Sleep-Related Breathing Disorders*
An Update
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Since the late 1960s a voluminous literature has accumulated testifying to the ubiquity of sleep-related breathing disorders. The realization that such conditions are not only prevalent, but also in some instances potentially life-threatening, has had considerable recent impact on pulmonary medicine. Clinical sleep laboratories which allow the study of ventilatory phenomena during sleep are proliferating in community hospitals and medical centers. This movement has had the additional benefit of focusing the attention of the medical community on a wide variety of sleep-related pathophysiologic phenomena.1

Earlier work was concerned primarily with empiric descriptions of various clinical entities associated with sleep-related obstruction of the upper airway. The behavioral and cardiopulmonary manifestations of this condition, i.e., hypsomolence, snoring, arrhythmias, and right ventricular failure are by now well established.2 Recent clinical investigative efforts have concentrated on delineating pathogenesis and alternative approaches to treatment and on describing a variety of other sleep-related respiratory disorders. In an effort to avoid covering already familiar aspects of diagnosis and treatment, this brief review will highlight new material concerning the complex pathophysiology and diversity of the syndromes of obstructive sleep apnea. Recent work concerning surgical and nonsurgical approaches to the treatment of obstructive sleep apnea will also be discussed, in addition to other nonapneic sleep-related respiratory disorders.

Epidemiology and Pathogenesis

The actual incidence of the syndrome of obstructive sleep apnea is difficult to determine due to the poor correlation between obstruction of the upper airway and the cardiopulmonary and behavioral symptoms; however, there is little doubt that this syndrome is common by medical standards, and the incidence is certainly greater than would have been imagined ten years ago.

Epidemiologic studies by Lugaresi et al3 have described a relationship between snoring and hypertension. A total of 5,713 individuals were surveyed in this study. Seventeen percent of the male subjects and 14 percent of the female subjects described themselves as habitual snorers. The frequency of snoring clearly increases with age. Over 60 years of age, 60 percent of the men and 40 percent of the women were described as habitual snorers. Hypertension (defined as systolic blood pressure greater than 160 mm Hg) was more frequent among habitual snorers than among nonsnorers, especially after the age of 40 years. In the group aged 41 to 60 years, the incidence of hypertension among habitual snorers was double that of the nonsnorers (7.5 percent vs 15.2 percent). Thus, this study suggests that chronic obstruction of the upper airway during sleep is associated with cardiovascular dysfunction.

Early cineradiographic studies documented the site of the obstruction of the airway in patients with obstructive sleep apnea at the level of the hypopharynx.4 Studies by Sauerland and Harper5 showed the intimate relationship between the intrinsic functioning of the genioglossus muscle and the respiratory cycle. Inspiratory efforts are associated with a phasic burst of activity from this muscular structure, producing a slight protrusion of the tongue associated with inspiratory effort. These data provided considerable support for the popular notion that the primary pathophysiologic mechanism in obstructive sleep apnea is related to a relative hypotonia of the genioglossus muscle, allowing the tongue to prolapse during sleep and eventually collapse against the posterior pharyngeal wall. Since it is clear that the genioglossus muscle is a major dilator of the upper airway, the role of the tongue in occlusion of the airway cannot be ignored; however, it does seem that the tongue is not nearly so predominant in the pathogenesis as had been originally thought. Considerable evidence exists now to implicate the collapse or in-

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vagination of the pharyngeal walls and a general hypotonia of the dilating muscles of the upper airway as a cause of sleep-related occlusion of the airway. The development of interest in respiratory functioning during sleep has led to many studies concerning the functioning of the respiratory muscles during waking and sleep and their contribution to the pathophysiology of obstructive sleep apnea. Martin et al described the timing and mechanics of occlusion of the airway during sleep. This study demonstrated that occlusion of the airway occurs at the onset of inspiration, that airway resistance increases in the few breaths prior to the onset of the occlusion, and that this occurs in spite of a decrease in inspiratory effort and presumably neural drive prior to the onset of the occlusion. Similar findings were reported by Onal et al with diaphragmatic and genioglossus electromyographic (EMG) recordings. These investigators demonstrated similar decreases in the EMG from these structures prior to the onset of occlusion of the airway in patients with obstructive sleep apnea. The onset of occlusion of the airway appears to be associated with a hypotonia of the dilating muscles of the upper airway. Both of these investigative efforts documented the continuation of decreasing esophageal pressure, as well as diaphragmatic and genioglossus EMG activity, subsequent to the onset of the occlusion, and then a gradual increase in these measures with continued occlusion of the airway. It is of interest that this same pattern of esophageal pressure was noted in asymptomatic snorers in a recent study; that is, this breathing pattern in response to spontaneous occlusion of the airway suggests a predisposing respiratory abnormality similar to that observed in symptomatic obstructive sleep apnea. A recent study by Strohl et al has described the importance of the timing of the activation of diaphragmatic and upper-airway respiratory muscles in the respiratory cycle. These investigators documented the onset of EMG activity of the muscles of the upper airway (primarily the alae nasi muscles) prior to the onset of airflow. They suggest that the precise timing of motoric activation of the upper airway is crucial to normal respiratory functioning particularly during sleep.

