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Jumping on the Bandwagon and Reinventing the Wheel in Order to Grab a Piece of the Pie

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The past year has seen a proliferation of guidelines, position papers, resolutions and proposals addressing the field of dental sleep medicine. Were all these documents necessary to improve patient care and inform clinicians?

The AASM/AADSM[1] guideline update, published in July 2015, is the third revision since the first version published in 1995.[2,3] This guideline reflects over 20 years of leadership dental sleep medicine. I declare my bias as I was a member of the task force that produced the updated guideline after over three years of review and analysis of the literature. This task force of dentists, sleep physicians, and research methods experts exhaustively reviewed the literature and produced a meta-analysis of randomized controlled trials addressing oral appliance therapy for obstructive sleep apnea. Given the stringent methodology to produce this guideline leads one to wonder what benefit would result from other groups producing guidelines utilizing less stringent methods.

Certainly when governance is the issue governing bodies need to give guidance to membership but why not borrow from an existing state of the art guideline? Why are so many groups spending time and money reinventing the wheel?

It is difficult not to be cynical reviewing this growth of guidelines, position papers and other documents. Now that there is growing strong evidence for the effectiveness of oral appliances compared to CPAP[4] other, redundant, documents are being released. It is hard not to speculate as to the reasons that organizations are attempting to claim the field for their specific group rather than general dentists with adequate qualifications in dental sleep medicine. There are groups producing their own documents and ignoring for the most part the twenty-five years of the work available. Some of these groups proclaim now suddenly their members are the ones most qualified to be the providers of oral appliance therapy. Are they just jumping on the bandwagon? Are there financial or commercial interests in the background driving some of the interest?

It is in our patients' best interest is to have the dental profession as a whole collaborate with physicians in the treatment of sleep disordered breathing. Let us not fall victim to divisive elements whose particular interests may be served by pitting groups against each other in the battle of "who owns dental sleep medicine?"

If there are groups with finances and expertise let them use their resources to add to the evidence base for dental sleep medicine—not duplicate another guideline or position statement. There are universities throughout the world with qualified dental sleep medicine researchers and capable students with very limited sources of funds. Groups with financial resources and a desire to further the field could look at awards to foster the growth of the science of dental sleep medicine rather than using another position paper to grab a bigger piece of the pie.

CITATION

Dort LC. Jumping on the bandwagon and reinventing the wheel in order to grab a piece of the pie. *Journal of Dental Sleep Medicine* 2016;3(1):3.

REFERENCES

1. Ramar K, Dort LC, Katz SG, et al. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. *Journal of Dental Sleep Medicine* 2015;2:71–125.
2. Kushida CA, Morgenthaler TI, Littner MR, et al. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances: an update for 2005. *Sleep* 2006;29:240–3.
3. Schmidt-Nowara W, Lowe A, Wiegand L, Cartwright R, Perez-Guerra F, Menn S. Oral appliances for the treatment of snoring and obstructive sleep apnea: a review. *Sleep* 1995;18:501–10.
4. Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs mandibular advancement devices and blood pressure in patients with obstructive sleep apnea: a systematic review and meta-analysis. *JAMA* 2015;314:2280–93.

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DISCLOSURE STATEMENT

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ORIGINAL ARTICLES

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Continuous Positive Airway Pressure and Oral Appliance Hybrid Therapy in Obstructive Sleep Apnea: Patient Comfort, Compliance, and Preference: A Pilot Study

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Study Objectives: Patients with obstructive sleep apnea syndrome (OSAS) using continuous positive airway pressure (CPAP) often report pressure-related discomfort. Both lower pressure and increased comfort may improve patients' compliance with CPAP-therapy, thereby improving therapeutic effectiveness. Combining CPAP with an oral appliance (hybrid therapy) could be an adequate alternative therapy.

Methods: Seven patients with moderate to severe OSAS who tolerated their CPAP despite high pressures (≥ 10 cm H_2O) were fitted with hybrid therapy. The mandible was set at 70% of patient's maximum protrusion, and CPAP pressure was set at 6 cm H_2O. When OSAS complaints persisted, pressure was increased. After 3 months, a polysomnographic study was performed. At baseline (conventional CPAP) and after 3 months (hybrid therapy) patients filled in questionnaires assessing comfort, compliance, and satisfaction with treatment, excessive daytime sleepiness, and quality of life.

Results: Four of seven patients reported hybrid therapy to be more comfortable and effective and preferred it over conventional CPAP. There were no differences between baseline (conventional CPAP) and follow-up (hybrid therapy) scores in compliance, satisfaction, daytime sleepiness, and quality of life. Effectiveness of hybrid therapy was good as apnea-hypopnea index (AHI) significantly decreased from median AHI 64.6/h (interquartile range [IQR] 31.0–81.0) at diagnosis to median AHI 1.5/h (IQR 1.0–33.4) with hybrid therapy. There was no statistical difference in effectiveness between conventional CPAP and hybrid therapy (median AHI with conventional CPAP was 2.4/h [IQR 0.0–5.0]).

Conclusions: Although pressure could be lowered and hybrid therapy seems a comfortable alternative to conventional CPAP, there were no differences between both therapies regarding compliance, satisfaction, and both objective and experienced effectiveness. Combined therapy is feasible in OSAS and should now be investigated in a RCT including assessment of comfort and long-term compliance.

Keywords: obstructive sleep apnea syndrome; continuous positive airway pressure; oral appliance; treatment

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INTRODUCTION

Treatment with continuous positive airway pressure (CPAP) prevents upper airway collapse by pneumatically "splinting" the upper airway during sleep[1] and is the most frequently prescribed treatment for OSAS.[2] In severe OSAS (apnea-hypopnea index [AHI] > 30/h), it is the current standard of treatment and improves symptoms and quality of life as well as cardiovascular outcomes.[2–4] Oral appliance therapy, however, has become an attractive alternative, especially in mild and moderate OSAS.[5] Oral appliance therapy aims at relieving upper airway collapse during sleep by modifying the position of the mandible, tongue, and pharyngeal structures. Side effects have been reported to be mild, improve with time, and are mostly reversible.[6–9]

Patients with moderate to severe OSAS using CPAP often report pressure-related discomfort or intolerance. Other frequently mentioned complaints with the device are claustrophobia, comfort problems due to the mask or straps on the head, leakage, and dry eyes and nose. Discomfort can ultimately result in reduced therapeutic compliance.

Optimal compliance is essential for a therapy such as CPAP to be successful and effective. It is important to search for alternative treatment options that are equally effective to CPAP in the treatment of moderate to severe OSAS. Combining CPAP with an oral appliance could be such an alternative therapy (hybrid therapy). By combining both therapies, CPAP pressure may be lowered substantially as an oral appliance increases upper airway patency. Second, the CPAP nose mask can be fixed onto the oral appliance, which could improve the comfort of the treatment (no headstrap required, no shifting of the hose/tube). Both lower pressure and increased comfort may improve patients' compliance with therapy, thereby improving therapeutic effectiveness.

To date, only two case reports[10,11] and one pilot study,[12] reporting on the simultaneous use of CPAP and oral

Figure 1

Continuous positive airway pressure (CPAP) with nose-probe interface combined with a Thornton Adjustable Positioner 3.

appliance therapy in OSAS, have been published. These studies included only patients intolerant to CPAP, and in two studies[10,12] patients were ineffectively treated with an oral appliance. Furthermore, the studies provide insufficient information about comfort and compliance. In one other case report, the use of an oral appliance in combination with noninvasive ventilation in a patient with amyotrophic lateral sclerosis was described.[13]

The aim of this study was to evaluate whether hybrid therapy is an adequate alternative to conventional CPAP in moderate to severe OSAS. For this study, patients being effectively treated with conventional CPAP and who did tolerate their CPAP and were satisfied with it, despite relative high therapeutic pressures (i.e., > 10 cm H_2O) were selected. Primary outcomes were comfort and compliance with hybrid therapy. Secondary outcomes were effectiveness of hybrid therapy and the effect of this treatment on quality of life.

METHODS

Subjects

Patients were eligible for the study when they: (1) were diagnosed with moderate to severe OSAS (apnea-hypopnea index (AHI) ≥ 15/h) during overnight poly(somno)graphy, (2) used conventional CPAP with pressure ≥ 10 cm H_2O and could tolerate this pressure, (3) were aged > 18 years.

Exclusion criteria were (1) previously treated with an oral appliance, (2) dental contra-indications for oral appliance therapy (i.e., extensive periodontal disease or tooth decay, active temporomandibular joint disease [including severe bruxism], restrictions in mouth opening [< 25 mm] or advancement of the mandible [< 5 mm], partial or complete edentulism [< 8 teeth in upper or lower jaw]),[5] (3) morphologic abnormalities of the upper airway, (4) current untreated endocrine dysfunction, (5) reported or documented severe cardiac or pulmonary comorbidity, and (6) patients being treated for psychiatric disorders at the moment of inclusion for the study.

Patients were considered effectively treated with conventional CPAP when AHI reduced to < 5/h or reduced ≥ 50% from the diagnostic value to an absolute value < 20/h[5] (confirmed by poly(somno)graphic evaluation), or when subjective obstructive sleep apnea symptoms were absent and CPAP machine software readout showed sufficient suppression of AHI (therefore in the latter category of patients no poly(somno)graphic evaluation had been performed).

Study Design

This study is a longitudinal quantitative as well as a qualitative study without a control group. The oral appliance (Thornton Adjustable Positioner [TAP3, Airway Management Inc., Dallas, TX, USA]) was custom-made for each patient. The Thornton Adjustable Positioner is an oral appliance that consist of 2 separate parts for both the maxilla and the mandible. The mandibular protrusion can be adjusted with 0.2-mm increments with a propulsion screw, which was incorporated anteriorly in the oral appliance. The maximum range of mandibular protrusion was first determined with a George-Gauge (H-Orthodontics, Michigan City, IN, USA). When initiating oral appliance therapy, the mandible was set at 70% of the patient's maximum protrusion or at 60% when 70% was uncomfortable to the patient.

After adjusting the oral appliance, nose-probes from a CPAP interface were attached to the oral appliance by means of a connection-unit (**Figure 1**). No headstraps were used for hybrid therapy.

When starting with hybrid therapy CPAP pressure was set at 6 cm H_2O for all patients. After an adjustment period of about 2–4 weeks, the degree of mandibular protrusion or CPAP pressure was adjusted if necessary, based on patients' reported symptoms, until the desired effectiveness had been reached or until the adjustments became uncomfortable to the patient. Whether the degree of mandibular protrusion or CPAP-pressure had to be adjusted was decided in accordance with the patient. There was, however, not a strict adjustment protocol.

After 3 months of hybrid therapy, current CPAP pressure was assessed and effectiveness of the therapy was measured with home-based polysomnography. Furthermore, patients were asked about their treatment preference regarding comfort, efficacy, and satisfaction when comparing hybrid therapy with conventional CPAP therapy.

At baseline (conventional CPAP) and after 3 months (hybrid therapy) patients filled in questionnaires assessing comfort of, and compliance and satisfaction with their current treatment, excessive daytime sleepiness (Epworth Sleepiness Scale (ESS),[14] quality of life (Short-Form 36-item Health Survey (SF-36),[15] and Functional Outcomes of Sleep Questionnaire (FOSQ),[16] and anxiety and depressive feelings (Hospital Anxiety and Depression Scale (HADS).[17]

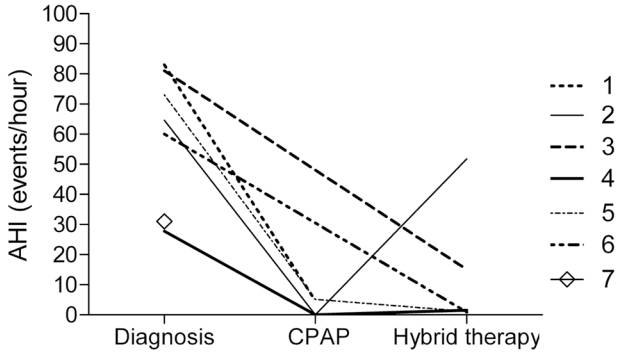
The study was approved by the local Ethical Committee (METc University Medical Center Groningen; METc2010/051). All patients gave written informed consent for using their data for this study and publication before inclusion.

Table 1—Demographic characteristics.

Age (years)	54.0 ± 8.9
Gender (male/female)	6/1
Body mass index (kg/m^2)	37.4 ± 5.5
Neck circumference (cm)	48.1 ± 3.9
Score on Epworth sleepiness scale at diagnosis (0–24)	16.0 ± 4.2
Score on Epworth sleepiness scale under conventional CPAP (0–24)	9.0 ± 5.3

N = 7. Age and body mass index assessed at the moment of inclusion for the study. CPAP, continuous positive airway pressure.

Figure 2



Apnea-hypopnea index for each patient at diagnosis, with conventional continuous positive airway pressure (CPAP) and with hybrid therapy.

Measurements

Polysomnography

Polysomnographic overnight home-based evaluations (Vitaport-4 PSG, Temec Instruments BV, Kerkrade, the Netherlands) were used to diagnose OSAS and to assess the effect of the hybrid therapy at follow-up. Sleep stages were measured with surface electroencephalography, left and right electrooculography, and submental electromyography. Oxygen saturation was recorded with pulse oximetry. Oronasal airflow was recorded with a pressure cannula. Respiratory effort was monitored with thoracic and abdominal strain bands. Apnea was defined as a complete obstruction resulting in a cessation in airflow (i.e., reduction of airflow ≥ 90%) ≥ 10 seconds. Hypopnea was defined as a substantial (i.e., ≥ 30%) reduction in airflow ≥ 10 seconds when associated with oxygen desaturation (≥ 4%).[18]

Compliance, Satisfaction, and Preference

The number of nights per week and hours per night using therapy were assessed through a self-report questionnaire. Satisfaction with the current therapy was assessed with a visual analog scale of 0–100 mm without anchors. Patients were asked to draw a vertical line crossing the horizontal scale. After 3 months, patients were asked to indicate whether they preferred conventional CPAP or hybrid therapy based on satisfaction with therapy, long-term use, comfort, and effectiveness, (i.e., the experience that the device is effective in reducing sleep apnea symptoms).

Comfort

Complaints with conventional CPAP (e.g., irritation of CPAP mask; leakage; dry eyes; claustrophobia), oral appliance (e.g., tooth or molar pain; painful jaws, joint, muscles), and the combination of both therapies (hybrid therapy) (e.g., hindered by therapy when falling asleep; awakened by poorly fitted or lose equipment) were assessed through a self-report questionnaire. Patients scored how frequently they experienced a specific complaint on a 4-point scale, ranging from never to often (0–3).

Data Analysis

Descriptive statistics are presented as means ± standard deviations or medians and interquartile ranges (IQR) for continuous variables. Categorical variables are presented in terms of proportions. Wilcoxon signed-rank tests were performed to assess the difference between measurements at baseline and after 3 months. Data were analyzed with SPSS 20.0 statistical software. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Seven patients (6 men) participated (mean ± SD age 54 ± 8.9 years). **Table 1** contains the demographic characteristics of the patients at baseline. Pressure could be lowered from 11.5 ± 1.3 cm H_2O with CPAP to 6.4 ± 0.5 cm H_2O with hybrid therapy. Three patients had their pressure increased from 6 cm H_2O to 7 cm H_2O during the follow-up period on hybrid therapy. In 4 patients, the degree of mandibular protrusion was increased from 60% to 70% of the patient's maximum protrusion (of whom 2 patients also had their pressure increased from 6 cm H_2O to 7 cm H_2O).

Five patients used hybrid therapy for the full 3 months, of whom one stopped after the study period. Two patients could not cope with the hybrid therapy and stopped before the 3-month endpoint. Four patients preferred hybrid therapy on the long term over conventional CPAP and also reported hybrid therapy as more comfortable and effective, (i.e., the experience that the device is effective in reducing sleep apnea symptoms) than conventional CPAP. The reasons to stop were feelings of dyspnea and anxiety, and being very restless during sleep due to the therapy and having specific oral appliance related complaints which were indicated as frequently occurring (tooth or molar pain, feeling that teeth are "out of place" in the morning, painful jaws, joints and chewing muscles). The patient who stopped after the study could not get used to hybrid therapy (claustrophobia), and hybrid therapy was not effective in this patient (AHI at follow-up of 51.8/h, **Figure 2**).

There were no differences in compliance between conventional CPAP (median 7.0 nights/week [IQR 6.0–7.0]); 6.5 h/night [IQR 5.0–8.0]) and hybrid therapy (median 7.0 nights/week [IQR 2.8–7.0]); 6.0 h/night [IQR 4.5–8.1]), both p = 1.0. Satisfaction rates on the visual analog scale did not differ

Table 2—Overview per patient.

	Pressure (cm H_2O)		Compliance				Satisfaction (0–10)		Preference
			Conventional CPAP		Hybrid Therapy				
	Conventional CPAP	Hybrid Therapy	nights/w	h/night	nights/w	h/night	Conventional CPAP	Hybrid Therapy	
1.†	12.0	–	7	8.0	–	–	9.0	–	Conventional CPAP
2.††	11.0	6.0	7	6.5	7	5.0	9.0	9.5	Conventional CPAP
3.	14.0	7.0	2	3.0	3	3.0	6.0	5.7	Hybrid therapy
4.	11.0	7.0	6	5.0	7	6.0	9.0	9.1	Hybrid therapy
5.	12.0	6.0	7	5.5	7	6.0	6.9	9.4	Hybrid therapy
6.	10.5	7.0	7	8.0	7	8.0	10.0	10.0	Hybrid therapy
7.†,*	10.0	–	7	8.5	2	8.5	5.5	0.0	Conventional CPAP

†Patient 1 and 7 stopped during the study and before the 3 month follow-up. ††Patient 2 stopped after 3 months. *Patient 7 filled in a shortened questionnaire about EDS, satisfaction and comfort with hybrid therapy. CPAP, continuous positive airway pressure.

between conventional CPAP (median 90.0 [IQR 60.0–90.0]) and hybrid therapy (median 92.5 [IQR 42.8–96.3]), p = 0.89. Nevertheless, when explicitly asked to make a choice between both treatment modalities, 4 of 7 patients reported to be more satisfied with hybrid therapy (**Table 2**).

