Effect of Mandibular Position on Upper Airway Collapsibility and Resistance

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. 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/m²) 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

Polysonmographic Measurements
All subjects underwent routine hemodynamic monitoring (systolic and diastolic blood pressure and pulse rate), polysonmographic 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 (SpO2) 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 (Pn) over the range -15 to +15 cm H2O. 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).

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: VMax = (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 H2O), 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 (Perit, Rua, eCPAP) were studied by an ANOVA for repeated measures, with a post hoc protected Fisher's test (Stat View 5.0, SAS Institute,
Tokyo, Japan). A value of \( p < 0.05 \) was considered significant. \( \text{Pcrit} \) and \( \text{Rua} \) 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 \( P_n \) (second channel from top) during sedation (Fig. 2) showed progressive sub-atmospheric levels of nasal pressure \( (P_n) \) applied in a stepwise manner (left to right) and kept constant at each pressure level for 5 or 6 breaths. At \( P_n \) values below \( 3 \) cm H\(_2\)O, inspiratory flow limitation ensued, as indicated by a flattening of the inspiratory airflow contour (see downward arrow from left), while the esophageal pressure \( (P_{eso}) \) continued to become increasingly more negative. We obtained maximal inspiratory flow \( (V_{max}) \) 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 \( (P_{eso}) \), hypopharyngeal pressure \( (P_{phypo}) \), and oropharyngeal pressure \( (P_{oro}) \) during inspiratory efforts, together with failure of these pressure changes to be transmitted to the nasopharynx. Similar findings were observed in all subjects.

When \( P_n \) values were below \( 3 \) cm H\(_2\)O, 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, \( P_{eso} \) 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 \( (P_{eso}) \), hypopharyngeal pressure \( (P_{phypo}) \), and oropharyngeal pressure \( (P_{oro}) \) 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, \( \text{Pcrit} \) was \( -4.2 ± 2.9 \) cm H\(_2\)O, and \( \text{Rua} \) was \( 23.3 \) cm H\(_2\)O/L/sec. In centric occlusion (filled circle), \( \text{Pcrit} \) was \( -8.0 \) cm H\(_2\)O, and \( \text{Rua} \) was \( 15.0 \) cm H\(_2\)O/L/sec, while in the 'incisor aligned' position (open square), \( \text{Pcrit} \) was \( -9.3 \) cm H\(_2\)O and \( \text{Rua} \) was \( 14.3 \) cm H\(_2\)O/L/sec. In the mandibular advancement position (filled square), \( \text{Pcrit} \) was \( -18.5 \) cm H\(_2\)O, and \( \text{Rua} \) was \( 27.3 \) cm H\(_2\)O/L/sec.

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**Figure 2.** A representative polysomnographic recording is illustrated, showing the change in upper inspiratory airflow \( (VI) \) (top channel) and nasal pressure \( (P_n) \) (second channel from top). As shown, progressively sub-atmospheric levels of nasal pressure \( (P_n) \) were applied in stepwise manner (left to right) and kept constant at each pressure level for 5 or 6 breaths. At \( P_n \) values below \( 3 \) cm H\(_2\)O, inspiratory flow limitation ensued, as indicated by a flattening of the inspiratory airflow contour (see downward arrow from left), while the esophageal pressure \( (P_{eso}) \) continued to become increasingly more negative. We obtained maximal inspiratory flow \( (V_{max}) \) 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 \( (P_{eso}) \), hypopharyngeal pressure \( (P_{phypo}) \), and oropharyngeal pressure \( (P_{oro}) \) 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 \( (P_n) \) vs. inspiratory flow \( (V_{max}) \) relationship in one subject. Nasal resistance \( (\text{Rua}) \) was defined as the reciprocal of the slope of the relationship between \( V_{max} \) and \( P_n \), and \( \text{Pcrit} \) as the x intercept of the regression line, as illustrated. In the neutral position (open circle), \( \text{Pcrit} \) was \( -4.2 \) cm H\(_2\)O and \( \text{Rua} \) was \( 23.3 \) cm H\(_2\)O/L/sec. In centric occlusion (filled circle), \( \text{Pcrit} \) was \( -8.0 \) cm H\(_2\)O, and \( \text{Rua} \) was \( 15.0 \) cm H\(_2\)O/L/sec, while in the 'incisor aligned' position (open square), \( \text{Pcrit} \) was \( -9.3 \) cm H\(_2\)O and \( \text{Rua} \) was \( 14.3 \) cm H\(_2\)O/L/sec. In the mandibular advancement position (filled square), \( \text{Pcrit} \) was \( -18.5 \) cm H\(_2\)O, and \( \text{Rua} \) was \( 27.3 \) cm H\(_2\)O/L/sec.
the incisors' mandibular position or maximum mandibular advancement position, whereas 1.7 ± 1.3 cm H2O CPAP was required in the centric mandibular position and 8.5 ± 2.8 cm H2O 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 volunteers 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 Perit was -7.1 cm H2O 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 Perit, 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 H2O. 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 H2O 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 Perit 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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