Commentary

Therapeutic approaches of obstructive sleep apnea in China

Wen-Yang Li, Wei Wang
Institute of Respiratory Disease, The First Hospital of China Medical University, Shenyang, China

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of complete and partial obstructions of upper airway during sleep. In general population, OSA is highly prevalent and affects approximately 34% of men and 17% of women in aged 30-70 years.[1] Individuals with OSA experience a variety of symptoms and conditions such as fatigue, excessive daytime sleepiness, impaired cognitive performance, headache, and an increased incidence of motor vehicle accidents. Many studies have shown a link between OSA and cardiovascular disease, chronic heart failure, arrythmia, stroke, and impaired glucose tolerance.[2] Therefore, accurate diagnosis and treatment of OSA is strongly recommended so as to improve quality of life and reduce the associated morbidity and mortality.

Many factors can give rise to OSA, such as skeletal malformations, soft tissue crowding, and respiratory instability. Sometimes these factors are interacting. Thus, from a clinical point of view, the patient-directed therapeutic approaches should be individually scheduled based on personalized situation. The current treatment of OSA in China focuses on the alleviation of symptoms and upper airway obstruction during sleep. Up to now, the effective therapeutic approaches include positive airway pressure ventilation, mandibular advancement oral appliance, sleep position adjustment, weight loss, and surgical treatment (including otorhinolaryngologic and oral & maxillofacial surgery).[3]

HOW TO GUARANTEE THE EFFECTIVENESS OF CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) AMONG OSA PATIENTS?

CPAP is currently the primary treatment for symptomatic, moderate to severe cases of OSA. It prevents upper airway collapse, improves sleep architecture and alleviates daytime symptoms.[3] Many researches indicate that effective treatment with CPAP can reverse the negative cardiac and neurocognitive consequences of untreated disease.[4] Although highly effective in abolishing sleep disordered breathing events and minimizing symptoms of OSA, CPAP therapy is not always well tolerated by all patients. Long-term adherence to CPAP is a key point issue. One study in Hong Kong documented a high prevalence of OSA among the community elders. There was significant improvement of subjective sleepiness and cognitive function among those on CPAP treatment. However, home CPAP acceptance was low. Up to 78.7% of the subjects with OSA refused CPAP treatment. Many of them did not clearly understand the importance of CPAP. Of the 30 subjects who accepted CPAP therapy, only 44% of them adhered to the treatment with more than 4 hours per night.[5] Therefore, the outcome of CPAP therapy could be compromised due to poor adherence. Barriers to the long-term adherence of CPAP therapy has been listed as follows: mask discomfort, nasal congestion, local irritation, claustrophobia, and so on.[6] In the Sleep Apnea cardiovascular Endpoints

Address for Correspondence:
Dr. Wei Wang, Institute of Respiratory Disease, The First Hospital of China Medical University, 155 Nanjing Northern Street, Heping District, Shenyang110001, Liaoning Province, China
E-mail: wwbycmu@126.com

Access this article online

Website: www.intern-med.com

DOI: 10.2478/jtim-2018-0004

Quick Response Code:

(SAVE) study, the factors to predict CPAP adherence were the average time of nightly CPAP usage and side effects during the first month of therapy. This raised the possibility that early intensive interventions could improve long-term CPAP compliance.[7] It is regretful that there are few randomized and controlled clinical trials regarding the effectiveness of CPAP among Chinese OSA patients.

A laboratory CPAP titration is performed to determine the proper pressure to eliminate apnea, but this procedure is time consuming. Auto-CPAP could solve this issue, but it should be avoided in some patients, such as those with substantial lung disease, congestive heart failure, or obesity hypoventilation syndrome. Therefore, a CPAP prediction formula is needed in clinical practice, especially in these specific populations. Regarding the prediction of the optimal CPAP pressure for Asian OSA patients, Lee *et al.* established an equation based on data from Asian patients. This new formula was better to predict optimal CPAP level in Asian subjects than the previously established one among Caucasians named Hoffstein formula. The predictive equation was shown as follows: predicted pressure (cm H_2O) = 6.656 + 0.156 × (body mass index [kg/m^2]) – 0.071 × (minimal SpO_2 [%]) + 0.041 × (respiratory disturbance index) + 0.094 × (score of Epworth Sleepiness).[8] Noteworthy, this formula provided an optimal estimation of CPAP pressure for a low proportion of subjects (38%), thus the predictive equation is not a sufficient substitute for the manual CPAP titration. But the use of the CPAP prediction formula may improve manual CPAP titration success by customize the starting pressure of the titration, especially during split-night studies.