AHI decreased significantly with hybrid therapy (median AHI 1.5/h [IQR 1.0–33.4]) compared to AHI at diagnosis (median AHI 64.6/h [IQR 31.0–81.0]), p < 0.05. There was no statistical difference in effectiveness between conventional CPAP and hybrid therapy (median AHI with conventional CPAP was 2.4/h [IQR 0.0–5.0]).

Scores on the Epworth sleepiness scale dropped from 10.3 ± 4.4 (n = 6) at baseline with conventional CPAP to 9.2 ± 6.2 with hybrid therapy (p = 0.68). Quality of life, measured with the FOSQ, increased from 15.9 ± 3.2 (n = 5) with conventional CPAP to 16.3 ± 3.6 with hybrid therapy (p = 0.79). The physical subscale of the SF-36 increased from 50.9 ± 8.7 (n = 5) with conventional CPAP to 51.4 ± 6.2 with hybrid therapy (p = 0.73) and the mental subscale of the SF-36 increased from 42.7 ± 17.2 with conventional CPAP to 47.5 ± 16.3 with hybrid therapy (p = 0.41). Anxiety and depressive feelings, measured with the HADS, dropped from 12.4 ± 12.6 (n = 5) with conventional CPAP to 8.0 ± 9.0 with hybrid therapy (p = 0.16). All results were in the desired direction, but none of the differences were statistically significant.

Six patients filled in the self-report questionnaire on complaints both at baseline (conventional CPAP) and at follow-up (hybrid therapy). **Figure 3** displays the percentages of reported complaints for both therapies per category (calculated as the actual number of reported side effects or complaints for that category divided by the maximum expected number of reported complaints, i.e., the situation when all patients would have scored the same category). Mean scores per (specific) complaint were calculated in order to compare complaints for conventional CPAP with hybrid therapy (**Figure 4**).

Patients had fewer CPAP complaints in combination with the oral appliance (hybrid therapy) than with conventional CPAP alone (**Figure 3A**). Specific oral appliance related complaints were reported as not frequently occurring (**Figure 3B**). Most complaints with conventional CPAP, such as stuffy nose, irritation of the mask, painful nose bridge, leakage, dry eyes, dry mucous membrane mouth and nose became less of a problem when using hybrid therapy, while the swallowing of air, and the presence of a headache appeared to increase slightly with hybrid therapy (**Figure 4**). When patients had to indicate the severity of their complaints on a scale of mild to severe, most complaints with conventional CPAP were indicated as mild (once absent, 5 times mild, and once moderate). Complaints with hybrid therapy were also indicated as mild most of the times (once absent, 3 times mild, once moderate, and once severe).

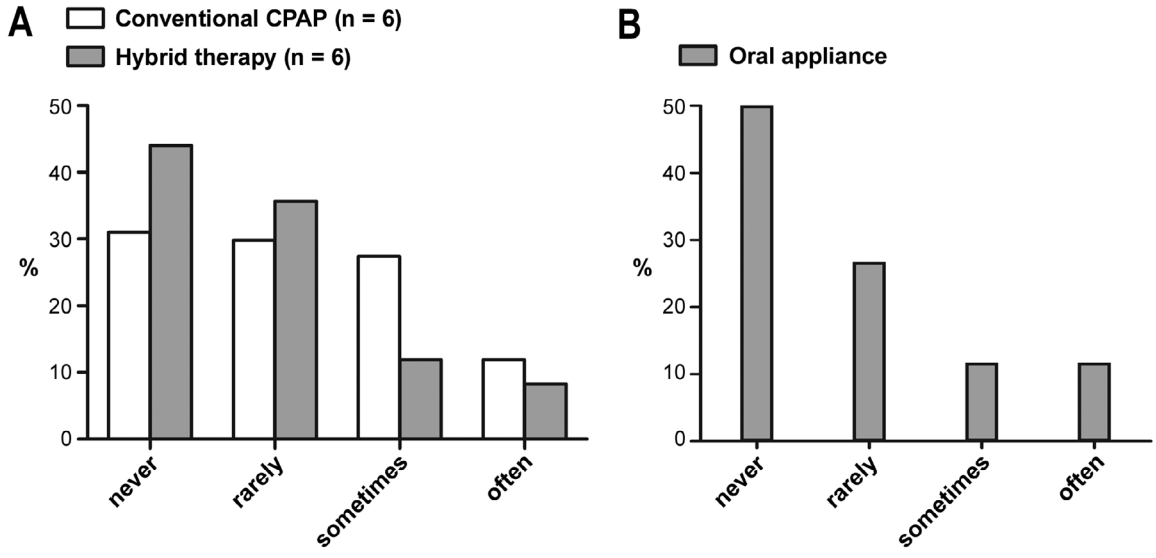
DISCUSSION

This study showed that CPAP – oral appliance hybrid therapy could be a comfortable and effective alternative to conventional CPAP in many but not all patients with moderate to severe OSAS. Patients were equally compliant with hybrid therapy and conventional CPAP.

Pressure could be lowered from 11.5 ± 1.3 cm H_2O with conventional CPAP to 6.4 ± 0.5 cm H_2O with hybrid therapy. In addition complaints were less frequently mentioned with hybrid therapy when compared with conventional CPAP.

The case reports by Denbar[10] and Upadhyay et al.[11] and the pilot study by El-Solh et al.[12] showed similar positive effects on therapeutic CPAP pressure and AHI reduction. Both studies, however, have some limitations. Patients in the study by El-Solh et al.[12] used the combination therapy for only 3 days. Furthermore, the only patients selected were intolerant of CPAP and were ineffectively treated with an oral appliance. No overnight sleep study was performed at the end. The study of Denbar[10] describes the treatment of one patient over a time period of 4.5 years, of which the last 1.5 years consisted of hybrid therapy. Both conventional CPAP and an oral appliance therapy were

Figure 3



(A) Complaints with conventional continuous positive airway pressure (CPAP) and hybrid therapy. **(B)** Complaints specifically related to oral appliance.

unsuccessful for this specific patient. Upadhyay et al.[11] describe the treatment of one patient, who was intolerant of CPAP and was declared unfit for uvulopalatopharyngoplasty. The study describes a treatment period of 90 days during which the patient lost 9 kilograms in weight, which could have amplified the positive study results.

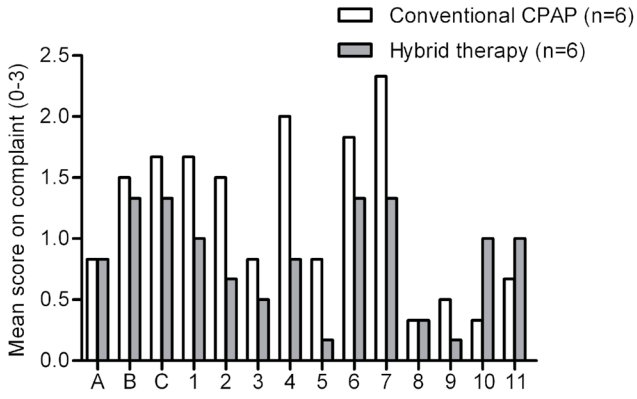
It is plausible that ineffectively treated patients or patients who regard their current treatment as uncomfortable are more eager to start, and are more satisfied with a new therapeutic modality. In order to avoid this bias we selected patients who did tolerate their CPAP and were satisfied with it, despite relative high therapeutic pressures (i.e., > 10 cm H_2O). Including only patients who tolerate their CPAP therapy raises another possible bias, as those patients might tend to prefer the therapy they know. Our results show however that four patients preferred hybrid therapy over the long term over conventional CPAP.

Pressure could be lowered in all patients (mean 11.5 ± 1.3 cm H_2O with conventional CPAP to mean 6.4 ± 0.5 cm H_2O with hybrid therapy). Pressure was not again titrated before the start of this study. It is therefore possible that the conventional CPAP was not at the minimum efficient pressure as the CPAP pressure was the pressure patients were on before the period with hybrid therapy started. The conventional CPAP pressure was, however, increased until OSAS complaints were no longer present and the sleep study, or CPAP machine software readout showed sufficient suppression of the AHI. A lower efficient pressure is therefore not very likely.

Complaints were indicated as not frequently occurring for conventional CPAP as well as for hybrid therapy. Patients reported less specific CPAP complaints with hybrid therapy than with conventional CPAP, suggesting higher comfort with the hybrid therapy.

Our theory that lower pressure and better comfort could result in a better therapeutic compliance was not confirmed by our data. Moreover, satisfaction scores on the visual analog scale were similar. However, when forced to make a choice for one of the two treatments, four of seven patients preferred hybrid therapy over conventional CPAP. They reported hybrid therapy as more comfortable and effective. These patients continued using the hybrid therapy after completion of the study. Unfortunately, due to the small sample size, no statistics could be applied to assess whether complaints were significantly less with hybrid therapy than with conventional CPAP.

Figure 4—Mean scores on complaints with conventional continuous positive airway pressure (CPAP) and hybrid therapy.



Complaint therapy: A = hindered by therapy when falling asleep; B = hindered by therapy during sleep; C = awakened by mall fitted or lose equipment. CPAP complaint: 1 = irritation of CPAP mask; 2 = painful nose bridge; 3 = sound CPAP machine; 4 = leakage; 5 = dry eyes; 6 = dry mucous membrane mouth, nose; 7 = stuffy nose; 8 = claustrophobia; 9 = nosebleed; 10 = swallowing of air; 11 = headache.

In our study, one patient had his AHI worsened using hybrid therapy. A possible explanation for this could be that this patient had gained weight compared to the time when the OSAS was diagnosed and also when compared to baseline (137 kg with hybrid therapy compared to 123 kg with conventional CPAP).

There are some other limitations to consider for this study. Unfortunately, we did not have polysomnographic data for all patients while using conventional CPAP, making a good comparison on objective effectiveness between conventional CPAP and hybrid therapy difficult. Four patients had polysomnography performed with both treatment modalities; the other three patients reported no subjective obstructive sleep apnea symptoms, and CPAP machine software readout showed sufficient suppression of AHI. Therefore, no follow-up poly(somno)graphic evaluation was indicated at that moment.

During the study period the degree of mandibular protrusion or CPAP pressure was adjusted when necessary. There was, however, not a strict protocol regarding which one to perform first. To date, there are no data to substantiate which approach is best in titrating hybrid therapy. This should be a point of attention in future studies assessing hybrid therapy.

The results of our study should be interpreted with caution, as this study consists only of a small patient sample and because there was no control group. Furthermore, a follow-up of 3 months may be too short to reveal effects on quality of life data.

CONCLUSIONS

In conclusion, although pressure could be lowered substantially, this pilot study did not show large differences between conventional CPAP and hybrid therapy regarding compliance, satisfaction, and both objective and experienced effectiveness. There are, however, some differences in scores on CPAP complaints, which could explain why hybrid therapy is preferred by four of the seven patients. Therefore, CPAP – oral appliance hybrid therapy could be a comfortable and effective alternative to conventional CPAP when high pressure is needed or in case of high pressure intolerance. Larger, longer term, and preferably randomized studies are needed to answer the question whether hybrid therapy can result in lower pressures leading to a more comfortable and effective treatment for patients with moderate to severe OSAS.

ABBREVIATIONS

AHI, apnea-hypopnea index
CPAP, continuous positive airway pressure
IQR, interquartile range
OSAS, obstructive sleep apnea syndrome

REFERENCES

1. Schwab RJ, Pack AI, Gupta KB, et al. Upper airway and soft tissue structural changes induced by CPAP in normal subjects. *Am J Respir Crit Care Med* 1996;154:1106–16.
2. Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev* 2006;3:CD001106.
3. Diamanti C, Manali E, Ginieri-Coccossis M, et al. Depression, physical activity, energy consumption, and quality of life in OSA patients before and after CPAP treatment. *Sleep Breath* 2013;17:1159–68.
4. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365:1046–53.
5. Hoekema A, Stegenga B, Wijkstra PJ, van der Hoeven JH, Meinesz AF, de Bont LG. Obstructive sleep apnea therapy. *J Dent Res* 2008;87:882–7.
6. 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 to moderate obstructive sleep apnoea. *Thorax* 1997;52:362–8.
7. Doff MH, Veldhuis SK, Hoekema A, et al. Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on temporomandibular side effects. *Clin Oral Investig* 2012;16:689–97.
8. Doff MH, Finnema KJ, Hoekema A, Wijkstra PJ, de Bont LG, Stegenga B. Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on dental side effects. *Clin Oral Investig* 2013;17:475–82.
9. Fritsch KM, Iseli A, Russi EW, Bloch KE. Side effects of mandibular advancement devices for sleep apnea treatment. *Am J Respir Crit Care Med* 2001;164:813–8.
10. Denbar MA. A case study involving the combination treatment of an oral appliance and auto-titrating CPAP unit. *Sleep Breath* 2002;6:125–8.
11. Upadhyay R, Dubey A, Kant S, Singh BP. Management of severe obstructive sleep apnea using mandibular advancement devices with auto continuous positive airway pressures. *Lung India* 2015;32:158–61.
12. El-Solh AA, Moitheennazima B, Akinnusi ME, Churder PM, Lafornara AM. Combined oral appliance and positive airway pressure therapy for obstructive sleep apnea: a pilot study. *Sleep Breath* 2011;15:203–8.
13. Veldhuis SK, Doff MH, Stegenga B, Nieuwenhuis JA, Wijkstra PJ. Oral appliance to assist non-invasive ventilation in a patient with amyotrophic lateral sclerosis. *Sleep Breath* 2015;19:61–3.
14. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540–5.
15. Ware JE Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
16. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep* 1997;20:835–43.
17. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
18. Iber C, Ancoli-Israel S, Chesson AL, Quan SF; for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications, 1st ed. Westchester, IL: American Academy of Sleep Medicine, 2007.

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REVIEW ARTICLES

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Pathogenesis of Upper Airway Obstruction and Mechanical Intervention during Sedation and Sleep

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Upper airway patency is balanced by both oro-pharyngeal muscle activity and the intraluminal negative pressure caused by respiratory muscles during sleep and anesthesia. The mechanical upper airway properties may become the dominant factor governing upper airway collapsibility both during sleep and sedation due to the significant depression of consciousness and the impairment of neural mechanisms controlling compensatory neuromuscular responses. It is recognized that the pathogenesis of upper airway obstruction, due to alteration of consciousness during sleep and sedation, might be similar. Furthermore, the clinicians who manage obstructive sleep apnea patients should also be aware of the pathogenesis of upper airway obstruction during sleep. Anesthesiologists and surgeons who are responsible for airway management during procedures under sedation and the perioperative period should therefore be well versed with the physiological and pathophysiological mechanisms affecting upper airway patency. This review article presents the current understanding of mechanisms for maintaining upper airway patency during sleep and sedation based on the similarity of the pathophysiology governing upper airway patency. Possible mechanical interventions based on a quantitative analysis of upper airway collapsibility analyzing inspiratory flow limitation are also discussed.

Keywords: upper airway obstruction, sleep, sedation, obstructive sleep apnea, maxillofacial surgery

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INTRODUCTION

Upper airway patency depends on an appropriate balance between the dilating force of the pharyngeal muscles and the collapsing force of negative intraluminal pressure, which is generated by respiratory pump muscles. It is well accepted that maintenance of upper airway patency is a critical issue during sleep and sedation, because loss of consciousness may induce a depression of central respiratory output[1–3] by altering hypercapnic and hypoxic ventilatory drives, and it may decrease muscle contractility via cellular mechanisms by blocking sarcolemmal sodium channels.[4] Furthermore, it has been suggested that the neuromuscular activity of upper airway dilator muscles, such as the genioglossus and geniohyoid, may be affected by depression of hypoglossal motor neurons, which regulate tonic activation of these muscles. These influences, in association with depression of consciousness during sleep and sedation, may result in hypopnea and apnea due to upper airway obstruction. It has been suggested that the pathophysiology of upper airway obstruction might be similar in sleep and sedation.[5,6] Furthermore, the maintenance of mechanical upper airway properties may contribute significantly to upper airway patency. Therefore, understanding of the pathogenesis of upper airway obstruction may help establish clinical diagnostic and treatment methods in both sleep and sedation. Clinicians who are responsible for airway management during sleep and sedation should, therefore, be familiar with the physiological mechanisms influencing upper airway patency. This review article presents the current understanding of mechanisms for maintaining upper airway patency and discusses the developmental aspects of the mechanisms, based on a quantitative analysis of upper airway collapsibility using the concept of flow limitation. Furthermore, the similarity of the pathophysiology of upper airway obstruction between sleep and anesthesia based on the features of upper airway obstruction is also discussed. Lastly, the implications of the changes of upper airway patency by mechanical interventions during sleep and anesthesia are discussed.

