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A M E R I C A N C O L L E G E O F



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airway closure, thereby precipitating obstruction. It is conceivable that elastic fiber decomposition may occur in the lung interstitium too. But histologic evidence in stable patients with chronic asthma is still lacking. Anyway, I am afraid that, in using the method of Gelb et al as described in this issue to discern airways from lung, the effect of a decline in parenchymal elasticity on expiratory flow would be confounded by a simultaneous loss of airway elastic force, resulting in peripheral obstruction.

In case there really is something like lung parenchymal remodelling in patients with chronic asthma, a great many questions about clinical manifestation, temporal course, therapeutic response, and control need to be answered. Is lung remodelling a uniform feature of all types of asthma (*eg*, seasonal vs perennial, allergic vs nonallergic, nocturnal vs nonnocturnal, etc.)? Does it coincide with airway remodelling? Unless it does, which comes first? When does remodelling begin? Can it be reversed with the help of therapy with inhaled corticosteroids or other anti-inflammatory drugs?

Prospective longitudinal studies in well-defined subgroups of asthma patients including invasive procedures (*eg*, BAL or transbronchial biopsy) will be required in order to assess the persistence or reversibility of loss of recoil, and to delineate structure-function relationships. Gelb and coworkers have poured fresh oil into good old lung mechanics. The challenge is on.

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Treatment of Obstructive Sleep Apnea

No Longer Just a Lot of Hot Air

Obstructive sleep apnea (OSA) has in recent years assumed a somewhat more notorious prominence in the lay press and in the medical literature. With a prevalence of 2 to 4% in the United States,¹ where the predisposing factor of obesity is epidemic,^{2,3} OSA can no longer be regarded as limited to the overweight hypercapnic or morbidly sleepy patient. Moreover, epidemiologic studies have demonstrated an independent relationship between OSA and cardiovascular disease,^{4,5} OSA and cerebrovascular disease,^{6,7} and indeed a dose-response relationship with hypertension.⁸ OSA, therefore, is now recognized as having far-reaching implications on cardiovascular health as well as on the quality of life of an increasingly large and diverse population.

Perhaps in response to such a growing realization, a substantial amount of research effort has been devoted to extending the ability to diagnose OSA. Limited respiratory monitoring technology,⁹ simpler oximetry evaluations,¹⁰ and abbreviated split-night studies¹¹ have been rigorously evaluated and have subsequently made the ability to diagnose sleep-disordered breathing more accessible to patients and more affordable for third-party payers. Consequently, more people with milder disease and more subtle symptoms have been found and have been

made aware. Finding more tolerable and successful treatment options for OSA, however, has not kept pace with such diagnostic advances. Well-intentioned physicians may all too often be faced not with the satisfied contentment of having found an answer to vague and puzzling symptoms, but with having to ask themselves, What now?

Weight loss is easy to recommend but difficult to comply with. It may have become less relevant as a treatment recommendation, since a greater number of nonobese patients are receiving diagnoses. Compliance with the standard treatment of continuous positive airway pressure (CPAP) falls off as patients with lesser degrees of daytime impairment are fitted. In fact, a recent study¹² suggests CPAP may be inappropriate unless daytime sleepiness exists, even as more and more patients with relatively asymptomatic disease, but with a recognized risk factor for future cardiovascular events, are receiving diagnoses.

Surgery such as uvulopalatopharyngoplasty (UPPP) has limited long-term efficacy,¹³ poses unacceptable risk for the patient with important comorbidities or old age, and may in any case be considered excessive for milder degrees of sleep-disordered breathing or minimal daytime impairment. Medications with purported activity on upper-airway tone, such as the selective serotonin reuptake inhibitors, have been explored but to date also have shown limited efficacy.¹⁴