HOW TO OPTIMIZE THE THERAPEUTIC EFFECT OF MANDIBULAR ADVANCEMENT ORAL APPLIANCES (OA)?

For those who fail to CPAP therapy, mandibular advancement OA might be considered as an acceptable alternative since it is less intrusive and disruptive to personal life. It is worn intraorally at night to hold the lower mandible in anterior and inferior position during sleep and effectively open the passive pharynx in a dose-dependent manner. Mandibular advancement with OA can enlarge the upper airway space, especially in the lateral dimension of the velopharyngeal region.[9] It is effective not only in reducing snoring and obstructive breathing events but also in improving sleepiness and life quality.[10] Besides, overall long-term efficacy of OA treatment is fairly good. Current practice parameters of the American Academy of Sleep Medicine (AASM) indicate OA as a first line therapy in patients with mild-to-moderate OSA and in severe OSA patients who fail to CPAP therapy.[11] Of note, craniofacial factors were deemed as characteristic of Asian populations, which is also well recognized as determining factors of OSA. For the same level of OSA severity, compared to Caucasians, Asians show a greater restriction in craniofacial skeletal measurements associated with OSA, such as restricted maxillary and mandibular retro-positioning.[12,13] To take this important point into account, it seems that Chinese patients with OSA could be more prone to benefit from the OA treatment than Caucasians. Unfortunately, currently there is no available clinical study to confirm such hypothesis.

For mandibular advancement OA, customized devices fabricated from dental casts of a patient's dentition and bite registrations by a dentist are highly time and money consuming.[14] Furthermore, there is no reliable predictor of OA success. The patients have to cover the cost of the appliance without guaranty to normalize breathing during night. Therefore, there is a strong need to have reliable tools to prospectively identify favorable candidates for OA therapy and to identify precise protrusion distance for OA. Recently, collaborated with Laval Hospital in Canada, we used remotely controlled mandibular positioner (RCMP) device to accurately identify patients who are likely to be successful OA candidates. With a temporary dental appliance connected to a RCMP device, the mandible could be progressively, mildly and precisely protruded in only anterior-posterior dimension without disturbing sleep. With PSG monitored simultaneously, it is possible for us to identify the OA responders and the best protrusion level for the OA to eliminate obstructive apnea and hypopnea, particularly in REM sleep while supine. Remmers *et al.* recently tested this device as a prediction tool for OA treatment response. The positive and negative predictive values were 94% and 83%, respectively.[15] Moreover, identification of effective distance from the one-night mandibular titration, may also avoid long duration and multiple visits to the dentist for adjusting OA. Thus, the introduction of this novel approach into China could open a new era of OA treatment among Chinese OSA patients. From our clinical experience, those with younger age, less BMI, wider retroglossal spaces and lower Mallampati score were more prone to be responders to OA treatment and would benefit more from this approach. We are currently performing an ongoing pilot study to compare the differences in predicted therapeutic outcome and optimal protrusion position of OA between Canadian and Chinese OSA patients. Our available data revealed that although the habitual occlusive position of lower mandible was lower in Chinese patients, the predicted success rate of OA treatment according to in-lab RCMP titration does not differ significantly between the Chinese and Canadian OSA patients, with similar level of optimal mandibular advancement.

It's worth noting that the above device-based treatments are only efficacious when they are correctly used. Their long-term effect on cardiovascular complications was still unknown. Nevertheless, patients who fail the approaches of CPAP or OA may benefit from lifestyle changes such as weight loss.

HOW TO EVALUATE THE ROLE OF SURGERY IN OSA MANAGEMENT?