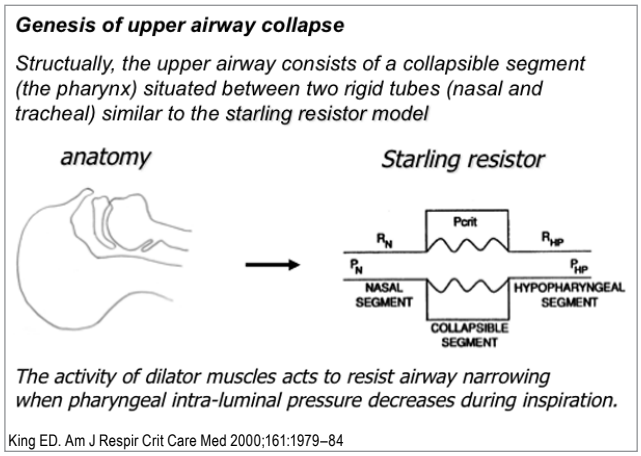
PATHOGENESIS OF UPPER AIRWAY OBSTRUCTION UNDER ANESTHESIA

The anatomical structure of the upper airway is characterized by a balanced combination of soft tissue components (tongue, soft palate, and pharyngeal mucosa) and bony structure components (maxilla, mandible, and vertebrae).[7] Upper airway patency is determined by precise interaction between the mechanical properties of the upper airway (anatomical mechanisms) and neural regulation of pharyngeal dilator muscle activity (neural mechanisms). Previously, the Neural Balance Model[8] and the Anatomical Balance Model[9] were introduced to understand how the upper airway is protected against upper airway obstruction during anesthesia.

RESPONSE TO ACUTE AND SUSTAINED PARTIAL UPPER AIRWAY OBSTRUCTION

Upper airway obstruction during sleep plays a pivotal role in the pathogenesis of obstructive sleep apnea[10] and is caused by structural defects and disturbances in neuromuscular

Figure 1—Mechanical analogue of upper airway consists of a two tube with a collapsible segment, upstream (nasal) and downstream (hypopharyngeal) segments.



The collapsible segment collapses only when tissue surrounding pressure exceeds intraluminal pressure. Under the conditions of airflow limitation, maximal flow (V_I max) is determined by the gradient between the upstream nasal pressure (P_N) and the P_{CRIT}, and the resistance (R_N) upstream as described in the equation, $V_I \max = (P_N - P_{CRIT}) / R_N$. P_N = nasal pressure, P_{HP} = hypopharyngeal pressure, R_N = resistance in nasal segment, P_{HP} = resistance in hypopharyngeal segment.

control.[6] Upper airway obstruction can elicit neuromuscular responses that mitigate and/or compensate for the obstruction. Under conditions of upper airway obstruction (inspiratory airflow limitation), immediate responses in respiratory timing indices can help restore ventilation[11] and blunt disturbances in gas exchange.[12] Nevertheless, the impact of respiratory pattern responses on ventilation during periods of upper airway obstruction remains unclear. It has recently been suggested that the respiratory cycle, but not the respiratory rate, determines the individual's ability to compensate for inspiratory airflow limitation during sleep[13] and during propofol anesthesia,[5] and it may represent a quantitative phenotype for obstructive sleep apnea susceptibility.

It has also been indicated that the compensatory neuromuscular response to upper airway obstruction is partly intact during propofol anesthesia with spontaneous breathing.[5] Interestingly, it has been reported that there was a significant difference in the compensatory neuromuscular response to upper airway obstruction between male and female subjects during midazolam sedation.[14] In natural NREM sleep, there was a significant difference in the compensatory neuromuscular response to upper airway obstruction between OSA patients and healthy subjects.[6] It is easy to expect that patients with depressed neuromuscular activity, such as cerebral palsy patients, may have weaker effects of this function. Furthermore, similar to OSA, aging may affect the magnitude of the compensatory neuromuscular response to upper airway obstruction.

During natural sleep, when sustained partial obstruction or complete obstruction occurs, the obstructed upper airway is re-opened by a brief arousal response, resulting in the return of muscle tone.[15] During sedation, the decrease in muscle tone associated with reduction of consciousness is compounded by specific drug-induced inhibition of upper airway neural and muscular activity and suppression of protective arousal responses. This depression of the arousal reflex during sedation even more than during NREM sleep might increase upper airway obstruction, such that external mechanical intervention may be needed to overcome the obstruction. Furthermore, the role of chemoreceptors from carotid body and retroambiguus nucleus may be depressed during sedation and anesthesia.[16] Although the arousal response against sustained upper airway obstruction is a fundamental defensive mechanism in the compensatory neural system to maintain upper airway patency, this arousal response may be even more depressed as anesthetic depth increases.

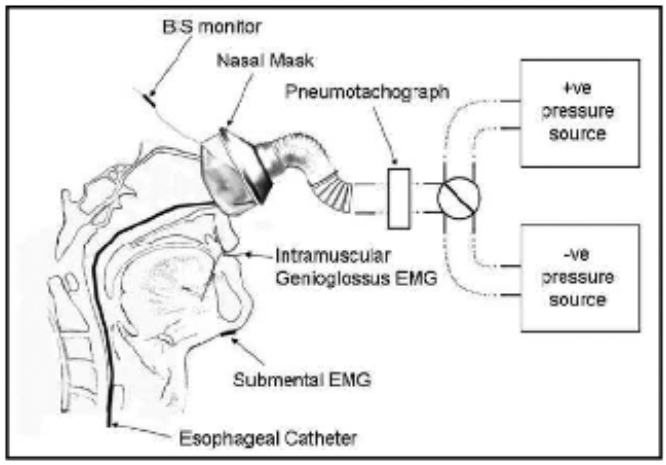
EVALUATION OF UPPER AIRWAY COLLAPSIBILITY

Concept of Flow Limitation and Critical Closing Pressure (P_{CRIT}) (Figures 1–4)

Upper airway collapsibility is evaluated by static imaging analysis via 2 dimension computerized tomography (CT) or magnetic resonance imaging (MRI), and 2 dimension cephalography X-ray, as well as dynamic analysis using the pressure-flow/volume relationship and pressure-cross-sectional area curves.

Among these quantitative analyses of upper airway patency, determination of the airway pressure that causes airway collapse and inspiratory airflow limitation in patients with obstructive sleep apnea has been used extensively in sleep apnea research. The application of negative airway pressure to determine the collapsibility of the upper airway using pressure-flow relationships, as seen with flow limitation or complete obstruction, has been used during anesthesia and sleep. The concept of critical closing pressure (P_{CRIT}) arises from modeling the upper airway as a simple collapsible tube and generation of multipoint pressure flow (P-Q) relationships, which are then used to assess upper airway patency.[17] Schwartz et al.[18] indicated that the upper airway patency can be explained by a Starling resistor model (**Figure 1**), in which inspiratory flow limitation occurs once upper airway upstream pressure falls below a critical closing pressure (P_{CRIT}). It has been shown that P_{CRIT} (representing nasal pressure at zero flow, an index of upper airway collapsibility) and resistance (which reflects the degree of upper airway narrowing upstream to the site of collapse) are key elements governing upper airway patency. P_{CRIT} can be estimated for the quantitative evaluation of upper airway patency based on nasal pressure and maximum inspiratory airflow in laboratory and has been validated for clinical usage or a research tool, even though this is not easy to extract from ordinary respiratory parameters. It is worth mentioning the clinical significance of P_{CRIT}. In fact, a ~5-cm H_2O decrease in $P_{CRIT,}$ due to increased neuromuscular activity, has the same stabilizing effect as applying ~5 cm H_2O of continuous positive airway pressure (CPAP) in reversing upper airway obstruction in obstructive apnea patients. It was previously suggested that a

Figure 2—Diagram of the experimental setup.

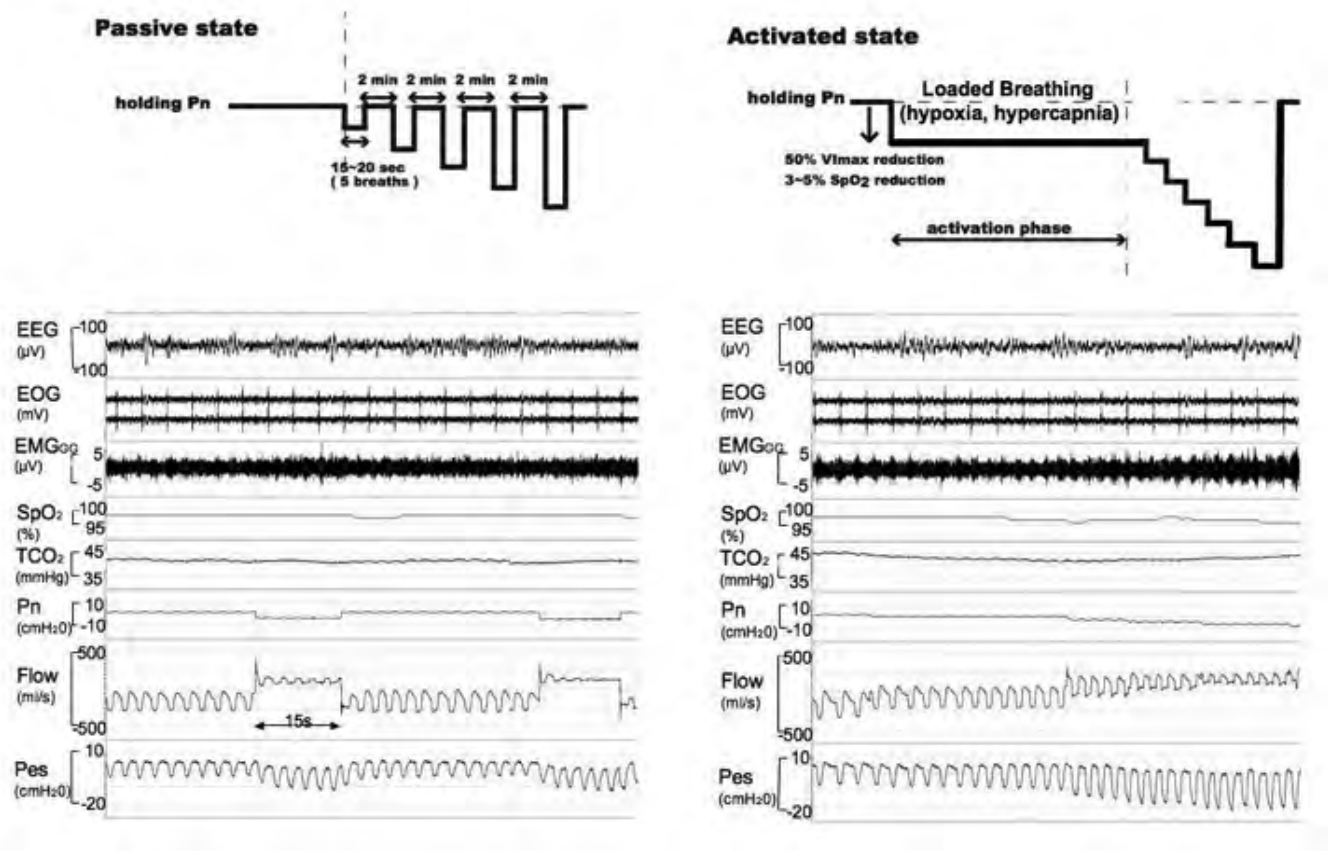


Maximally inspiratory flow (VImax)
Nasal pressure (Pn)
Esophageal pressure (Peso)
Inductance plethymogram (SUM)
Electroencephalograms (EEG: C3-A2)
Electrooculograms (EOG)
Submental electromyograms (EMG)
$ETCO_2$, SpO_2, BP

Hoshino Y. Respir Physiol Neurobiol 2009;166(1):24–31.

A nasal mask attached to a pneumotachograph is connected via tubing to either a positive (+ve) or negative (−ve) pressure source. Electromyography of the genioglossus muscle (EMG_{GG}) was recorded using fine wire intramuscular electrodes positioned percutaneously. Respiratory effort was determined by an esophageal pressure transducer-tipped catheter that was inserted via the nares. The bispectral index (BIS), electroencephalography, and submental surface EMG were recorded to monitor depth of anesthesia.

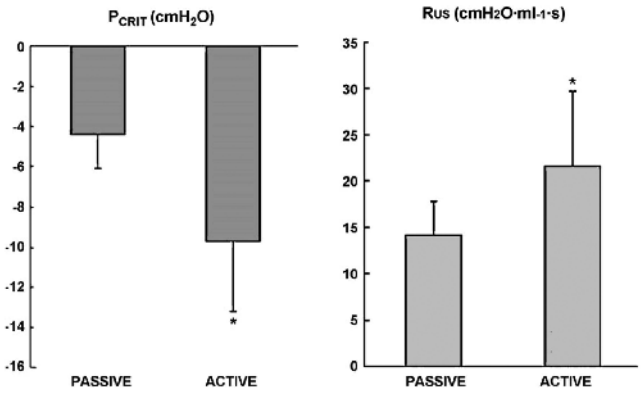
Figure 3—A schematic of the experimental protocol for producing upper airflow obstruction.



Hoshino Y. Respir Physiol Neurobiol 2009;166(1):24–31.

The polysomnographic recordings include the electroencephalogram (EEG), electro-oculogram (EOG), intramuscular genioglossus electromyogram (EMG_{GG}), nasal mask pressure (P_N), pneumotach airflow (V = Flow), esophageal pressure (*P*eso), and impedance plethysmography (RESP). A stable unobstructed breathing pattern was initially maintained at a positive holding pressure. Thereafter, P_N was lowered by 2 cm H_2O steps until a quasi-steady state flow-limited breathing pattern associated with a 40% to 50% reduction in V_I max (partial obstruction) was achieved. Subsequently, P_N was lowered in a stepwise fashion by 2 cm H_2O every 5 breaths, until zero flow of complete obstruction associated with an increase in respiratory negative pressure was obtained or SpO_2 reached a lower limit of 88% to 90%.

Figure 4—The change of compensatory neuromuscular response during propofol anesthesia.



Hoshino Y. Respir Physiol Neurobiol 2009;166(1):24–31.

The analysis of critical closing pressure (P_{CRIT}) and upper airway resistance (R_{US}) is shown. P_{CRIT} is calculated as a value of nasal pressure at zero flow by a linear regression analysis between maximum inspiratory airflow and nasal pressure.

change in P_{CRIT} of ~5 cm H_2O due to neuromuscular activity is clinically relevant,[6] since this represents the magnitude of the response required to convert either obstructive apneic events to less severe hypopneic events or hypopneic events to stable breathing. Because the P_{CRIT} measurements can be clinically relevant for evaluating upper airway collapsibility in patients during anesthesia and sleep, this method might be useful for investigating the pathophysiology of upper airway obstruction occurring during monitored anesthesia care. The advantage of this model is that it gives a global measure of upper airway collapsibility that includes both the structural and neuromuscular factors that determine upper airway collapsibility. More recently, advanced methods for evaluating both the mechanical properties and the compensatory neuromuscular responses to upper airway obstruction were predicted.[5,6] The most recent paper revealed that the P_{CRIT} can be assessed by the analysis software (P_{CRIT} Analysis Software in a numerical computing enviroment with 4th generation programming language: PAS) to streamline P_{CRIT} analysis using quantitative airflow measurement data in clinical cohorts study.[19]

PATIENT FACTORS PREDISPOSING TO UPPER AIRWAY OBSTRUCTION

Patient Position during the Procedure

Supine Position

The supine posture predisposes to upper airway obstruction, as the effects of gravity increase the extra-luminal compressive forces exerted by the tongue, soft palate, and related structures, resulting in narrowing of the retropalatal and retrolingual spaces.[20]

Head Down Posture:

The table tilt with head down position is recognized as being unfavorable, because of loss of longitudinal tension on the upper airway and fluid displacement into the upper airway region. Fluid displacement from the lower body to upper airway regions may increase upper airway collapsibility. Shepard et al. suggested that fluid accumulation in soft tissues surrounding the upper airway may increase pharyngeal collapsibility in patients with OSA.[21] It has also been shown that ~375 mL of fluid displacement from the legs by lower body positive pressure increases upper airway collapsibility by about 7.6 ± 1.9 cm H_2O in healthy, non-obese men while awake.[22] More recent studies have shown that fluctuation of estrogen and progesterone levels is coupled to fluid shifts from the vascular into the interstitial fluid compartments, causing edema.[23–25]

Neck Flexion

Neck flexion reportedly decreases pharyngeal size and increases passive P_{CRIT} in anesthetized patients.[9,26] Walsh et al.[26] reported that neck flexion with 10-degree deviation from the neutral position produced a 4.9 ± 3.1 cm H_2O increase in passive P_{CRIT}. Head elevation with a pillow seems to dose-dependently improve pharyngeal patency, although the possibility of simultaneous neck flexion would attenuate the beneficial effects of head elevation.[27] Accidental neck flexion may easily occur during surgical procedures in the oro-pharyngeal region.

Bite (Mouth) Opening

It is essential to keep the mouth open during oral-maxillofacial surgical procedures and dental treatment. However, as has been previously reported, this may cause obstruction.[28,29] Mouth opening decreases the space enclosed by the maxilla, mandible, and cervical vertebrae and increases the soft tissue volume inside the bony box, similar to that with neck flexion, since the mandibular movement with mouth opening is essentially the same as that which occurs with neck flexion.[9,28] Accordingly, the resultant increase in passive P_{CRIT} is predictable by the possible anatomical imbalance during mouth opening. In fact, passive P_{CRIT} increased significantly by 5.1 cm H_2O with the mouth open.[28] Mouth opening may change the vector force direction of the pharyngeal dilator muscles. Obviously there are high risks of increased upper airway collapsibility by existence of large tonsils[30–32] and macroglossia.[33,34]

Mechanical Displacement of the Tongue

Clinically, the tongue is frequently manipulated during surgical procedures in the mouth, with compression by instruments (tongue retractor) to avoid accidental injury by surgical instruments or to maintain the surgical view. In contrast to the beneficial effect of tongue protrusion on upper airway collapsibility[35] during sleep, downward displacement (retrograde) of the tongue in supine position might increase upper airway collapsibility during sleep.[36,37] Although the effect of tongue displacement on upper airway collapsibility during anesthesia has not been well established, we should be aware of the potential risk of surgical procedures in the oro-pharyngeal region.

