngeal pressure (Phypo), and oropharyngeal pressure (Poro) during inspiratory efforts, together with failure of these pressure changes to be transmitted to the nasopharynx.

Effect of Mandibular Advancement on Upper Airway Function

We generated a pressure-flow relationship from the flow-limited respiratory cycles of each experiment. A typical sample of pressure-flow relationship in each condition (neutral, centric occlusion, incisor position, mandibular advancement) is shown in Fig. 3, and the mean data for all subjects for all experimental conditions are listed in the Table. In the resting condition, Pcrit was -4.2 ± 2.9 cm H_2O, and Rua was 21.2 ± 3.7 cm H_2O/L/sec. In centric occlusion, Pcrit was -7.1 ± 5.2 cm H_2O, and Rua was 16.6 ± 4.4 cm H_2O/L/sec. In the 'incisors aligned' position, Pcrit was -10.7 ± 4.4 cm H_2O, and Rua was significantly decreased to 14.0 ± 3.0 cm H_2O/L/sec. In mandibular advancement, Pcrit was -13.3 ± 3.2 cm H_2O, and Rua was 22.1 ± 6.3 cm H_2O/L/sec ($p <$ 0.05 *vs.* the 'mouth closed' and 'moderately opened' conditions). Essentially no CPAP was needed to overcome flow limitation in

Table. Effect of Mandibular Advancement on Each Parameter

	Neutral	Centric Occlusion	Incisors Aligned	Advancement (75% max)
Pcrit (cm H_2O)	4.2 ± 2.9 (10.0 ~ 1.7)	7.1 ± 5.2 (17.5 ~ 3.3)	10.7 ± 4.4[a] (19.4 ~ 1.9)	13.3 ± 3.2[a,b] (19.7 ~ 6.9)
Rua (cm H_2O/L/min)	21.2 ± 3.7 (13.8 ~ 28.6)	16.6 ± 4.4 (7.8 ~ 25.4)	14.0 ± 3.0[a] (8.0 ~ 20.0)	22.1 ± 6.3[c] (9.5 ~ 34.7)
eCPAPd (cm H_2O)	8.5 ± 2.8 (2.9 ~ 14.1)	1.7 ± 1.3 (0.9 ~ 4.3)	negative	negative

[a] $p < 0.05$ *vs.* neutral.
[b] $p < 0.05$ *vs.* centric occlusion.
[c] $p < 0.05$ *vs.* incisor alignment.
[d] eCPAP = minimally effective CPAP.

the incisors' mandibular position or maximum mandibular advancement position, whereas 1.7 ± 1.3 cm H_2O CPAP was required in the centric mandibular position and 8.5 ± 2.8 cm H_2O CPAP was required in the neutral mandibular position. This upper airway collapsibility was improved at the same site at the velopharynx in centric occlusion, incisor position, and mandibular advancement.

DISCUSSION

In this study, we investigated the effects of mandibular position on upper airway patency (Pcrit and Rua). We developed a standardized method for characterizing upper airway function using pressure-flow relationships in volunters during sedation. There were 4 major findings in the present study: (1) The critical closing pressure and the upstream resistance were significantly decreased in the incisor-aligned mandibular position; (2) maximum mandibular advancement further decreased the critical pressure, but did not change the upstream resistance; (3) the effective site of airflow obstruction remained in the velopharynx during mandibular advancement; and (4) the minimally effective CPAP was sub-atmospheric in the 'incisor aligned' position with maximum mandibular advancement. These findings indicate that mandibular advancement in the 'incisor aligned' position decreases both upper airway collapsibility and resistance during midazolam sedation, and that maximal mandibular advancement may not be necessary for the preservation of upper airway patency.

Current evidence indicates that midazolam can decrease upper airway neuromuscular tone, which can increase upper airway collapsibility (Pcrit). We found that Pcrit was -7.1 cm H_2O in the mouth-closed resting position, which was comparable with that found during natural non-REM sleep (Ayuse *et al.*, 2004). This finding suggests that upper airway properties during midazolam sedation may predict the presence of upper airway obstruction during sleep.

Changes in Pcrit and Rua can help us understand how mandibular advancement changes upper airway function and identify the site where this takes place. We found that mandibular advancement produced isolated decreases in Pcrit, indicating a decrease in collapsibility at the flow-limiting site (Ayuse *et al.*, 2004). However, since Rua did not change, this suggests that mandibular advancement did not dilate the segment upstream to the flow-limiting site. A decrease in collapsibility was probably localized to the velopharynx, because this segment is the predominant flow-limiting site during sleep (Shepard and Thawley, 1990), sedation (Mathru *et al.*, 1996; Eastwood *et al.*, 2002; Litman *et al.*, 2002b), and anesthesia (Isono *et al.*, 1995, 1997). It is also notable that Rua did not increase with mandibular advancement, as might have occurred had this maneuver increased axial rather than radial traction of the pharyngeal mucosa (Rowley *et al.*, 1996). We speculate that this dilating effect was mediated through a zone of apposition between the soft palate and the dorsum of the tongue.

Our findings have significant implications for clinical care in sleep apnea patients. We found that Pcrit decreased with increasing mandibular advancement. Moreover, current evidence indicates that mandibular advancement should ameliorate sleep apnea, if Pcrit falls by 5 to 10 cm H_2O. More modest mandibular advancement should be clinically effective in patients in whom obstructive hypopneas, rather than apneas, predominate, because reductions in Pcrit of only 3 to 5 cm H_2O relieve airflow obstruction during sleep in this group. Thus, our findings suggest that mandibular advancement can be titrated to relieve obstruction in patients with partial or complete upper airway occlusion during sleep.

We acknowledge several limitations in interpreting our findings. First, it may be difficult to extrapolate from responses during midazolam anesthesia to sleep. Nevertheless, baseline measurements of Pcrit in our sedated normal subjects were comparable with measurements from subjects in NREM sleep (Schwartz *et al.*, 1998a) (Gold and Schwartz, 1996). Second, responses to mandibular advancement in sleep apnea patients, and particularly in those who are obese (Isono *et al.*, 1997), may not be comparable with responses from our normal 'lean' subjects. Therefore, additional work is required to compare Pcrit and mandibular advancement in 'lean' and obese sleep apnea patients. Third, side-effects—which include excessive salivation, discomfort, and temporomandibular joint pain—may limit the use of mandibular advancement, and these cannot be evaluated during midazolam sedation. Fourth, responses to mandibular advancement may vary, depending on the site of airflow obstruction in the pharynx. Nevertheless, we expect that acute measurements during sedation will help clinicians select appropriate patients and estimate the desired level of mandibular advancement in oral appliance therapy.

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