In 2013, American College of Physicians recommended that surgery was no longer the initial therapy for OSA patients.[16] However, some OSA patients have hypertrophic tonsils, macroglossia or hypertrophic lingual tonsils, redundant pharyngeal pillars, a crowded oropharynx, an elongated uvula, or a combination of these anatomic features. If CPAP or OA can not be applied to these patients, surgical intervention can help them to enlarge the volume of the upper airway and decrease its closing pressure.[17]

A list of common sleep surgery procedures used for the treatment of OSA is shown in Table 1. Identifying surgical candidates through overall assessment of the OSA patients (*i.e.* thorough medical history) should be strongly recommended prior to surgery. For patients who are considered appropriate surgical candidates, surgical plans should be patient-directed and based on individualized anatomic characteristics acquired by thorough physical/objective examinations. A large meta-analysis of mixed multilevel surgeries demonstrated a 66% success rate [50% reduction in apnea hypopnea index (AHI) and a postoperative AHI < 20].[18] The ERS task force also recommended multilevel surgery as a salvage procedure after CPAP failure and noted that it was most effective for those younger than 60 years of age who have no significant comorbidities and a BMI <30.[19] Recently, a modified MMA has been proved to be effective in treating patients with moderate-to-severe OSA without negatively affecting facial appearance or dental occlusion. To achieve a better outcome, surgical-orthodontic integration is warranted and the surgery-first approach can achieve early improvement.[20]

HOW ABOUT OTHER NOVEL ALTERNATIVE THERAPIES?

Alternative therapies are still being studied. Some of them were only applied for a small group of OSA patients. The results were inconsistent and inconclusive. The new method of rehabilitation (such as exercise training programs, hypoglossal nerve stimulation) for OSA patients is a hot topic. Some previous findings have shown beneficial effects of rehabilitation. For those who have abnormal function of upper airway dilator muscles, it seems to be an attractive alternative approach to ameliorate OSA.

Upper airway muscle training

The contraction of the upper airway dilator muscles plays a crucial role in maintaining upper airway patency and represents an important counteracting force against collapsing forces (tissue weight, upper airway shape and dimension, negative intraluminal pharyngeal pressure). There is some evidence that upper airway muscle dysfunction is a key factor of OSA pathophysiology.[21]. Some scholars observed that the people playing double reed musical instrument (bassoon) was associated with a lower risk of OSA.[22] Thus, they hypothesized that enhancing activity/efficacy of upper airway dilator muscles might represent a new, effective treatment approach for OSA. In this view, some investigators proposed upper airway muscle exercises as an alternative to conventional OSA therapy. Various upper airway exercises emerged, including oropharyngeal exercises,[23-25] instrumental playing therapy (didgeridoo),[26] singing exercises and electrical stimulation of upper airway musculature, and they did effectively reduce severity or symptoms of OSA and alleviate snoring in some OSA patients. One reported that one-week tongue task training improved disordered breathing in OSA patients (OSA severity decreased from moderate to mild in 50% of subjects, and a 48% decrease of obstructive breathing disturbance was observed during rapid eye movement stage), while maximum protruding force training remained unchanged.[27] Our research further confirmed that tongue task training is not oriented toward strength gain, but rather toward an enhancement in genioglossus cortical excitability and improvement in the coordination of the genioglossus protrusion task. There are still some issues deserves further investigation, such as who will benefit more from this approach and the design of the suitable upper airway muscle training?

Table 1: Surgical procedures commonly used for the treatment of OSA

Category	Procedure
Nasal	Septoplasty
	Resection of inferior tubinates
	Rhinoplasty/ nasal valve surgery
Oral/ palatal	Tonsillectomy
	Uvulopalatopharyngopasty
	Laser-assisted uvuloplasty
	Radiofrequency of soft palate
	Pillar implants
Hypopharyngeal	Radiofrequency ablation of the tongue
	Midline glossectomy
	Lingual tonsillectomy
	Tongue-base suspension
	Hyoid suspension
	Genioglossus advancement
Others	Maxillomandibular advancement
	Hypoglossal nerve stimulation
	Tracheostomy