Patients' Individual Anatomical Factors

It is well recognized that obesity, micrognathia, macroglossia and maxillary hypoplasia, acromegaly, Down syndrome, Pierre-Robin syndrome, or other craniofacial abnormalities

are major anatomical risk factors for upper airway obstruction. The degree of obstruction depends on the anatomical abnormalities in the pharynx. Furthermore, sex and age may other factors for controlling upper airway patency.

Recently, we demonstrated that female patients in the luteal phase of their menstrual cycle had an increased passive P_{CRIT} during propofol anesthesia. This conceivably reflects the development of pharyngeal edema due to the effect of sex hormones.[38] Based on evidence that there is a significant increase in edema formation in the upper airway region during the late-luteal phase in premenstrual dysphoric disorders,[39] we speculated that upper airway collapsibility may be significantly increased by edema formation[40] in the premenstrual phase, especially when there is a reduction of neuromuscular activity during shifts in progesterone level. We believe that our findings may provide new insight into the management of sedation in pregnant women, since they have much higher estrogen levels and significant upper airway edema.

Several studies have shown that surface tension[41–43] and saliva production[44] are important factors controlling upper airway patency, because surface tension is important for re-opening closed upper airways. These studies demonstrated that reduction of the surface tension in the upper airway mucosa by one-third can reduce the difference between the opening pressure and the closing pressures of the upper airway by 2 cm H_2O. Furthermore, our recent study found that an increase of 100-nM phosphatidylcholine decreases surface tension of saliva by ~17 mN/m. Surface tension may be increased in Sjögren syndrome.[45] Kirkness et al.[42] revealed that changes in surface tension significantly reflect the changes in upper airway opening pressure without affecting the upper airway closing pressure in humans. Deformation of the upper airway by negative transmural pressure during inspiration alters the activity of upper airway mechanoreceptors, causing a reflex increase in upper airway muscle activity. There may be significant influence of inflammation of pharyngeal tissue and neuropathic changes in tissue on reduction of reactivity in maintaining upper airway patency.

EFFECT OF SEDATION ON UPPER AIRWAY COLLAPSIBILITY (P_{CRIT})

It has been reported that the upper airway tends to get obstructed during sedation. Changes in upper airway patency during sedation appear to vary with the agents used, which include intravenous anesthetics (propofol) and sedative drugs (midazolam).[46,47] Midazolam and propofol are common anesthetic agents administered to provide anxiolysis, sedation, and amnesia during interventional procedures due to their rapid onset and limited duration of action. Although the effects of midazolam and propofol anesthesia are believed to be equivalent in terms of upper airway patency[47] during moderate levels of monitored anesthesia care, upper airway collapsibility dose-dependently increases as depth of anesthesia increases with each anesthetic agent.[46,48] Norton et al.[47] suggested that midazolam and propofol anesthesia have the same propensity for causing upper airway obstruction with mild to moderate sedation, based on an analysis using dynamic negative airway pressures. Using P_{CRIT} analysis (**Figure 1**), we confirmed that upper airway mechanical properties are similar with midazolam (mean value of passive P_{CRIT} = −5.1 cm H_2O) and propofol (mean value of passive P_{CRIT} = −4.4 cm H_2O) even during deeper stages of anesthesia.[5,28] This value of passive P_{CRIT} during anesthesia is similar to the mean value of passive P_{CRIT} values (−4.5 ± 3.0 cm H_2O) in normal subjects during natural sleep.[6] Therefore, we concluded that tonic neuromuscular activity of upper airway dilator muscles is relatively intact during monitored anesthesia care with midazolam and propofol, and the upper airway mechanical properties are the same as those during sleep. Interestingly, Eikermann et al.[49] showed that ketamine is a respiratory stimulant that abolishes the coupling between loss of consciousness and upper airway dilator muscle dysfunction over a wide dose range. They also indicated that ketamine might help stabilize upper airway patency during anesthesia. During sedation or hypnotic-induced sleep, repeated measurements of upper airway collapsibility appear to have less variability, suggesting that arousal and alterations in posture contribute to mechanical alterations in upper airway properties.[50]

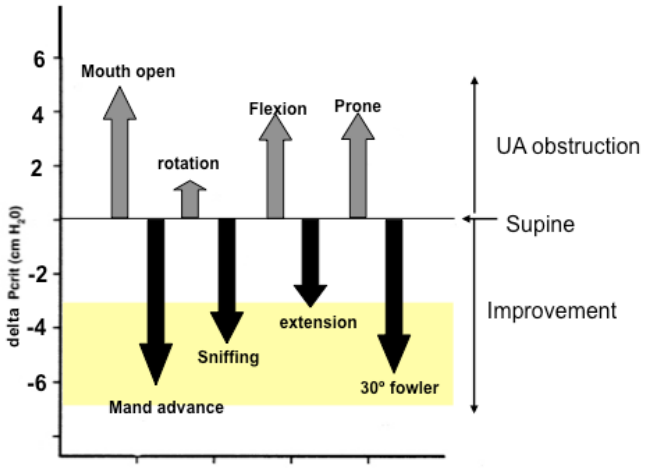
Recently, there appears to be a clinical advantage to use dexmedetomidine (DEX) for procedural sedation in pediatric patients and OSA patients.[51,52] In contrast to other sedative agents, DEX can provide better sedative properties similar to natural NREM sleep, without major respiratory depression. Therefore, DEX has recently been recommended for sedation during procedural sedation with local anesthesia for children and OSA patients.

Topical anesthesia of the upper airway mucosa, which greatly reduces this reflex response,[53,54] causes an increase in upper airway resistance and, thus decreases airflow during sleep. Berry et al. suggested that topical lidocaine applied to the nasal trigeminal area and hypopharynx-laryngeal area markedly induced airflow limitation due to reduction of the amount of phasic activity of the genioglossus electromyogram[53] during NREM sleep. A previous study[54] also showed that topical anesthesia might increase pharyngeal resistance during stage 1 sleep and at the wake to sleep transitions due to elimination of upper airway mucosal mechanoreceptors. Although the effect of local anesthesia on upper airway collapsibility during anesthesia has not been understood, the influence of local anesthesia in the oro-pharyngeal region may further modify sensitivity to negative airway pressure and chemical reflexes, increasing the patients' risk during monitored anesthesia care.

HOW CAN UPPER AIRWAY PATENCY BE MAINTAINED? (Figures 5, 6)

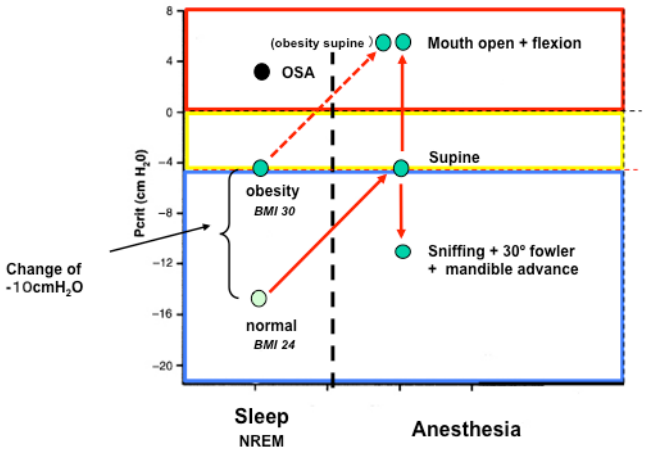
It is fundamentally impossible to keep the mouth closed during a procedure in order to maintain upper airway patency by avoiding the effect of mouth opening on the increase in upper airway collapsibility. Therefore, we should establish another mechanical intervention to maintain upper airway patency. How can we minimize the risk of upper airway obstruction during a procedure?

Figure 5—Effects of head and upper body position on upper airway collapsibility during sedation.



Opening of the mouth, rotation of the neck, neck flexion, and prone positioning cause upper airway obstruction. In contrast, mandible advancement, sniffing position, neck extension, and the 30-degree Fowler position decrease upper airway collapsibility.

Figure 6—Predicted effects of mechanical intervention on changes in critical closing pressure (P_{CRIT}) in obese patients during sedation.



During NREM sleep, the P_{CRIT} is higher in obese patients (BMI 30 kg/m^2) than that in normal subjects (BMI 24 kg/m^2) and lower than that in moderate OSA patients. If obese patients are managed under sedation in the supine position, upper airway collapsibility may increase, with higher P_{CRIT} values than during sleep. Positional change of mouth opening may further increase upper airway collapsibility with higher P_{CRIT} values. Mechanical intervention by the attending clinician, in the form of maintaining the patient's head and neck in the 30-degree fowler position or sniffing position, might improve upper airway collapsibility. Furthermore, simultaneous mandibular advancement may further improve upper airway collapsibility, similar to that during NREM sleep in normal subjects.

Effects of Mandible Advancement on Upper Airway Patency

Previously, we found that mandibular advancement significantly decreased P_{CRIT} to −13.3 ± 3.2 cm H_2O ($p < 0.05$ vs. the centric position), but it did not significantly affect upstream airway resistance (Rua) calculated by equation of V_I max = (P_N − P_{CRIT}) / Rua (22.1 ± 6.3 cm H_2O/L/s) during midazolam sedation.[55] In this study, we evaluated upper airway collapsibility in three different mandibular positions, centric occlusion position, incisors aligned position, and mandible advancement position (75% of the subject's maximum possible protrusion without any excessive discomfort and pain). Briefly, three different types of rigid-type custom mandible appliance were made during awake condition at different experimental day prior to experimental sedation condition. Three mandibular appliances with centric occlusion position, incisors aligned position, and mandible advancement position (75% of the subject's maximum possible protrusion) was constructed of clear acrylic resin and 1-mm polyethylene plate (Erkodur; Erkodent Inc.; Pfalzgrafenweiler, Germany) for each subject in reference to previous study by Tsuiki et al.[56] This study indicated that mandibular advancement in the incisor-aligned position can decrease both upper airway collapsibility by changes of P_{CRIT} and resistance during midazolam sedation, and that maximal mandible advancement (maximal comfortable protrusion) may not be necessary for the preservation of upper airway patency. We found that mandibular advancement produced isolated decreases in P_{CRIT}, indicating a decrease in collapsibility at the flow-limiting site.[28] Moreover, this evidence indicates that mandibular advancement should ameliorate sleep apnea if P_{CRIT} falls by 5 to 10 cm H_2O. In patients in whom moderate upper airway obstruction predominates, more modest degrees of mandibular advancement (possibly 25% to 50% of the patient's maximum possible protrusion) should be clinically effective, since decreases in P_{CRIT} of only 3 to 5 cm H_2O are required to relieve airflow obstruction during sleep and sedation. We have also suggested that the degrees of mandibular advancement can be titrated progressively to relieve obstruction in patients with partial or complete upper airway occlusion during sleep,[57] possibly due to the allowing muscle fibers adaptation. However, it should be noted that mandible advancement with mouth opening might alter the respiratory phase resetting during swallowing and the timing of swallowing in relation to the respiratory cycle phase. This finding indicates that mandible re-positioning may strongly affect coordination between nasal breathing and non-nutritive swallowing by altering respiratory parameters and by inhibiting movement of the tongue-jaw complex.[58]

Neck Extension and Chin Lift

Isono et al. reported that neck extension significantly decreased closing pressure of the velopharynx and oropharynx.[9] They observed an approximately 3.5-cm H_2O reduction in passive P_{CRIT} in the velopharynx and oropharynx and suggested that neck extension significantly decreases compliance of the oropharyngeal airway wall. Previous studies reported that the chin lift caused widening of the entire pharyngeal airway during propofol sedation.[59,60] They also suggested that the improvement in airway collapsibility during the chin lift is caused by a combination of increased tension of the pharyngeal muscles and forward movement of the muscles attached to the mandible. A previous study also confirmed that drug-induced

sleep endoscopy completed with a simulation bite approach for the prediction of the outcome of treatment of obstructive sleep apnea with mandibular repositioning appliances.[61]

Sniffing Position (Head Elevation)

Placing the head in the "sniffing position"[62] (lower cervical flexion, upper cervical extension with full extension of head on neck) increases longitudinal tension on the upper airway and decreases its collapsibility. Similar to neck extension, the sniffing position increases the distance between the mentum and cervical column, consequently increasing the space enclosed by the maxilla, mandible, and cervical vertebrae. This possibly results in a predictable reduction in passive P_{CRIT} due to improvement of mechanical factors in the sniffing position, although no information is available on changes in soft tissue volume in the pharynx. Recently Kobayashi et al. found a significant reduction in passive P_{CRIT} by a mean value of 4.3 cm H_2O in response to 6-cm head elevation during propofol anesthesia with spontaneous breathing.[63] They demonstrated that the optimal height of head elevation in normal-weight subjects under propofol anesthesia with spontaneous breathing through the closed mouth was approximately 6.0 cm.

Lateral Position

Boudewyns reported that P_{CRIT} fell from 1.8 cm H_2O in the supine position to –1.1 cm H_2O (delta 2.9 cm H_2O) in the lateral recumbent position.[64] Another study found that the upper airway of a spontaneously breathing child who was deeply sedated with propofol widened in the lateral position.[65]

Head Rotation

We previously demonstrated that head rotation decreased upper airway collapsibility in adult subjects during midazolam sedation.[66] However, we concluded that the therapeutic effect was insufficient to maintain upper airway patency. A previous study observed that passive P_{CRIT} (–2.8 cm H_2O) increased significantly when the head was rotated, compared to P_{CRIT} (–4.4 cm H_2O) in the supine condition (delta 1.6 cm H_2O) in pediatric patients, indicating a significant increase in pharyngeal airway collapsibility in the head rotated position.[67]

Upper Body Elevation (Sitting Position)

A previous study[68] found that a 30-degree elevation of the upper body resulted in an improvement of upper airway collapsibility compared with both the supine and lateral positions, as seen by measuring upper airway closing pressures in patients with obstructive sleep apnea. They reported that a 30-degree elevation caused a 4.3-cm H_2O decrease in P_{CRIT}, while adopting the lateral position caused a 1.4-cm H_2O decrease in P_{CRIT} relative to the supine position. In our previous study,[66] we found a 5.4-cm H_2O decrease in closing pressure after 30-degree upper body elevation compared to the supine position. A previous study indicated that postural change from supine to sitting positions enlarged both retropalatal and retroglossal airways and decreased P_{CRIT} in both pharyngeal segments by approximately 6 cm H_2O in completely paralyzed and anesthetized patients with OSA.[69] They postulated that this improvement can be due to mechanical interaction between the thorax and upper airway, such that caudal movement of the larynx with increasing lung volume results in secondary stiffening and dilatation of the pharynx.[69]

CONCLUSION

Mechanical upper airway anatomy may become the dominant factor governing upper airway collapsibility during sleep and sedation due to the significant impairment of neural mechanisms controlling compensatory neuromuscular responses. It is, therefore, important to understand the effectiveness of mechanical interventions and develop a systematic approach to evaluating the factors that contribute to maintenance of upper airway patency during sleep and sedation.

REFERENCES

1. Eastwood P, Bultynck L, van Eekelen A, Norman C. Towards better-quality research reporting in Respirology. *Respirology* 2014;19:1093–4.
2. Hillman D, Singh B, McArdle N, Eastwood P. Relationships between ventilatory impairment, sleep hypoventilation and type 2 respiratory failure. *Respirology* 2014;19:1106–16.
3. Horner RL, Hughes SW, Malhotra A. State-dependent and reflex drives to the upper airway: basic physiology with clinical implications. *J Appl Physiol* 2014;116:325–36.
4. Haeseler G, Stormer M, Bufler J, et al. Propofol blocks human skeletal muscle sodium channels in a voltage-dependent manner. *Anesth Analg* 2001;92:1192–8.
5. Hoshino Y, Ayuse T, Kurata S, et al. The compensatory responses to upper airway obstruction in normal subjects under propofol anesthesia. *Respir Physiol Neurobiol* 2009;166:24–31.
6. Patil SP, Schneider H, Marx JJ, Gladmon E, Schwartz AR, Smith PL. Neuromechanical control of upper airway patency during sleep. *J Appl Physiol* 2007;102:547–56.
7. Isono S, Remmers JE, Tanaka A, Sho Y, Sato J, Nishino T. Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. *J Appl Physiol* 1997;82:1319–26.
8. Remmers JE, deGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol* 1978;44:931–8.
9. Isono S, Tanaka A, Tagaito Y, Ishikawa T, Nishino T Influences of head positions and bite opening on collapsibility of the passive pharynx. *J Appl Physiol* 2004;97:339–46.
10. King ED, O'Donnell CP, Smith PL, Schwartz AR A model of obstructive sleep apnea in normal humans. Role of the upper airway. *Am J Respir Crit Care Med* 2000;161:1979–84.
11. Schneider H, Patil SP, Canisius S, et al. Hypercapnic duty cycle is an intermediate physiological phenotype linked to mouse chromosome 5. *J Appl Physiol* 2003;95:11–9.
12. Tagaito Y, Schneider H, O'Donnell CP, Smith PL, Schwartz AR. Ventilating with tracheal gas insufflation and periodic tracheal occlusion during sleep and wakefulness. *Chest* 2002;122:1742–50.
13. Schneider H, Schwartz AR, Smith PL, Patil SP, Krishnan V, Pichard L. Duty cycle responses to flow limitation predict nocturnal hypoventilation. *Eur Respir J* 2008;32:255–8.
14. Ayuse T, Hoshino Y, Kurata S, et al. The effect of gender on compensatory neuromuscular response to upper airway obstruction in normal subjects under midazolam general anesthesia. *Anesth Analg* 2009;109:1209–18.
15. Eckert DJ, Catcheside PG, McDonald R, et al. Sustained hypoxia depresses sensory processing of respiratory resistive loads. *Am J Respir Crit Care Med* 2005;172:1047–54.
16. Cortelli P, Lombardi C, Montagna P, Parati G. Baroreflex modulation during sleep and in obstructive sleep apnea syndrome. *Auton Neurosci* 2012;169:7–11.
17. Gold AR, Schwartz AR. The pharyngeal critical pressure. The whys and hows of using nasal continuous positive airway pressure diagnostically. *Chest* 1996;110:1077–88.