Prosthetic mandibular advancement is becoming a more realistic and efficacious alternative in the treatment armamentarium for OSA, not only for milder and/or atypical patients, but for *any* patient with OSA. In this issue of *CHEST* (see page 739), Walker-Engstrom et al have supplied important efficacy and compliance information on mandibular advancement through a rigorous and long-term evaluation. Ninety-five male patients with overall mild OSA (mean apnea/hypopnea index [AHI] approximately 20 episodes per hour) were randomized to *initial* treatment with either UPPP or mandibular advancement, and were followed up for an average of 4 years. The authors used a one-piece device that achieved a fixed mandibular advancement of 50% of each patient's maximum protrusive capacity, a degree of advancement somewhat less than the 66 to 75% movement used in many previous studies.¹⁵⁻¹⁷

Compliance with the dental appliance was 82% at 1-year follow-up and 62% at 4 years, a rate comparable to acceptance rates with CPAP.¹⁸ With respect to efficacy, success (defined by reduction in the AHI by at least 50% of baseline) was 72% at 4 years with the oral appliance. This differed significantly from the 4-year success rate of 35% with UPPP. Data for normalization of OSA (apnea index < 5/h, AHI < 10/h) at 4 years was similar. Sixty-three percent of patients still using the mandibular device attained an

AHI < 10/h, while only 33% of patients treated with UPPP achieved such a result.

This current study adds further weight to the growing body of evidence supporting prosthetic mandibular advancement as a valid treatment for OSA. Mandibular advancement has been subjected to the same stepwise evaluation as have treatment modalities for other diseases. Initial uncontrolled case series or anecdotal reports establishing feasibility^{15,19} have been followed by studies investigating a mechanistic explanation for success in treatment of OSA.²⁰ Randomized controlled trials of mandibular advancement have subsequently followed, providing further scientific credence to the use of mandibular advancement in OSA.

Two such randomized crossover investigations, both published in 1996,^{16,21} compared oral appliance therapy to the virtual "gold standard" treatment of CPAP and reached similar conclusions. In patients with mild-to-moderate OSA, mandibular advancement and CPAP were both efficacious. CPAP proved more effective in lowering posttreatment AHI, but mandibular advancement was tolerated better and was preferred by a greater number of patients. A more recent placebo-controlled trial¹⁷ of mandibular advancement against a placebo dental plate in 24 patients confirmed partial or complete response in two of three patients regardless of OSA severity, and demonstrated favorable compliance (87%) and satisfaction (96%) rates among users.

Walker-Engstrom et al have extended these findings by confirming a similar degree of efficacy in a larger patient population. The fact that these patients were actually randomized to one of two (non-CPAP) treatments, made possible by the mild-to-moderate severity of their disease, makes the favorable efficacy and side effect profile results especially meaningful. Another important strength of this study was its prolonged duration. The 4-year length of follow-up showed that the relatively low rate of both subjective complaints and objective complications found in previous studies of oral appliances can be maintained despite a much longer period of use.

This long-term controlled trial therefore represents a major step forward in catching treatment options for OSA up to the recent progress made in detecting the disease. The answer to "What now?" lies not in relying on any particular "gold standard" of therapy, but on assuring the clinician that *several* validated and almost complementary options exist, which may be individualized according to particular patient and disease characteristics. CPAP appears to be less tolerated in the very population of patients with mild disease and/or symptoms in which mandibular advancement

achieves best results. Previous studies^{17,22,23} do need to be emphasized, however, that demonstrate successful mandibular advancement efficacy can be achieved in patients with more severe degrees of OSA as well.

Treatment of OSA has therefore progressed to a state where enough varied therapeutic options exist to allow greater individualization among patients, which hopefully will result in better long-term compliance and satisfaction. Moreover, these expanded treatment options should no longer be regarded in an “either/or” light. Rather, it may now be appropriate to regard upper-airway surgery, pneumatic splinting, and mandibular advancement as independent treatment options for certain patients, but as synergistic stepwise treatments for others. Millman et al,²⁴ for example, showed that mandibular advancement can accomplish a complete response in certain patients with an unsatisfactory result from UPPP alone. Indeed, the current study by Walker-Engstrom et al demonstrated similar results in a smaller number of patients. Six of 10 patients initially randomized to UPPP normalized sleep-disordered breathing only after “rescue” mandibular advancement. The utility of mandibular advancement as a rescue modality for at least surgical failures becomes even more important in light of evidence that CPAP utility may actually be compromised in patients previously treated with UPPP.²⁵ Given that other mechanistic studies²⁰ have found that anterior mandibular advancement may impact on velopharyngeal (soft palate, uvula) tissues as well as on the posterior airway space, adjunctive orthodontic manipulation of pharyngeal tissues is supported by physiologic as well as epidemiologic evidence.