Hypoglossal Nerve Stimulation

The hypoglossal nerve stimulator (HNS) was approved by the US Food and Drug Administration in 2014. It is an implantable stimulator that stimulates the hypoglossal nerve to the tongue during inhalation to keep the retroglossal airway open during sleep. The HNS is recommended for adults with moderate to severe sleep apnea (AHI > 20 but < 65 events/h) who do not have concentric collapse of the palate on drug-induced sleep endoscopy evaluation. In a separate multicenter, prospective, single-group cohort study, upper airway stimulation has been shown to result in significant improvements in both lifequality and AHI of OSA patients.[28].ne study performed by Dr. Zhang in Nanjing evaluated the efficiency of transcutaneous stimulation of genioglossus on remaining mild-moderate OSA after uvulopalatopharyngoplasty. They found that nocturnal AHI, microarousal index, ratio of duration of pulse oxygen desaturation significantly decreased.[29] Risks associated with this procedure include hypoglossal nerve injury, infection, device failure and dislodgement. Tan *et al.* also demonstrated that hyperbaric oxygen and pharyngeal neuromuscular electrical stimulation could effectively ameliorate the symptom of OSA.[30] It could be served as an alternative therapy for some OSA patients with upper airway muscles dysfunction.

CONCLUSIONS

In brief, the high prevalence of OSA in China and its attendant morbidity and mortality provide a strong impetus to improve recognition of this disorder, especially in primary health care centers. The application of noninvasive CPAP device or OA offers an opportunity to OSA patients. Upper airway muscle training and hypoglossal nerve stimulation are potential interventions for the management of OSA. These novel approaches can be an alternative to conventional treatment or beneficial for patients with poor compliance to CPAP therapy, OA, or ineffective results of surgical procedures as well. Nevertheless, there is a clear need for randomized and controlled clinical trials that introduce novel approaches (*i.e.* rehabilitation) as an element of therapy in OSA patients. Such trials need to focus not only on OSA indices but also general health outcomes.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 2013; 177:1006-14.
2. Young T, Palta M, Dempsey J, Peppard PE, Nieto FJ, Hla KM..Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep. WMJ 2009; 108:246-9.
3. Lévy P, Pépin JL, Tamisier R, Launois-Rollinat S. Outcomes of OSA and indications for different therapies. In: Sleep Apnoea (out of print). Editors: McNicholas WT, Bonsignore MR. European Respiratory Society Monographs 2010: pp. 225-243.
4. Kushida CA, Nichols DA, Holmes TH, Quan SF, Walsh JK, Gottlieb DJ, *et al.* Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: the Apnea Positive Pressure Long-term Efficacy Study (APPLES). Sleep 2012; 35:1593-602.
5. Ng SS, Chan TO, To KW, Chan KK, Ngai J, Tung A, *et al.* Prevalence of obstructive sleep apnea syndrome and CPAP adherence in the elderly Chinese population. PLoS One 2015;10:e0119829.
6. Baltzan MA, Elkholi O, Wolkove N. Evidence of interrelated side effects with reduced compliance in patients treated with nasal continuous positive airway pressure. Sleep Med 2009; 10:198-205.
7. Chai-Coetzer CL, Luo YM, Antic NA, Zhang XL, Chen BY, He QY, *et al.* Predictors of long-term adherence to continuous positive airway pressure therapy in patients with obstructive sleep apnea and cardiovascular disease in the SAVE study. Sleep 2013; 36:1929-37.
8. Lee GH, Kim MJ, Lee EM, Kim CS, Lee SA. Prediction of optimal CPAP pressure and validation of an equation for Asian patients with obstructive sleep apnea. Respir Care 2013; 58:810-5.
9. Chan AS, Sutherland K, Schwab RJ, Zeng B, Petocz P, Lee RW, *et al.* The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. Thorax 2010; 65:726-32.
10. Andrén A, Hedberg P, Walker-Engström ML, Wahlén P, Tegelberg A. Effects of treatment with oral appliance on 24-h blood pressure in patients with obstructive sleep apnea and hypertension: a randomized clinical trial. Sleep Breath 2013; 17: 705-12.
11. Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, *et al.* Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. J Clin Sleep Med 2015; 11:773-827.
12. Lee RW, Vasudavan S, Hui DS, Prvan T, Petocz P, Darendeliler MA, *et al.* Differences in craniofacial structures and obesity in Caucasian and Chinese patients with obstructive sleep apnea. Sleep 2010; 33: 1075-80.
13. Sutherland K, Lee RW, Cistulli PA. Obesity and craniofacial structure as risk factors for obstructive sleep apnoea, impact of ethnicity. Respirology 2012; 17: 213-22.
14. Phillips CL, Grunstein RR, Darendeliler MA, Mihailidou AS, Srinivasan VK, Yee BJ, *et al.* Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomised controlled trial. Am J RespirCrit Care Med 2013; 187: 879-87.
15. Remmers J, Charkhandeh S, Grosse J, Topor Z, Brant R, Santosham P,*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.
16. Qaseem A, Holty JE, Owens DK, Dallas P, Starkey M, Shekelle P, *et al.* Management of obstructive sleep apnea in adults: A clinical practice guideline from the American College of Physicians. Ann Intern Med 2013;159: 471-83.
17. Verse T, Hörmann K. The surgical treatment of sleep-related upper airway obstruction. Dtsch Arztebl Int 2011; 108:216-21.
18. Lin HC, Friedman M, Chang HW, Gurpinar B. The efficacy of multilevel surgery of the upper airway in adults with obstructive sleep apnea/hypopnea syndrome. Laryngoscope 2008; 118: 902-8.
19. Randerath WJ, Verbraecken J, Andreas S, Bettega G, Boudewyns A, Hamans E, *et al.* Non-CPAP therapies in obstructive sleep apnoea. Eur-Respir J 2011; 37:1000-128.
20. Liao YF, Chiu YT, Lin CH, Chen YA, Chen NH, Chen YR. Modified maxillomandibular advancement for obstructive sleep apnoea: towards a better outcome for Asians. Int J Oral Maxillofac Surg 2015;44:189-94.