18. Schwartz AR, Smith PL, Wise RA, Bankman I, Permutt S. Effect of positive nasal pressure on upper airway pressure-flow relationships. *J Appl Physiol* 1989;66:1626–34.
19. Wei T, Erlacher MA, Grossman P, et al. Approach for streamlining measurement of complex physiological phenotypes of upper airway collapsibility. *Comput Biol Med* 2013;43:600–6.
20. Joosten SA, O'Driscoll DM, Berger PJ, Hamilton GS. Supine position related obstructive sleep apnea in adults: pathogenesis and treatment. *Sleep Med Rev* 2014;18:7–17.
21. Shepard JW, Jr., Pevernagie DA, Stanson AW, Daniels BK, Sheedy PF. Effects of changes in central venous pressure on upper airway size in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 1996;153:250–4.
22. Su MC, Chiu KL, Ruttanaumpawan P et al. Lower body positive pressure increases upper airway collapsibility in healthy subjects. *Respir Physiol Neurobiol* 2008;161:306–12.
23. Kasai T, Motwani SS, Elias RM, et al. Influence of rostral fluid shift on upper airway size and mucosal water content. *J Clin Sleep Med* 2014;10:1069–74.
24. White LH, Lyons OD, Yadollahi A, Ryan CM, Bradley TD. Night-to-night variability in obstructive sleep apnea severity: relationship to overnight rostral fluid shift. *J Clin Sleep Med* 2015;11:149–56.
25. Rosenfeld R, Livne D, Nevo O, et al. Hormonal and volume dysregulation in women with premenstrual syndrome. *Hypertension* 2008;51:1225–30.
26. Walsh JH, Maddison KJ, Platt PR, Hillman DR, Eastwood PR. Influence of head extension, flexion, and rotation on collapsibility of the passive upper airway. *Sleep* 2008;31:1440–7.
27. Boidin MP. Airway patency in the unconscious patient. *Br J Anaesth* 1985;57:306–10.
28. Ayuse T, Inazawa T, Kurata S, et al. Mouth-opening increases upper-airway collapsibility without changing resistance during midazolam sedation. *J Dent Res* 2004;83:718–22.
29. Meurice JC, Marc I, Carrier G, Series F. Effects of mouth opening on upper airway collapsibility in normal sleeping subjects. *Am J Respir Crit Care Med* 1996;153:255–9.
30. Bonuck K, Parikh S, Bassila M. Growth failure and sleep disordered breathing: a review of the literature. *Int J Pediatr Otorhinolaryngol* 2006;70:769–78.
31. Soultan Z, Wadowski S, Rao M, Kravath RE. Effect of treating obstructive sleep apnea by tonsillectomy and/or adenoidectomy on obesity in children. *Arch Pediatr Adolesc Med* 1999;153:33–7.
32. Mallory GB Jr., Fiser DH, Jackson R. Sleep-associated breathing disorders in morbidly obese children and adolescents. *J Pediatr* 1989;115:892–7.
33. Singhal P, Gupta R, Sharma R, Mishra P. Association of naso-oro-pharyngeal structures with the sleep architecture in suspected obstructive sleep apnea. *Indian J Otolaryngol Head Neck Surg* 2014;66:81–7.
34. Chin CJ, Khami MM, Husein M. A general review of the otolaryngologic manifestations of Down Syndrome. *Int J Pediatr Otorhinolaryngol* 2014;78:899–904.
35. Ferguson KA, Love LL, Ryan CF. Effect of mandibular and tongue protrusion on upper airway size during wakefulness. *Am J Respir Crit Care Med* 1997;155:1748–54.
36. Pae EK, Lowe AA, Sasaki K, Price C, Tsuchiya M, Fleetham JA. A cephalometric and electromyographic study of upper airway structures in the upright and supine positions. *Am J Orthod Dentofacial Orthop* 1994;106:52–9.
37. Lowe AA. The tongue and airway. *Otolaryngol Clin North Am* 1990;23:677–98.
38. Hoshino Y, Ayuse T, Kobayashi M, et al. The effects of hormonal status on upper airway patency in normal female subjects during propofol anesthesia. *J Clin Anesth* 2011;23:527–33.
39. Chang CT, Sun CY, Pong CY, et al. Interaction of estrogen and progesterone in the regulation of sodium channels in collecting tubular cells. *Chang Gung Med J* 2007;30:305–12.
40. Su MC, Chiu KL, Ruttanaumpawan P, et al. Difference in upper airway collapsibility during wakefulness between men and women in response to lower-body positive pressure. *Clin Sci (Lond)* 2009;116:713–20.
41. Lam JC, Kairaitis K, Verma M, Wheatley JR, Amis TC. Saliva production and surface tension: influences on patency of the passive upper airway. *J Physiol* 2008;586:5537–47.
42. Kirkness JP, Eastwood PR, Szollosi I, et al. Effect of surface tension of mucosal lining liquid on upper airway mechanics in anesthetized humans. *J Appl Physiol* 2003;95:357–63.
43. Kawai M, Kirkness JP, Yamamura S, et al. Increased phosphatidylcholine concentration in saliva reduces surface tension and improves airway patency in obstructive sleep apnoea. *J Oral Rehabil* 2013;40:758–66.
44. Usmani ZA, Hlavac M, Rischmueller M, et al. Sleep disordered breathing in patients with primary Sjogren's syndrome: a group controlled study. *Sleep Med* 2012;13:1066–70.
45. Hilditch CJ, McEvoy RD, George KE, et al. Upper airway surface tension but not upper airway collapsibility is elevated in primary Sjogren's syndrome. *Sleep* 2008;31:367–74.
46. Eastwood PR, Platt PR, Shepherd K, Maddison K, Hillman DR. Collapsibility of the upper airway at different concentrations of propofol anesthesia. *Anesthesiology* 2005;103:470–7.
47. Norton JR, Ward DS, Karan S, et al. Differences between midazolam and propofol sedation on upper airway collapsibility using dynamic negative airway pressure. *Anesthesiology* 2006;104:1155–64.
48. Hillman DR, Walsh JH, Maddison KJ, et al. Evolution of changes in upper airway collapsibility during slow induction of anesthesia with propofol. *Anesthesiology* 2009;111:63–71.
49. Eikermann M, Grosse-Sundrup M, Zaremba S, et al. Ketamine activates breathing and abolishes the coupling between loss of consciousness and upper airway dilator muscle dysfunction. *Anesthesiology* 2012;116:35–46.
50. Kirkness JP, Peterson LA, Squier SB, et al. Performance characteristics of upper airway critical collapsing pressure measurements during sleep. *Sleep* 2011;34:459–67.
51. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *Anesthesiology* 2003;98:428–36.
52. Mahmoud M, Jung D, Salisbury S, et al. Effect of increasing depth of dexmedetomidine and propofol anesthesia on upper airway morphology in children and adolescents with obstructive sleep apnea. *J Clin Anesth* 2013;25:529–41.
53. Berry RB, McNellis MI, Kouchi K, Light RW. Upper airway anesthesia reduces phasic genioglossus activity during sleep apnea. *Am J Respir Crit Care Med* 1997;156:127–32.
54. Doherty LS, Nolan P, McNicholas WT. Effects of topical anesthesia on upper airway resistance during wake-sleep transitions. *J Appl Physiol* 2005;99:549–55.
55. Inazawa T, Ayuse T, Kurata S, et al. Effect of mandibular position on upper airway collapsibility and resistance. *J Dent Res* 2005;84:554–8.
56. Tsuiki S, Ono T, Kuroda T. Mandibular advancement modulates respiratory-related genioglossus electromyographic activity. *Sleep Breath* 2000;4:53–58.
57. Ayuse T, Hoshino Y, Inazawa T, Oi K, Schneider H, Schwartz AR. A pilot study of quantitative assessment of mandible advancement using pressure-flow relationship during midazolam sedation. *J Oral Rehabil* 2006;33:813–9.
58. Ayuse T, Ishitobi S, Yoshida H, et al. The mandible advancement may alter the coordination between breathing and the non-nutritive swallowing reflex. *J Oral Rehab* 2010;37:336–45.
59. Shorten GD, Armstrong DC, Roy WI, Brown L. Assessment of the effect of head and neck position on upper airway anatomy in sedated paediatric patients using magnetic resonance imaging. *Paediatr Anaesth* 1995;5:243–8.
60. Reber A, Wetzel SG, Schnabel K, Bongartz G, Frei FJ. Effect of combined mouth closure and chin lift on upper airway dimensions during routine magnetic resonance imaging in pediatric patients sedated with propofol. *Anesthesiology* 1999;90:1617–23.
61. Vanderveken OM, Vroegop AM, Van de Heining PH, Braem MJ. Drug-induced sleep endoscopy completed with a simulation bite approach for the prediction of the outcome of treatment of obstructive sleep apnea with mandibular repositioning appliances. *Open Tech Otolaryngol* 2011;22:175–82.

62. Isono S, Tanaka A, Ishikawa T, Tagaito Y, Nishino T. Sniffing position improves pharyngeal airway patency in anesthetized patients with obstructive sleep apnea. *Anesthesiology* 2005;103:489–94.
63. Kobayashi M, Ayuse T, Hoshino Y, et al. Effect of head elevation on passive upper airway collapsibility in normal subjects during propofol anesthesia. *Anesthesiology* 2011;115:273–81
64. Boudewyns A, Punjabi N, Van de Heyning PH, et al. Abbreviated method for assessing upper airway function in obstructive sleep apnea. *Chest* 2000;118:1031–41.
65. Litman RS, Wake N, Chan LM, et al. Effect of lateral positioning on upper airway size and morphology in sedated children. *Anesthesiology* 2005;103:484–8.
66. Ikeda H, Ayuse T, Oi K. The effects of head and body positioning on upper airway collapsibility in normal subjects who received midazolam sedation. *J Clin Anesth* 2006;18:185–93.
67. Ishikawa T, Isono S, Aiba J, Tanaka A, Nishino T. Prone position increases collapsibility of the passive pharynx in infants and small children. *Am J Respir Crit Care Med* 2002;166:760–4.
68. Neill AM, Angus SM, Sajkov D, McEvoy RD. Effects of sleep posture on upper airway stability in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 1997;155:199–204.
69. Tagaito Y, Isono S, Tanaka A, Ishikawa T, Nishino T. Sitting posture decreases collapsibility of the passive pharynx in anesthetized paralyzed patients with obstructive sleep apnea. *Anesthesiology* 2010;113:812–8.

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PRO/CON DEBATE

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PRO: Upper Airway Resistance Syndrome Represents a Distinct Entity from Obstructive Sleep Apnea Syndrome

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Controversy exists over whether the upper airway resistance syndrome (UARS) represents an entity whose pathophysiology and clinical characteristics are distinct from those of obstructive sleep apnea syndrome (OSAS). Many clinicians remain unconvinced of its clinical relevance as a unique disorder and instead believe it lies along the same spectrum as OSAS. We believe that ample evidence suggests UARS indeed represents a separate clinical phenomenon as opposed to simply a less severe form of OSAS, and that there is utility in considering it as a separate disorder.

UARS is a form of sleep disordered breathing characterized by repeated increases in upper airway resistance with concomitant increased respiratory effort, resulting in brief arousals. Such events are termed respiratory effort-related arousals or RERAs, where arousals are defined as a brief shift in alpha or fast theta frequency on the electroencephalogram (EEG) lasting from 3–10 seconds. RERAs are distinct from apneas or hypopneas in that they lack frank apneas or oxygen desaturation and are typically shorter (1 to 3 breaths), thereby failing to meet the generally accepted criteria for either apneas or hypopneas. RERAs are distinct from apneas or hypopneas in that they lack frank cessation of airflow or oxygen desaturation and are typically shorter (one to three breaths). By definition, the apnea-hypopnea index (AHI) in patients with UARS is less than five.

The gold standard measurement of RERAs in UARS is considered esophageal pressure monitoring (P_{es}), which detects progressive elevations in intrathoracic pressures with respiration leading up to an arousal. Most early publications of UARS utilized esophageal pressure monitoring and several abnormal forms of P_{es} tracings were described.[1] P_{es} crescendo is characterized by a progressively increased negative peak inspiratory pressure in each breath, terminating with either an arousal or burst of delta wave on EEG. A second abnormality seen involves sustained continuous respiratory effort with a relatively stable and persistent negative peak inspiratory pressure seen on the P_{es} tracing to a degree greater than seen in baseline, non-obstructed breaths. The third form is P_{es} reversal, characterized by a sequence of increased respiratory efforts followed by a sudden decrement in respiratory effort indicated by a less negative peak inspiratory pressure.

Despite its utility, esophageal pressure monitoring has not been routinely adopted as part of standard polysomnographic setup in most sleep laboratories, since it involves the semi-invasive placement of a pediatric feeding catheter into the patient's nostril down to the esophagus and the potential discomfort associated with this procedure. Ample evidence now suggests that RERAs may be adequately detected with nasal cannula pressure transducers (NCPTs) and this technology has been widely across the United States. We agree that sufficient data exists to accept NCPTs used in combination with respiratory inductive plethysmography (RIP) volume signals as an adequate substitute for esophageal pressure monitoring[2,3] and certainly one with greater accuracy than a thermistor, for detecting flow-limited respiration in UARS.[4] The superior tolerance of NCPTs by patients renders it a more convenient means of identifying subtle breathing abnormalities during sleep. The presence of flow limitation on the NCPT appears as a flattening of the normal bell-shaped curve of a normal breath with a drop in the amplitude by < 30% compared to normal breaths immediately preceding the drop.

Based on this definition alone, UARS would seem to potentially represent a milder degree of upper airway obstruction than is present in OSAS. If UARS existed simply on a spectrum with OSAS, however, we would expect to see the symptoms of this disorder on a continuum as well. Instead, research supports several symptoms unique/distinct to UARS and less predominant in OSAS (**Table 1**).

One of the central arguments in favor of UARS as a distinct entity stems from the differences in the population it affects. UARS patients tend to be leaner, with a mean BMI ≤ 25 kg/m^2, younger, with a mean age of 37.5 years, and equally present in males and females[5] (although representing a greater proportion of sleep related breathing disorders in women[6]). Cephalometry has revealed craniofacial abnormalities in the upper airway anatomies of many UARS patients, including the presence of a long face, short and narrow chin with reduced mouth opening, retrolingual narrowing, increased overjet, high and narrow hard palate.[7]

A second argument in support of UARS as a distinct entity draws its support from the presenting complaints of these patients. UARS may occur in the absence of clinically significant snoring and may be an occult cause of excessive daytime sleepiness.[8] UARS patients generally present with more subjective perception of daytime dysfunction in association with sleepiness than do OSAS patients.[9] They complain of worse subjective sleep quality than OSAS patients as measured by standardized scales of insomnia, subjective sleepiness and sleep quality[10] and higher rates of insomnia related to sleep initiation.[6] Somatic complaints are more common and distinct personality characteristics are seen in these patients. Patients with UARS have been noted to complain more frequently of chronic insomnia and daytime sleepiness or fatigue than those with OSAS. Reports of headaches, vasomotor rhinitis, irritable bowel syndrome, difficulty in concentrating, and depressed mood have been described in association with UARS more frequently than OSAS. Patients with UARS tend to score more

Table 1—Clinical Features in upper airway resistance syndrome (UARS) and obstructive sleep apnea syndrome (OSAS).