Many issues remain unresolved despite such progress. The appropriate patient population for mandibular advancement, at least as monotherapy, may need to be redefined. Patients with only mild-to-moderate OSA, such as the patients in the current study, have generally been considered to offer the best chance of success with oral appliances. As stated above, however, several studies have shown that even more severe cases may respond.

Different types of oral devices have been used, making comparison between studies somewhat problematic. One-piece or two-piece construction, as well as adjustable vs fixed advancement capabilities, present opportunities for future investigations, and undoubtedly impact on tolerance, efficacy, and cost considerations. The degree of mandibular movement is also far from resolved, but may be as important a variable as the level of positive pressure delivered by CPAP. A majority of

investigators^{15–17,23,26} have recommended at least 75% of maximal protrusion, a value representing absolute mandibular advancement of between 5 mm and 11 mm. One such study²³ with an adjustable oral device even used an average movement of 88% of maximal protrusion (8.8- to 16.5-mm absolute advancement). Importantly, a substantial number of patients in that study achieved improvement despite severe OSA (mean AHI 52 ± 28 /h for all patients), perhaps as a result of such profound advancement. Although the incidence of side effects was not detailed, another recent 2.5-year study²⁷ specifically focusing on side effects instead of efficacy found only minor orthodontic and occlusive side effects despite initial anterior mandibular movement of 75% of maximal protrusion. Subjective discomfort was prevalent but relatively minor, and was outweighed by overall subjective improvement in daytime symptoms. It is possible, therefore, that the relatively lower degree of advancement achieved by the authors of this current study could be exceeded in future clinical trials. In so doing, an even better risk benefit ratio could be achieved, even with long-term use.

It may be that lessons learned from years of CPAP therapy may provide the answer to at least the last issue. Future studies should emphasize *adjustable* mandibular advancement devices, with objective titration trials similar to CPAP titration. Initial advancement may depend more on objective reduction of AHI, while long-term compliance may rely more on subsequent patient-driven adjustment.

However these issues are resolved, responsible use of oral appliances depends on factors that should not be open to discussion. Success of mandibular advancement needs to be confirmed by objective follow-up polysomnographic verification, as some studies have reported subjective daytime improvement without corresponding resolution of OSA. Perhaps as important if not more so, fitting and manufacture of oral appliances should be conducted by dentists with particular interest and experience in sleep disorders. In fact, the particular device probably does not have as much bearing on eventual clinical effectiveness as does the dentist and associated sleep center prescribing it.

The variable compliance and success rates seen up to now in the treatment of OSA would not be found acceptable with other prevalent diseases such as hypertension, coronary artery disease, or diabetes. This rigorous and ambitious study will hopefully lead to expanding treatment options by building greater confidence in the orthodontic treatment of OSA. Utilization of both monotherapy and combined therapies have become standard in the treatment of

these other diseases. The growing number of patients with OSA may benefit from such a philosophy as well, even if such treatment options and combinations are sutured, worn, and inserted instead of swallowed.

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Pulmonary Blastomycosis

A Great Masquerader

Blastomyces dermatitidis is one of the dimorphic fungi known to cause disease primarily within certain endemic areas scattered throughout the world. The endemic regions of North America blastomycosis include the southeastern, south central, and midwestern states (especially areas bordering the Mississippi and Ohio Rivers and the Great Lakes), adjacent areas of Canada, and a small area in upper New York State and Canada that follows the St. Lawrence River. Within these areas, blastomycosis has occurred sporadically or in outbreaks. Infection is acquired via inhalation of airborne spores from disturbed contaminated soil. Although *B dermatitidis* is highly infectious, symptomatic disease seems to develop in less than half of those infected.

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