21. Li WY, Gakwaya S, Saey D, Sériès F. Assessment of tongue mechanical properties using different contraction tasks. J Appl Physiol (1985) 2017;123:116-25.
22. Ward CP, York KM, McCoy JG. Risk of obstructive sleep apnea lower in double reed wind musicians. J Clin Sleep Med 2012; 8:251-5.
23. Guimarães KC, Drager LF, Genta PR, Marcondes BF, Lorenzi-Filho G. Effects of oropharyngeal exercises on patients with moderate obstructive sleep apnea syndrome. Am J RespirCrit Care Med 2009; 179:962-6.
24. Villa MP, Brasili L, Ferretti A, Vitelli O, Rabasco J, Mazzotta AR,*et al*. Oropharyngeal exercises to reduce symptoms of OSA after AT. Sleep Breath 2015;19:281-9.
25. Ieto V, Kayamori F, Montes MI, Hirata RP, Gregório MG, Alencar AM,*et al*. Effects of oropharyngeal exercises on snoring: a randomized trial. Chest 2015; 148:689-91.
26. Puhan MA, Suarez A, Lo Cascio C, Zahn A, Heitz M, Braendli O. Didgeridoo playing as alternative treatment for obstructive sleep apnoea syndrome: randomized controlled trial. BMJ 2006; 332:266-70.
27. Rousseau E, Silva C, Gakwaya S, Sériès F. Effects of one-week tonguetask training on sleep apnea severity: A pilot study. Can Respir J 2015; 22:176-8.
28. Strollo PJ Jr, Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, *et al*. Upper-airway stimulation for obstructive sleep apnea. N Engl J Med 2014; 370: 139-49.
29. Dong Y, Zhao M, Su M, Ding N, Zhang X. Efficacies of stimulation of genioglossus in mild-to-moderate obstructive sleep apnea syndrome patients after uvulopalatopharyngoplasty. Zhonghua Yi XueZaZhi 2014;94:1726-8.
30. Tan J, Long Y, Deng B. The observation on hyperbaric oxygen therapy and pharyngeal neuromuscular electrical stimulation inpatients with obstructive sleep apnea hypopnea syndrome. Chin J Rehabil Med (Chinese) 2013;, 28: 1025-9.

How to cite this article: Li WY, Wang W. Therapeutic approaches of obstructive sleep apnea in China. J Transl Intern Med 2018; 6: 16-20.