	UARS	OSAS
Epidemiology		
Age	All ages (mean age 38 years old)	Children Males > 40 years old Females after menopause
Male-to-female ratio	1:1	2:1
Body habitus	Lean or normal (BMI often < 25 kg/m^2)	Often overweight or obese
Blood pressure	Low or normal	High
Neck circumference	Low or normal	Large
Clinical Presentation		
Snoring	Common but may be minimal or absent in 10–15%	Near-universal
Witnessed apneas	Absent	Common
Daytime Symptoms	Excessive daytime sleepiness, fatigue, morning headaches, myalgias, difficulty concentrating	Excessive daytime sleepiness, morning headaches
Sleep Disturbances	Frequent nocturia, difficulties initiating sleep, insomnia, bruxism, restless legs syndrome, unrefreshing sleep	Snoring, gasping, witnessed apneas, nocturia
Autonomic Nervous System	Hypotension, orthostasis, cold hands and feet	Rare
Functional somatic syndrome associations	Depression, anxiety, chronic fatigue syndrome, irritable bowel syndrome, fibromyalgia	Rare
Polysomnography		
Sleep onset latency	Long	Short
AHI	< 5/h	≥ 5/h
Minimum O_2 saturation	> 92%	Often < 92%
Respiratory effort-related arousals	Predominant	Minimal
Cyclic alternating patterns	Frequent	Less common
Power spectral EEG analysis	Higher α power, higher δ in stage REM	Less α or δ

Adapted from Bao and Guilleminault, Table 1 and Table 2.[1] AHI, apnea-hypopnea index as events per hour.

strongly toward neuroticism than OSAS patients on personality inventories[8] and demonstrate increased somatic arousal as measured by self-report questionnaires.[11] These observations have led to the suggestion that UARS may represent a functional somatic syndrome such as chronic fatigue syndrome and fibromyalgia. There are also objective measures suggesting that UARS is distinct from OSAS. Patients with UARS have been noted to perform more poorly than OSAS patients on tests of psychomotor vigilance,[12] a proxy for daytime attentional function. In retrospective study of patients at an academic sleep center, a model fit to predict hypersomnolence among patients with both OSAS and UARS significantly underestimated hypersomnolence in UARS patients.[13]

A third line of argument comes from electroencephalographic spectral analysis, where EEG power is characterized for each sleep epoch on polysomnography. Patients with UARS are noted to have a general increase in alpha rhythm and relatively more delta power noted during stage REM sleep, in contrast to the reductions in both of these frequencies commonly observed in patients with OSAS.[1] Furthermore, the presence of cyclic alternating pattern (CAP) on EEG has also been observed with higher frequency in patients with UARS than those with OSAS. In patients with UARS, CAP is a marker of sleep instability and poor sleep quality, and correlated with subjective symptoms of sleepiness and fatigue. Sleep disturbances in this population are often identifiable only with sensitive measures such as CAP analysis and not with traditional diagnostic scoring systems.[14]

Fourth, one of the pathologic lesions present in OSAS—local neurogenic lesions in the pharynx and upper larynx that interfere with maintenance of normal airway patency—does not appear to be present in patients with UARS.[1] It has been hypothesized that this preservation of normal sensory input from the upper airways leads to faster arousal and recovery of normal breathing prior to the point of reaching levels of hypoxemia seen in OSAS.

A key question in this discussion is whether our current definition of OSAS, which allows for the scoring of hypopneas (reduced airflow or flow limitation) terminating not only in desaturation, but also in arousals, sufficiently captures all of those patients with clinical symptoms resulting from said arousals. We argue that it likely does not. OSAS is characterized by multiple pathologic perturbations including hypoxemia and re-oxygenation, increased intra-thoracic pressure and mechanical load, sympathetic activation, elevations of

inflammatory markers, and arousals. The degree to which of each of these pathologic events contributes to adverse clinical outcomes likely differs and growing research is beginning to elucidate these differences. Indeed, evidence suggests that the arousals and associated sleep disruption which are central to the pathophysiology of UARS may be sufficient in themselves to cause adverse outcomes, even in the absence of hypoxemia. Human studies have reported associations between arousals and subjective sleepiness, changes in hormone secretion patterns, increased metabolic rate and increased sensory arousal threshold.[15] Several studies have demonstrated a positive association between the number of arousals and awakenings seen on polysomnogram (PSG) and presence of hypertension. Evidence suggests that brief arousals from sleep, even for a single night, may affect levels of sleepiness the following day. For example, Philip et al. produced nocturnal auditory stimuli to elicit arousals and demonstrated a significant reduction in mean sleep latency on next-day multiple sleep latency testing (MSLT).[16] In a similar experiment, Martin and colleagues demonstrated effects of such stimulation on mood and cognitive function.[17]

Most initial descriptions of disease began with clinical observations of the most pronounced, easily identifiable examples of a disorder. Over time, as the less "classic" manifestations of a disease are characterized and its prevalence explored in other populations, it is often recognized that the initial ontology was oversimplified. A disease's expression in some populations may not be recognized until later on. This was in fact the case with obstructive sleep apnea, where reports of fatigue, headache, and mood disturbance rather than "classic" symptoms of snoring and witnessed apneas,[18] were observed more commonly in women, and were not recognized for several years after its initial description. Once this realization occurred, OSAS was recognized to be more widely prevalent in women than was previously believed. Particularly in the case of UARS, we believe that erring in the direction of *over-* as opposed to *under*-diagnosis is prudent. The former risks needlessly treating some additional patients with a virtually harmless therapy that may be withdrawn at any point; the latter risks missing an opportunity to improve patients' quality of life significantly. If we fail to acknowledge that UARS may represent a distinct clinical syndrome, we may less vigilantly ensure the scoring of RERAs and therefore miss opportunities to correlate these events with clinical outcomes in the future.[6]

We acknowledge that there are limitations in the current research on UARS, but view these as constructive starting points for further investigations as opposed to justification to dismiss the entity altogether. As the Greek playwright Sophocles stated, "Look and you will find it—what is unsought will go undetected." One limitation of research to date on UARS involves the absence of a standardized definition across research groups and even within the same groups over time, as well as heterogeneity in the characterization of events that have been considered to meet criteria as RERAs. A second limitation is that much of the research on UARS has been conducted by only a few research groups and not yet replicated by other teams in different patient populations. Finally, a third limitation is the potential of sample bias in existing literature to have influenced the description of this entity. Specifically, most of the initial investigations by Guilleminault and colleagues occurred in a population of patients who had presented to sleep clinics. It stands to reason that such patients differ from the population of patients at large, and even from those who might have been randomly recruited from primary care clinics, in that they suffered symptoms stereotypical enough to result in subspecialty referral. This issue of sample bias may be even more relevant to sleep disorders than other medical disorders, since detailed sleep histories are not routinely elicited in primary care settings.[19] Without comparison to the general population, it is therefore impossible to estimate the true risk conferred by polysomnographic findings of UARS as they relate to specific complaints or clinical outcomes. The first step to classification of any disease requires its recognition in a narrow patient population, but future work should more rigorously evaluate the prevalence of UARS symptoms and PSG findings in all patients, not simply in those with easily identifiable symptoms that drive them to seek care at a sleep clinic.

Even if the above definition of UARS evolves over time, as occurs with many disorders, it remains useful as a starting point. Indeed, our understanding of the pathophysiology of OSAS continues to evolve, with recent work suggesting the existence of multiple phenotypes of OSAS, characterized by the presence or absence of hypoxemia,[20] genioglossus muscle responsiveness during sleep, arousal threshold, and presence of loop gain.[21] A recent application of cluster analysis from the Icelandic Sleep Apnea Cohort has yielded a further classification scheme based on clinical subtypes that may eventually help us to identify patients with sleep apnea based on predominant presenting symptoms.[22] We anticipate that these lines of inquiry will be further pursued in coming years, leading to a refined understanding and revised definitions of the sleep-related breathing disorders, their variable clinical and pathophysiologic profiles, and in turn, to modified treatment pathways for managing these patients. The true prevalence of UARS in the general population is not known, but we suspect it is substantial, and therefore feel it warrants further study.

In summary, we feel that UARS indeed represents a unique sleep-related breathing disorder distinct from OSAS, the heterogenous nature of which has only recently begun to be elucidated. If the disorder truly existed along a continuum with OSAS, we would expect to see a dose-dependent response between the degree of sleep disordered breathing and clinical symptomatology. As the aforementioned studies make clear, such a relationship has not been consistently seen. Rather, several symptoms appear to occur with increased frequency among patients with UARS and not in those with OSAS. Further work is needed in order to advance our understanding of UARS and its relationship to the more conventionally accepted sleep breathing disorders so that symptomatic patients do not continue to go untreated.

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REFERENCES

1. Bao G, Guilleminault C. Upper airway resistance syndrome--one decade later. *Curr Opin Pulm Med* 2004;10:461–7.
2. Epstein MD, Chicoine SA, Hanumara RC. Detection of upper airway resistance syndrome using a nasal cannula/pressure transducer. *Chest* 2000;117:1073–7.
3. Ayappa I, Norman RG, Krieger AC, Rosen A, O'Malley RL, Rapoport DM. Non-Invasive detection of respiratory effort-related arousals (REras) by a nasal cannula/pressure transducer system. *Sleep* 2000;23:763–71.
4. Montserrat JM, Badia JR. Upper airway resistance syndrome. *Sleep Med Rev* 1999;3:5–21.
5. Exar EN, Collop NA. The upper airway resistance syndrome. *Chest* 1999;115:1127–39.
6. Guilleminault C, Kirisoglu C, Poyares D, et al. Upper airway resistance syndrome: a long-term outcome study. *J Psychiatr Res* 2006;40:273–9.
7. Pépin JL, Guillot M, Tamisier R, Lévy P. The upper airway resistance syndrome. *Respir Int Rev Thorac Dis* 2012;83:559–66.
8. Kristo DA, Lettieri CJ, Andrada T, Taylor Y, Eliasson AH. Silent upper airway resistance syndrome: prevalence in a mixed military population. *Chest* 2005;127:1654–7.
9. Deary V, Ellis JG, Wilson JA, Coulter C, Barclay NL. Simple snoring: not quite so simple after all? *Sleep Med Rev* 2014;18:453–62.
10. So SJ, Lee HJ, Kang SG, Cho CH, Yoon HK, Kim L. A comparison of personality characteristics and psychiatric symptomatology between upper airway resistance syndrome and obstructive sleep apnea syndrome. *Psychiatry Investig* 2015;12:183–9.
11. Broderick JE, Gold MS, Amin MM, Gold AR. The association of somatic arousal with the symptoms of upper airway resistance syndrome. *Sleep Med* 2014;15:436–43.
12. Stoohs RA, Knaack L, Blum HC, Janicki J, Hohenhorst W. Differences in clinical features of upper airway resistance syndrome, primary snoring, and obstructive sleep apnea/hypopnea syndrome. *Sleep Med* 2008;9:121–8.
13. Gold AR, Gold MS, Harris KW, Espeleta VJ, Amin MM, Broderick JE. Hypersomnolence, insomnia and the pathophysiology of upper airway resistance syndrome. *Sleep Med* 2008;9:675–83.
14. Guilleminault C, Lopes MC, Hagen CC, da Rosa A. The cyclic alternating pattern demonstrates increased sleep instability and correlates with fatigue and sleepiness in adults with upper airway resistance syndrome. *Sleep* 2007;30:641–7.
15. Jaimchariyatam N, Rodriguez CL, Budur K. Sleep-related cortical arousals in adult subjects with negative polysomnography. *Sleep Breath* 2014;19:989–96.
16. Philip P, Stoohs R, Guilleminault C. Sleep fragmentation in normals: a model for sleepiness associated with upper airway resistance syndrome. *Sleep* 1994;17:242–7.
17. Martin SE, Engleman HM, Deary IJ, Douglas NJ. The effect of sleep fragmentation on daytime function. *Am J Respir Crit Care Med* 1996;153:1328–32.
18. Redline S, Kump K, Tishler PV, Browner I, Ferrette V. Gender differences in sleep disordered breathing in a community-based sample. *Am J Respir Crit Care Med* 1994;149:722–6.
19. Senthilvel E, Auckley D, Dasarathy J. Evaluation of sleep disorders in the primary care setting: history taking compared to questionnaires. *J Clin Sleep Med* 2011;7:41–8.
20. Palma J-A, Iriarte J, Fernandez S, et al. Characterizing the phenotypes of obstructive sleep apnea: clinical, sleep, and autonomic features of obstructive sleep apnea with and without hypoxia. *Clin Neurophysiol* 2014;125:1783–91.
21. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. *Am J Respir Crit Care Med* 2013;188:996–1004.
22. Ye L, Pien GW, Ratcliffe SJ, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. *Eur Respir J* 2014;44:1600–7.

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PRO/CON DEBATE

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CON: Upper Airway Resistance Syndrome Does Not Exist as a Distinct Disease

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Upper airway resistance syndrome (UARS) does not exist as a discrete disease state, but as a milder form of the obstructive sleep apnea syndrome (OSAS). The elevation of UARS to a distinct medical "syndrome" in 1993 by Guilleminault and colleagues, attempting to set it apart from OSAS has no biological underpinnings. Since its creation, the concept of UARS has been subjected to endless debates between sleep clinicians and researchers, contesting its existence, its nature, its etiology, and its treatment.

UARS fails each of the defining areas needed to set itself apart from OSAS: (1) unique diagnostic criteria; (2) distinct clinical presentation; (3) discrete polysomnographic findings; (4) characteristic pathophysiology; (5) distinctive associated comorbidities, and (6) particular treatment(s). I will proceed to highlight shortcomings in each of these critical areas.

1) UARS as an Extension of OSAS Diagnostic Criteria

UARS was first described by Guilleminault and colleagues in 1993.[1] It was born from the systematic observation of patients with complaints of excessive daytime sleepiness (EDS) with otherwise non-diagnostic OSA polysomnography by formal apnea and/or hypopnea criteria. By implementing an esophageal balloon catheter (Pes) and airflow pneumotachography during the polysomnography (PSG), the author was able to identify more subtle inspiratory airflow limitation (IFL) coupled with brief cortical arousals as the etiology of EDS. In these patients, the use of continuous positive airway pressure (CPAP) reversed the upper airway resistance physiology, decreasing the number of cortical arousals, and improving the associated excessive daytime sleepiness. So, are these observations enough to set UARS apart from OSAS?: (1) there is no significant difference in maximal esophageal pressure measured by a balloon catheter between hypopneas (OSAS) and upper airway resistance episodes (UARS); (2) the increase in inspiratory flow limitation (IFL) parallels the increase in airway collapsibility found across the full spectrum of obstructive respiratory events in OSAS; (3) the fact that respiratory arousals can occur without concomitant oxygen desaturation reflects upon an individual variability in oxygen reserve in OSAS patients rather than an unique characteristic of UARS patients; (4) transient, respiratory-related cortical arousals are well known to produce sleep fragmentation and subsequent EDS in OSAS; and finally, (5) reversal of upper airway resistance with use of CPAP improves neurocognitive symptoms along the full spectrum of OSAS.[2–5]

So, more than two decades ago, the definition of UARS as a "new" syndrome was founded on nonspecific observations, overlapping with OSAS. It was created simply to fill the gap left by the rigid diagnostic criteria of OSAS, where the definition of apneas and hypopneas overlooked the spectrum of milder forms of airway resistance associated with cortical arousals and related symptoms.

(2) Clinical Presentation: UARS and OSAS are Indistinguishable

Both OSA and UARS often present with signs/symptoms of snoring, fragmented sleep, daytime sleepiness, and fatigue. However, in comparison to OSA patients, UARS patients are described by early studies as younger, predominantly female, and associated with greater prevalence of insomnia, fatigue, body pain, and irritable bowel (known as functional somatic syndrome).[6] In 2008, Gold and colleagues showed no difference in hypersomnolence symptoms between mild OSAS and UARS. In this study, the hypersomnolence symptoms increased in parallel to increase in OSAS severity. Contrary to hypersomnolence, the prevalence of insomnia increased with decrease in severity of upper airway collapsibility, being prominent in patients with mild OSAS. Therefore, the milder is the form of OSAS, the less severe is the hypersomnolence and, therefore, the higher is the incidence of sleep-onset insomnia, explaining the finding of sleep onset insomnia in UARS, as a mild form of OSAS.[7]

Finally, it has been shown that when compared UARS and OSAS patients, not even sleep disorders specialists are able to dissociate the two syndromes based upon clinical evaluation. Clinical presentation such as daytime sleepiness complaints and ESS scores are not different between patients with OSAS and those with UARS. Both syndromes also share similar report rates of unrefreshing sleep upon awakening in the morning as well as the need of taking naps during the daytime.[8,9]

3) Overlapping Polysomnographic Findings between UARS and OSAS

UARS is defined by the presence of EDS associated with more than 50% of respiratory related arousals (RERAS), otherwise "not better explained by another sleep disorder." This operational definition already recognizes that "RERAs" present in the mixed of other respiratory events, such as apneas and hypopneas, along the continuum of OSAS.

Unfortunately, the diagnosis of UARS based on PSG findings is overwhelmed by lack of standardization in measurement techniques and homogenous diagnostic criteria, challenging any attempt to compare study results; however, the following issues in PSG are worth highlighting:

a) The shortcoming of defining RERAs upon the absence of hypopneas

It is challenging to define a disease (UARS) by the absence of another (OSAS), when the definition of both diseases and scoring of respiratory events (e.g., hypopneas, RERAs) have been in continuous flux in the last two decades. The scoring of apneas and hypopneas is the result of a consensual designation of what a respiratory event is and the measurement techniques used. For example, hypopnea has been initially measured by using a thermistor, a method replaced by a nasal cannula pressure transducer. This method is more sensitive in detecting semiquantitative changes in flow amplitude, affecting hypopneas and RERA scoring, with subsequent changes in disease identification, severity grading, and comparability of results between different laboratories and research studies.[10]

b) Hypopneas and RERAs, two sides of the same coin

UARS is defined by RERAs. These are respiratory events of ≥ 10 seconds, characterized by increasing respiratory efforts (esophageal balloon) or by flattening of the nasal pressure waveform (or PAP device flow), leading to arousals when it does not meet criteria for apnea or hypopnea. Does RERAs scoring depend on hypopnea's definition? RERAs' score varies fundamentally based upon the hypopnea definition selected for scoring. The AASM Manual for Scoring, Rules and Terminology (version 2.0), states that a hypopnea is defined by a " ≥ 30% drop of nasal pressure for more or equal to 10 seconds, associated with a desaturation or arousal." If arousals instead of desaturation are chosen to define hypopneas, then the scoring of RERAs is relegated to subjective measures of pressure signal drop of < 30%.[11] Other serious limitations in the standard scoring of RERAs are: (1) RERA scoring requires a consistent good flow signal quality throughout the study; (2) inspiratory flow limitation is an indirect consequence of respiratory effort, which may be less accurate in REM; and finally, (3) RERAs are delineated by cortical arousals, which cannot be determined by current out-of-center sleep testing (OCST) technology, limiting UARS to an in-laboratory diagnosis.

c) Arousals as normal variance in the definition of UARS

The frequency of arousals in defining UARS has been traditionally defined by an arousal index (AI) of more than 10 arousals per hour of sleep. Unfortunately, this disease-defining criterion is already overlapping with well-established EEG arousal norms based on age, identifying normal AI of 16.8 ± 6.2 at age 31–40, increasing up to 21.9 ± 8.9 at age 51–60.[12] In fact, when compared with normal subjects, UARS patients have no difference in frequency of arousals (12.7 ± 5.8 in UARS patients vs. 10.1 ± 4.3, p-value 0.22).[13]

d) Common PSG findings between UARS and OSAS

In comparison to OSAS, UARS patients have no difference in polysomnographic sleep architecture parameters such as sleep efficiency, sleep latency, slow wave sleep latency, and REM sleep latency.[8]

Regarding electrocortical activity, alpha-delta sleep is defined by the intrusion of waking alpha rhythm into deep, slow wave sleep (delta). If present in a cyclical alternating pattern (CAP), it correlates with increased sleep instability and fatigue in UARS patients. However, CAP is a nonspecific electroencephalographic pattern present in a wide variety of other disorders, including OSAS.[14]

4) A Common Pathway and Risk Factors Shared by UARS and OSAS

If considered a distinct clinical entity from OSAS, UARS should present a different pathophysiology and natural history. However, when studied from the perspective of upper airway physiology, patients with UARS and patients with OSA are similar, although the severity of the upper airway collapsibility during the sleep is different. Recent data have suggested that patients with UARS present with upper airway closing pressures intermediate between OSAS and normal controls.[15] Notably, other studies have also found inspiratory flow limitation (IFL) during sleep associated with arousals even in healthy individuals. In comparison to healthy individuals, UARS patients have only slightly increased of IFL during supine, stage 2 sleep, and no difference in inspiratory effort. As they age, healthy individuals demonstrate increase of IFL, hypopneas, and even apneas during sleep.[16] These findings support the progression in the continuum of increasing upper airway collapsibility, where individuals may transition from "normal" (asymptomatic) all the way up to OSAS as they age.

The natural history of UARS further supports the idea that UARS belongs to the clinical spectrum of OSAS. During a 6-year follow-up study, a significant number of patients originally diagnosed with UARS developed signs of OSAS. In this study, the progression from UARS to OSAS was related to increase in BMI, a well-known risk factor for OSAS.[17]

5) Nosological Classification: UARS is Subsumed into OSAS

Since its original description in 1993, the American Academy of Sleep Medicine (AASM) has not recognized UARS as a separate disease from OSAS. Although, considered a preclinical stage of OSAS by the AASM Task Force in 1999, the UARS was only included into the group of OSAS in 2005.

The diagnosis of UARS is not recognized as a discrete nosological entity by the International Classification of Sleep Disorders (ICSD-3) published in 2014. This task force, composed of members of American Academy of Sleep Medicine (AASM), the World Sleep Federation (WSF), and Diagnostic and Statistical Manual of Mental Disorders (DSM-5), has agreed to subsume the so-called UARS into obstructive sleep apnea (ICD-9-CM code 327.23), as the "pathophysiology has not shown to differ from that of the obstructive sleep apnea."[18]

6) No Distinctive Cardiovascular Outcomes in UARS

Currently, there is lack of evidence to support an association or a cause-effect relationship between UARS and a cardiovascular disease or metabolic derangement. Conflicting data exist regarding blood pressure in patient with UARS. In a 4-year follow-up study, Guilleminault and colleagues have shown that untreated patients with UARS had no significant change in blood pressure or cardiovascular or neurological status.[19] Like mild OSAS, UARS have the lowest systolic and diastolic blood

pressure values, as well as type 2 diabetes when compared to moderate-severe OSA.[8] Until large epidemiological and/or interventional studies are available, the impact of UARS on cardiovascular outcomes remains unknown.

7) Treatment: No Difference in Treatment Recommendations for AURS and OSAS

Therapeutic data about UARS treatment are few and plagued by inadequate methodology and small patient samples, without precise sample estimation. Only small case series and observational studies support the beneficial impact of CPAP and/or mandibular advancement devices in UARS.[1,20] These therapeutic interventions are not different from those recommended for mild OSAS, also sharing barriers such as poor compliance and insurance refusal to cover treatment.

CONCLUSION

Does upper airway resistance syndrome exist as a discrete disease state?

The short answer is no. The independent existence of UARS from OSAS cannot be supported based on current literature. Therefore, the academic sleep community has not accepted UARS as a discrete nosological entity, separate from OSAS. Instead, it is considered a mild expression of OSAS in the continuum of increasing upper airway resistance associated with neurocognitive changes. The use of a new term (UARS) to describe what is already known (OSAS) will only introduce confusion of both patients and nonspecialists alike. I am confident that after reviewing the failure of UARS to reach the status of a distinct medical condition from OSAS, those who still call it *UARS*, not *OSAS*, should remember the old adage: "if it looks like a duck and swims like a duck, and quacks like a duck, then it probably is a duck."

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REFERENCES

1. Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness. The upper airway resistance syndrome. *Chest* 1993;104:781–7.
2. Tamisier R, Pepin JL, Wuyam B, Smith R, Argod J, Levy P. Characterization of pharyngeal resistance during sleep in a spectrum of sleep-disordered breathing. *J Appl Physiol* 2000;89:120–30.
3. Bradley TD, Martinez D, Rutherford R, et al. Physiological determinants of nocturnal arterial oxygenation in patients with obstructive sleep apnea. *J Appl Physiol* 1985;59:1364–8.
4. Punjabi NM, O'Hearn D J, Neubauer DN, et al. Modeling hypersomnolence in sleep-disordered breathing. A novel approach using survival analysis. *Am J Respir Crit Care Med* 1999;159:1703–9.
5. Engleman HM, Kingshott RN, Wraith PK, Mackay TW, Deary IJ, Douglas NJ. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 1999;159:461–7.
6. Gold AR, Dipalo F, Gold MS, O'Hearn D. The symptoms and signs of upper airway resistance syndrome: a link to the functional somatic syndromes. *Chest* 2003;123:87–95.
7. Gold AR, Gold MS, Harris KW, Espeleta VJ, Amin MM, Broderick JE. Hypersomnolence, insomnia and the pathophysiology of upper airway resistance syndrome. *Sleep Med* 2008;9:675–83.
8. Stoohs RA, Knaack L, Blum HC, Janicki J, Hohenhorst W. Differences in clinical features of upper airway resistance syndrome, primary snoring, and obstructive sleep apnea/hypopnea syndrome. *Sleep Med* 2008;9:121–8.
9. Guilleminault C, Black JE, Palombini L, Ohayon M. A clinical investigation of obstructive sleep apnea syndrome (OSAS) and upper airway resistance syndrome (UARS) patients. *Sleep Med* 2000;1:51–6.
10. Ruehland WR, Rochford PD, O'Donoghue FJ, Pierce RJ, Singh P, Thornton AT. The new AASM criteria for scoring hypopneas: impact on the apnea hypopnea index. *Sleep* 2009;32:150–7.
11. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2012;8:597–619.
12. Bonnet MH, Arand DL. EEG arousal norms by age. *J Clin Sleep Med* 2007;3:271–4.
13. Broderick JE, Gold MS, Amin MM, Gold AR. The association of somatic arousal with the symptoms of upper airway resistance syndrome. *Sleep Med* 2014;15:436–43.
14. Terzano MG, Parrino L, Boselli M, Spaggiari MC, Di Giovanni G. Polysomnographic analysis of arousal responses in obstructive sleep apnea syndrome by means of the cyclic alternating pattern. *J Clin Neurophysiol* 1996;13:145–55.
15. Gold AR, Marcus CL, Dipalo F, Gold MS. Upper airway collapsibility during sleep in upper airway resistance syndrome. *Chest* 2002;121:1531–40.
16. Pavlova MK, Duffy JF, Shea SA. Polysomnographic respiratory abnormalities in asymptomatic individuals. *Sleep* 2008;31:241–8.
17. Jonczak L, Plywaczewski R, Sliwinski P, Bednarek M, Gorecka D, Zielinski J. Evolution of upper airway resistance syndrome. *J Sleep Res* 2009;18:337–41.
18. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. *Anesthesiology* 2014;120:268–86.
19. Guilleminault C, Kirisoglu C, Poyares D, et al. Upper airway resistance syndrome: a long-term outcome study. *J Psychiatr Res* 2006;40:273–9.
20. Yoshida K. Oral device therapy for the upper airway resistance syndrome patient. *J Prosthet Dent* 2002;87:427–30.

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CASE REPORTS

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Remote Controlled Mandibular Positional Device to Determine Oral Appliance Efficacy and Therapeutic Protrusive Position

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Oral appliance therapy (OAT) for obstructive sleep apnea (OSA) has risen with the recent publication research confirming the positive effect of OAT on blood pressure and cardiovascular mortality. The problems that dentists and physicians face are in determining who will be responsive and what target protrusive position is most efficacious for the patient. This is a case report using a remote controlled mandibular positioning device to determine efficacy and the therapeutic or target protrusive position for the patient's oral appliance.

Keywords: remote controlled mandibular repositioner

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INTRODUCTION

In order to determine the final treated position, most of the early research studies on oral appliance therapy (OAT) for obstructive sleep apnea (OSA) relied on self-titration to a setting where patients reported a relief of symptoms. Patients often make comments at follow-up visits such as "My wife says I am not snoring, and I feel great, so I am sure my appliance is working." According to early studies, this kind of patient feedback would have directly corresponded to the determination of the patient's final treated position. However, Almeida reported that 17% to 35% of these patients require further calibration beyond the point where subjective symptoms are resolved in order to reach objective efficacy.[1]

The dentist is always faced with the dilemma of where to start the protrusive position of the oral appliance and how far to calibrate the device to reach an objective efficacious position. Fleury[2] used subjective observations and oximetry to determine this position, which often yielded positive results. Unfortunately, despite those positive results, Fleury's method does not always result in an OAT titration polysomnogram (PSG) that demonstrates resolution of OSA. This may be due to night-to-night variability and/or the inability of oximetry to accurately record total sleep time, sleep stages, or positional data.

Calibration of the appliance during a single night manual titration PSG, as used by Almeida, has proven to significantly improve OAT outcomes. Despite the improvement, there are limitations to these studies. In clinical practice, single-night manual titration PSG is inconsistent and impractical. It is inconsistent due to the lack of a single standardized protocol for the calibration of an oral appliance. In an urban setting, there are a multitude of sleep laboratories with varying degrees of experience calibrating appliances. The lack of standardization creates inconsistent terminology, protocols that change with the type of appliance, and the preference of each dentist referring into the lab. It is impractical because it disregards the significance of frequent disruptions to the patient's sleep architecture during each calibration. This lack of standardization and disruption of the patient's sleep creates uncertainty in the reliability and practicality of the study itself.

REPORT OF CASE

This case used a remote controlled mandibular positioning device (MATRx)[3] during PSG, which differed from previous calibration methods in that the patient was calibrated prior to the fabrication of a custom oral appliance. This enabled the sleep physician to determine whether the patient was responsive to oral appliance therapy and to then identify the target protrusive position that was most efficacious. The patient was a 30-year-old man who had a BMI of 37.9. His medical history was unremarkable except for a diagnosis of GERD. He had been diagnosed with moderate OSA: AHI (apnea hypopnea index) = 22.1, REM AHI = 32.2, O_2 nadir = 82%. He had trialed CPAP at a pressure of 14 cm but was noncompliant due to mask leakage and noise disruptions to his pregnant wife. Previous studies by Sutherland[4] and Tsuiki[5] would identify this patient as a potential failure with OAT due to the high CPAP pressure. However, due to his noncompliance with CPAP, the patient was referred to me by his sleep physician for a dental evaluation and fitting of the MATRx calibration trays for the study.

The patient had good periodontal health, a Class III occlusion on the right side, Class I on the left, and a bilateral cross bite. His tongue was Level III, tonsils Level III, and Mallampati Level II with an edematous and wide uvula. His soft palate was elongated with a lack of tone, his hard palate was vaulted, and his oropharynx was crowded. After the evaluation, stock MATRx trays were fabricated using bite registration material for the impressions. His maximum protrusive range was 9 mm. Using the MATRx mm ruler (10–20 mm), his range was determined to be 10 mm. The sleep lab technician was instructed to begin calibration at 60% of his maximum protrusive range.

During the PSG, the appliance was advanced in 0.6 mm (0.2 mm × 3) increments.[3] The goal was to stabilize the respiratory events to ≤ 1 apnea or hypopnea during a 5-minute window of supine REM sleep. The patient's final position was 19.7 mm

Table 1—Calibration polysomnogram details.

	Sleep Distribution			Apneas		Hypopneas		RERA	
Position (mm)	Duration (min)	% REM	% SWS	# CA	# OA	Count	AHI	Count	RDI
Baseline 12.3	34.0	0.0	0.0	0	0	0	0.0	7	13.8
13.2	11.7	0.0	0.0	0	0	0	0.0	0	0.0
14.0	11.9	0.0	0.0	0	0	0	0.0	1	5.0
14.6	5.5	0.0	18.2	0	0	0	0.0	1	10.9
15.3	2.1	0.0	100.0	0	0	0	0.0	0	0.0
15.9	11.8	0.0	100.0	0	0	0	0.0	0	0.0
16.5	6.6	0.0	100.0	0	0	0	0.0	0	0.0
16.9	7.9	0.0	100.0	0	0	0	0.0	0	0.0
17.6	3.8	0.0	100.0	0	0	0	0.0	0	0.0
18.2	46.7	0.0	36.0	0	0	0	0.0	1	1.4
18.9	154.6	6.5	32.7	0	0	1	0.4	7	3.1
19.7	81.3	23.4	0.0	1	0	0	0.8	7	6.2
19.0	5.7	0.0	0.0	0	0	0	0.0	0	0.0
18.4	8.7	0.0	0.0	0	0	0	0.0	0	0.0
17.5	10.3	0.0	0.0	0	0	0	0.0	0	0.0
16.9	33.2	25.6	0.0	0	0	1	1.9	2	5.6

Position, position of mandible relative to the MATRx measurement gauge; REM, rapid eye movement sleep; SWS, slow wave sleep; CA, central apnea; OA, obstructive apnea; RERA, respiratory effort related arousal; AHI, apnea/hypopnea index; RDI, respiratory disturbance index.

(MATRx scale) or 1 mm from his maximum protrusive range (8 mm of protrusion).

The PSG results showed resolution of OSA: AHI = 0, REM AHI = 0, RDI = 6.2, O_2 nadir = 91 (**Table 1**).

The patient had a TAP 3 TL oral appliance delivered at 5 mm from his maximum protrusive position. Following a one week acclimation period, the patient was instructed to begin advancing the appliance 1–2 turns (0.25–0.5 mm) every other night for a total of 20 turns. This would advance the appliance to his therapeutic treatment position of 1 mm from maximum protrusion. At the one month follow-up, he reported feeling rested (Epworth = 0) and noted that his wife was happy as his snoring was gone.

Three months after delivery, the patient had an ARES home sleep test for one night at the treated position. His results were as follows: AHI = 2, RDI = 12, O_2 nadir = 89. Due to his increased RDI and slight return of light snoring, the sleep physician suggested further titration. After 2 additional turns (0.5 mm), the patient's snoring was controlled.

He was seen 6 months later and was well rested with an Epworth of 0, and his BMI had dropped to 34.70. He was now 2.5 mm from his maximum protrusive as he had had 2 mm of horizontal change forward in his overjet. He was therefore encouraged to use his morning bite repositioner on a more regular basis.

CONCLUSION

The use of a remote controlled mandibular positioner (MATRx) provided a standardized, reliable, and practical solution for predicting the efficacy and target protrusion in single night PSG. It also allowed for remote calibration through the specified range of motion without significantly disturbing the patient's sleep architecture. The patient's high BMI, crowded oropharynx, large tongue, and severe AHI in REM may have dissuaded many physicians from prescribing OAT. However, the MATRx provided objective efficacy data at specific protrusive positions allowing the sleep physician to confidently prescribe OAT at a predetermined target protrusion. In addition, it provided the objective data needed to fabricate the custom appliance to the ordered target protrusion.

REFERENCES

1. Almeida FR, Parker JA, Hodges JS, Lowe AA, Ferguson KA. Effect of a titration polysomnogram on treatment success with a mandibular repositioning appliance. *J Clin Sleep Med* 2009;5:198–204.
2. Fleury B, Rakotonanahary D, Petelle B, et al. Mandibular advancement titration for obstructive sleep apnea: optimization of the procedure by combining clinical and oximetric parameters. *Chest* 2004;125:1761–7.
3. Remmers J, Charkhandeh S, Grosse J, et al. Remotely controlled mandibular protrusion during sleep predicts therapeutic success with oral appliances in patients with obstructive sleep apnea. *Sleep* 2013;36:1517–25.
4. Sutherland K, Phillips CL, Davies A, et al. CPAP pressure for prediction of oral appliance treatment response in obstructive sleep apnea. *J Clin Sleep Med* 2014;10:943–9.
5. Tsuiki S, Kobayashi M, Namba K, et al. Optimal positive airway pressure predicts oral appliance response to sleep apnoea. *Eur Respir J* 2010;35:1098–105.

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CASE REPORTS

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Lip Muscle Training Improves Halitosis and Obstructive Sleep Apnea Syndrome: A Case Report

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Halitosis is associated with mouth breathing, dry mouth, snoring, and obstructive sleep apnea syndrome (OSAS). A 40-year-old woman with moderate halitosis showed objective improvement following periodontal treatment for 1 year, but her unpleasant subjective symptoms remained. Lip muscle training using the Patakara trainer (PTR) was implemented to both increase salivary flow and treat her OSAS. After PTR training an increase in lip closure force and a decreased respiratory index (8.2 to 3.2 events/h) were observed. The patient reported resolution of mouth breathing, dry mouth, snoring, and foul odor. PTR training was associated with an improvement in halitosis and respiratory events.

Keywords: lip muscle training, halitosis, obstructive sleep apnea syndrome, dry mouth

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INTRODUCTION

Halitosis results from malodorous substances produced by anaerobic bacteria.[1] Standard treatment includes dental cleaning, tooth brushing, mechanical debridement of the tongue, and rinsing with antimicrobial agents.

Salivary flow may be central to the development of halitosis, since saliva has an antimicrobial action, and its slightly acidic pH (6.5) suppresses the growth of Gram-negative and anaerobic bacteria that produce malodorous substances.[2] Hence, dry mouth, a side effect of mouth breathing, can lead to halitosis due to reduced salivary flow.[1] Mouth breathing also increases upper airway collapsibility[3] and the occurrence[4] and severity of obstructive sleep apnea syndrome (OSAS) through a narrowed pharyngeal airway.[5]

A patient with moderate halitosis successfully treated with lip muscle training is presented.

REPORT OF CASE

A 40-year-old woman (BMI 22.1 kg/m^2) with no smoking history had a chief complaint of halitosis. She had papillary thyroid cancer and uterine fibroids (both in remission), childhood asthma and allergic rhinitis, and previously took levothyroxine sodium for hypothyroidism. She had no gastroesophageal tract problems.

Malodorous substances (H_2S, CH_3SH, and $(CH_3)_2S$) were analyzed using the Oral Chroma (Abimedical Corp., Osaka, Japan).[6] All tests were performed at least 2 hours after a meal, at the same time (10:00 am).

The respiratory disturbance index (RDI) and peripheral oxygen saturation (SpO_2) were collected for about 6 hours with the SAS-2100 (Teijin Home Healthcare Limited, Tokyo, Japan) during sleep. Data were downloaded and analyzed using QP-021W software, Ver.01-10 (Nihon Kohden, Tokyo, Japan).

Lip closure force (LCF) was measured with a lip device (BHC-V01; Patakara, Tokyo, Japan). The maximum and minimum values obtained in a 10-s period were recorded. LCFmax and LCFmin measurements were repeated three times, and mean values were calculated.

The Lip Muscle Trainer M-Patakara (Patakara Co., Ltd.) for LCF training, made from flexible, resilient plastic, and rubber, is used to increase the strength of the oral muscles. Training (5 min, 4 times/day) was performed for 2 months.[5]

In May 2012, the patient had no caries or missing teeth and no temporomandibular joint (TMJ) abnormalities. Tongue coating area was ≤ 1/3 on the dorsal tongue surface, with no soft tissue problems. She had periodontal pockets ≥ 4 mm in the molar region, and bleeding on probing around most teeth, with no tooth mobility (**Figure 1A**). H_2S was 856 ppb (recognition threshold 112 ppb), CH_3SH was 0 ppb, and $(CH_3)_2S$ was 14 ppb (recognition threshold 8 ppb, **Table 1**). The patient then received periodontal treatment for halitosis.

In July 2013, the patient showed improvement with periodontal pockets ≤ 3 mm around all teeth (**Figure 1B**). A second halitosis test showed improvement in $(CH_3)_2S$ from 14 to 5 ppb, and H_2S decreased to 206 ppb. (**Table 1**) However, halitosis remained a concern. Further questioning revealed she suffered from mouth dryness upon awakening and snoring. Her bed partner verified that she snored with her mouth open during sleep. A sleep test confirmed an RDI of 8.2 events/h and minimum SpO_2 of 91%, consistent with mild OSAS. A mandibular advancement device (MAD) was then fabricated as a routine treatment for OSAS. A Patakara trainer (PTR) was given to simultaneously treat the coexisting halitosis and OSAS. LCF measurements were taken. The patient discontinued the MAD after several days due to TMJ soreness, and lip muscle training alone was continued.

Two months after starting PTR (November 2013), both maximum and minimum LCF improved, RDI dropped to

Figure 1

A Periodontal condition at the first examination

MOB		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BOP			• •	• •	•	• •	• •	•				• •			•••	•••
				••	• •	•••	•••	••	•••	•••	• •	•	•	•		
Depth		222	333	323	232	322	222	222	222	222	212	212	222	223	233	223
		444	434	433	313	323	323	322	222	333	322	322	333	333	233	444
	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
Depth	645	436	543	333	323	322	212	212	212	222	222	323	333	433	334	334
	322	235	434	324	223	233	223	233	233	232	233	332	223	323	333	334
BOP	•	• •	••			•••	•		•••	•••	•	•	• •	•		
		•	••	•	•	•				•	•	•		•		••
MOB	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

B Periodontal condition at 1 year after treatment

MOB		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BOP																
Depth		322	223	222	223	222	223	223	222	222	222	223	323	323	222	222
		323	222	232	323	222	222	222	222	222	222	323	223	323	323	223
	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8
Depth	323	323	223	323	323	323	223	222	222	222	222	222	323	223	223	323
	322	333	223	222	323	223	222	222	222	222	223	323	222	323	323	223
BOP																
			•	•	•						•	•	•			
MOB	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Left panel **(A)** Periodontal condition at the first examination. Right panel **(B)** Periodontal condition at 1 year after treatment. Depth, periodontal pocket depth; BOP, bleeding on probing; MOB, tooth mobility.

Table 1—Changes of VSCs production.

	1st Test	2nd Test after periodontal treatment	3rd Test after lip muscle training
H_2S	856	206	39
CH_3SH	0	2	0
$(CH_3)_2S$	14	5	0

VSCs, volatile sulfur compounds; H_2S, hydrogen sulfide; CH_3SH, methyl mercaptan; $(CH_3)_2S$, dimethyl sulfide.

3.2 events/h, and the minimum SpO_2 increased to 97%. On the third halitosis test, H_2S was 39 ppb, below the recognition threshold (112 ppb, **Table 1**). In June 2014, the patient had continued PTR and showed favorable findings, with no snoring or malodor.

DISCUSSION

The lack of effectiveness of the periodontal approach to halitosis treatment in this case suggested other underlying contributory sources, and further questioning led to the diagnosis of OSAS. After PTR the H_2S level was below the recognition threshold, and halitosis was no longer detected. Additionally, RDI dropped and SpO_2 improved. These improvements paralleled an increase in LCF, suggesting that PTR strengthened the muscles around the lips and may have caused the decreased RDI and absence of snoring. Furthermore, following PTR training, there was a change from mouth to nose breathing with no snoring during sleep. She no longer experienced dry mouth, perhaps due to increased salivary flow associated with lip muscle training.

In conclusion, lip muscle training was associated with elimination of halitosis and improvement in the RDI and SpO_2, likely through increased LCF. A randomized, controlled trial is needed to test the efficacy of lip muscle training in patients with halitosis, OSAS, or coexisting halitosis and OSAS.

REFERENCES

1. Motta LJ, Bachiega JC, Guedes CC, Laranja LT, Bussadori SK. Association between halitosis and mouth breathing in children. *Clinics* 2011;66:939–42.
2. Doran A, Kneist S, Verran J. Ecological control: in vitro inhibition of anaerobic bacteria by oral streptococci. *Microb Ecol Health Dis* 2004;16:23–7.
3. Enoz M. Effects of nasal pathologies on obstructive sleep apnea. *Acta Medica (Hradec Kralove)* 2007;50:167–70.
4. Lee SH, Choi JH, Shin C, Lee HM, Kwon SY, Lee SH. How does open-mouth breathing influence upper airway anatomy? *Laryngoscope* 2007;117:1102–6.
5. Bachour A, Maasilta P. Mouth breathing compromises adherence to nasal continuous positive airway pressure therapy. *Chest* 2004;126:1248–54.
6. Oral Chroma instruction manual: measurement procedure and saving measurement data. Osaka Abimedical Corp, 2007.

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CASE REPORTS

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RPE and Orthodontic Protraction Facemask as an Alternative Therapy for Severe Obstructive Sleep Apnea Associated with Maxillary Hypoplasia

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Rapid palatal expander (RPE) and facemask therapy has been used as a treatment for maxillary hypoplasia. When the treatment is performed with an alternate constriction and expansion protocol, a greater degree of maxillary advancement could be achieved. This report demonstrates the treatment as an effective nonsurgical alternative for resolving a severe OSA associated maxillary hypoplasia in a preadolescent patient.

Keywords: protraction facemask, RPE, OSA, maxillary hypoplasia, orthodontic

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INTRODUCTION

Patients with craniofacial abnormalities have a higher prevalence of obstructive sleep apnea (OSA).[1] The treatment often focuses on improving an underlying skeletal pattern. A combined rapid palatal expander (RPE) and protraction facemask therapy has been traditionally advocated to treat maxillary hypoplasia.[2] The treatment is the most effective when performed in preadolescence.[3] An alternate expansion and constriction protocol for RPE/facemask allowed a greater degree of maxillary advancement compared to a conventional technique.[4]

The expansion of the maxilla with RPE has been shown to resolve OSA in pediatric patients by simultaneously expanding nasal cavity to increase airflow.[5] The use of protraction facemask to advance a maxilla was demonstrated to increase a sagittal nasopharyngeal airway.[6] However, a combined RPE/facemask therapy has never been reported to improve OSA symptoms or reduce apnea-hypopnea index (AHI). This case report demonstrates that RPE/protraction facemask therapy with alternate constriction/expansion protocol is an effective treatment for severe OSA associated with maxillary hypoplasia in a preadolescent patient.

REPORT OF A CASE

An 8-year-old female Caucasian patient presented with severe OSA with AHI of 51 episodes/hour. She was prescribed CPAP but could not tolerate it. As a result, she did not use CPAP regularly and continued to have clinical symptoms of OSA (witnessed loud snoring, apneic episodes, fatigue, and daytime sleepiness). She was also diagnosed with hypothyroidism, GERD, controlled epilepsy, and seasonal allergy. She has a history of adenoidectomy and tonsillectomy.

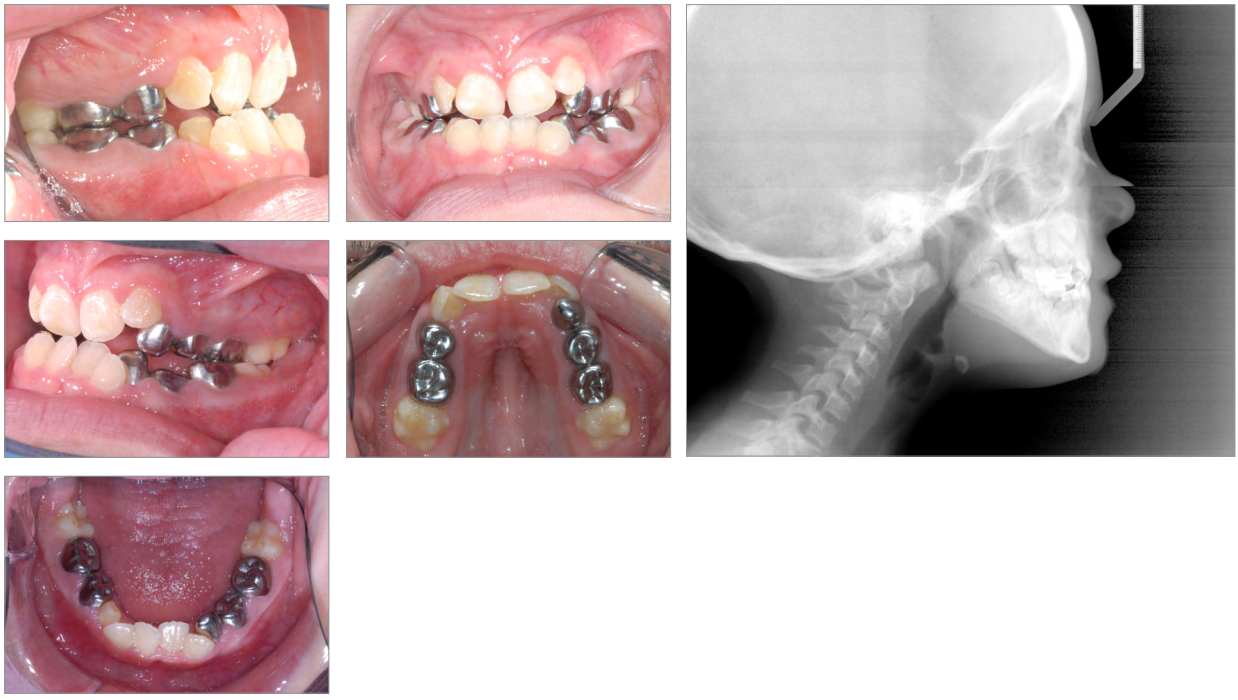
The patient presented with class III malocclusion with anterior crossbite and severe anterior crowding in mixed dentition. The palate is high vaulted and narrow (**Figure 1**). A cephalometric analysis indicated that both maxilla and mandible were hypoplastic (SNA = 74°, SNB = 74°) with Class III skeletal pattern (ANB = 0°). The lateral cephalogram (**Figure 1**) also showed a constricted sagittal nasopharyngeal space (u-mpaw = 2 mm).

Two treatment options were presented. The first option was to perform a maxillary advancement with distraction osteogenesis. The advancement would significantly increase a nasopharyngeal space and allow for an increased airflow during sleep. This treatment option also requires pre- and post-surgical orthodontic treatment. The second option was a combined use of RPE and protraction facemask with alternate expansion and constriction protocol. In this protocol, the maxilla is expanded, and then constricted, and re-expanded and re-constricted for several cycles before a facemask is applied to start maxillary protraction. This protocol allows for a greater degree of maxillary advancement.[4] No surgical procedure is involved in this protocol. The second option was chosen, as it was a less invasive treatment.

After bonding an RPE to upper posterior teeth, parents were instructed to activate the expansion screw 1 turn/day for 7 days. After the initial expansion, the parents were instructed to constrict the palate (1 turn/day) to the original width. The alternate expansion and constriction were repeated for 5 cycles. Following the last cycle, the parents were asked to activate the RPE (1 turn/day) only to expand the palate for 4 weeks. An orthodontic facemask was then delivered after the expansion was completed. The patient was instructed to wear it for 12 h/day. The patient used RPE and facemask for a period 7 months.

A sleep study performed 15 weeks after starting a facemask therapy showed a significant reduction of AHI to 7 episodes/h with an average oxygen saturation of 97%. No paradoxical breathing was observed during the sleep study. At 17 weeks, the overjet was recorded at 9 millimeters. The patient was then instructed to wear the facemask only a few hours/day to

Figure 1—Pretreatment intraoral pictures and lateral cephalogram.



maintain the maxillary position. The RPE and facemask were discontinued after 7 months, as the patient reported a significant improvement of OSA symptoms. A retention device was not considered necessary, as the maxilla was slightly overexpanded. Additionally, RPE was left in place with an adequate amount of time for the maxilla to become stabilized. The post-treatment lateral cephalogram showed a significant increase in both maxillary prominence and nasopharyngeal airway space (SNA = 79°, SNB = 74°, overjet = 8 mm, u-mpaw = 5 mm). The patient underwent another sleep study a month after discontinuation of RPE/facemask. The result showed the AHI was further reduced to 4 episodes/h with average oxygen saturation of 96%.

DISCUSSION

A combined orthopedic effects of maxillary expansion and advancement significantly increased nasopharyngeal space. The increased space subsequently led to AHI reduction and improvement of OSA symptoms for this patient. If OSA symptoms recur, the patient can undergo more invasive treatment options. This is the first case report demonstrating a combined RPE and facemask therapy as an effective alternative for treating a severe OSA associated maxillary hypoplasia.

REFERENCES

1. Luna-Paredes C, Antón-Pacheco JL, García Hernández G, Martínez Gimeno A, Romance García AI, García Recuero II. Screening for symptoms of obstructive sleep apnea in children with severe craniofacial anomalies: assessment in a multidisciplinary unit. *Int J Pediatr Otorhinolaryngol* 2012;76:1767–70.
2. Kama JD, Ozer T, Baran S. Orthodontic and orthopaedic changes associated with treatment in subjects with Class III malocclusions. *Eur J Orthod* 2006;28:496–502.
3. Suda N, Ishii-Suzuki M, Hirose K, Hiyama S, Suzuki S, Kuroda T. Effective treatment plan for maxillary protraction: is the bone age useful to determine the treatment plan? *Am J Orthod Dentofacial Orthop* 2000;118:55–62.
4. Liou EJ. Effective maxillary orthopedic protraction for growing Class III patients: a clinical application simulates distraction osteogenesis. *Prog Orthod*. 2005;6:154–71.
5. Villa MP, Malagola C, Pagani J, Montesano M, Rizzoli A, Guilleminault C, Ronchetti R. Rapid maxillary expansion in children with obstructive sleep apnea syndrome: 12-month follow-up. *Sleep Med* 2007;8:128–34.
6. Sayinsu K, Isik F, Arun T. Sagittal airway dimensions following maxillary protraction: a pilot study. *Eur J Orthod* 2006;28:184–9.

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NEWS AND UPDATES

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AADSM 2016 Educational Calendar of Events

AADSM Staff

AADSM National Office, Darien, IL

February 20–21
Essentials of Dental Sleep Medicine Course
Charleston, SC

February 20–21
Board Review Course
Charleston, SC

March 18
Practical Demonstration Course
Darien, IL – AADSM National Office

June 9–11
25th Anniversary Meeting
Denver, CO