The data cited previously fit quite nicely into the most comprehensive and parsimonious theory concerned with the pathophysiology of occlusion of the airway during sleep. This theory, suggested by Remmers et al, postulates that occlusion of the airway occurs when the pharyngeal negative pressure exceeds the dilating force of the muscles of the upper airway. This theory explains how occlusion of the airway can occur with increasing upper airway resistance occurring simultaneously with decreasing neural drive and inspiratory effort; that is, the hypotonia of the muscles of the upper airway documented by the study by Onal et al becomes sufficiently great to allow collapse of the upper airway even with decreasing negative intrathoracic pressure (neural drive). The same theory again explains the termination of occlusion of the airway in that the resumption of airflow occurs one to three breaths subsequent to a decrease from the peak negative inspiratory effort described in the study by Martin et al. Thus, the pharyngeal pressure decreases at a time when the muscles of the upper airway, particularly the genioglossus muscle, show increasing activity. This allows the ratio of the dilating forces of the upper airway to exceed the collapsing pharyngeal closing pressure. This pathophysiologic hypothesis also would explain very well why subtle anatomic abnormalities of the upper airway would lead to an increased risk for obstructive sleep apnea. Thus, a narrowing of the upper airway by excessive adipose tissue in obesity, hypertrophied tonsils, micrognathia, or macroglossia would create a situation whereby negative pharyngeal pressures generated in inspiration would require considerably more inspiratory activity from the dilating muscles of the upper airway to maintain patency of the airway. It could be hypothesized that over some period of time, these muscles would simply fatigue or "wear out," thereby being unable to continue to maintain the increasing dilating activity necessary to prevent closure of the airway with inspiration.

The hypothesis of Remmers et al and the supporting data described relate primarily to the mechanisms of closure and reopening of the airway. They do not specifically describe to events subsequent to closure of the airway leading to a reestablishment of ventilation. Since occasional episodes of obstruction of the airway appear to be reasonably common in the normal population, prompt termination of the obstruction would appear to be an important factor in preventing cardiopulmonary sequelae.

The occlusion of the upper airway provokes a variety of immediate responses. Episodes of obstruction of the upper airway during sleep produce a number of profound physiologic stimuli which lead to a variety of reflex cardiopulmonary and behavioral responses. Presumably, these all have survival value in that they should lead to a reestablishment of ventilation. There are immediate reflex responses which lead to a prompt increase in inspiratory effort. The intensity of this Müller's maneuver also produces additional intrathoracic hemodynamic changes which affect gas exchange in the lungs, as well as producing afferent feedback to the central nervous system through tracheal mechanoreceptors. Obstruction of the upper airway leads to an elevation in carbon dioxide concentration and a decrease in oxygen concentration, each of which is known to produce an arousal response. In the acute airway-occlusive event, it seems clear that hypoxemia is the
major arousal stimulus. Drops in oxygen saturation can be precipitous in many patients, and the retention of carbon dioxide over a comparatively short interval of time (less than two minutes) would not appear to be as significant. This point becomes even more important with the realization that many patients with obstructive sleep apnea have underlying restrictive or obstructive pulmonary disease which would exacerbate the hypoxemia during episodes of occlusion of the airway. The resulting hypoxemia leads to increases in activity of the muscles of the upper airway which, even in the absence of an arousal response, eventually would produce a dilation of the upper airway, presumably reestablishing ventilation.\textsuperscript{9,14}

Although this hypoxic reflex dilation of the upper airway is an important mechanism, the arousal response should not be overlooked. Normal subjects have an immediate increase in inspiratory effort and an arousal response within two to three breaths upon spontaneous occlusion of the airway. This suggests that defective arousal responses or defective upper airway reflexes (or both) require an intact hypoxic response to reestablish ventilation.\textsuperscript{8} Abnormalities relating to the neural control of the muscles of the upper airway cannot completely explain the development of symptomatic obstructive sleep apnea. Decreases in inspiratory effort prior to the onset of occlusion of the airway, as well as continued decreasing inspiratory efforts subsequent to the onset of an occlusion, suggest a fundamental alteration in neural regulation of breathing and in reflex responses to occlusion of the airway.\textsuperscript{9,10} The pathophysiology of this condition involves a complex network of both respiratory and neurobehavioral dysfunctions.

\textbf{Varieties of Clinical Presentation}

The description by Burwell et al\textsuperscript{19} of the pickwickian syndrome and the subsequent studies by Gastaut and colleagues\textsuperscript{46} documenting obstructive sleep apnea in this clinical entity focused considerable attention on what was believed to be an interesting but relatively rare condition. This realization that profound alterations in respiratory phenomena could accompany sleep and could explain a diversity of behavioral and cardiopulmonary manifestations prompted extensive investigation into these previously unstudied disorders.

It has become clear that the pickwickian syndrome as initially described by Burwell et al\textsuperscript{19} is a virtually meaningless entity. Numerous studies have documented that obesity, waking carbon dioxide retention, polycythemia, and signs of right ventricular failure are not necessarily consequences of obstructive sleep apnea.\textsuperscript{9,17} It now seems quite clear that a patient with several hundred episodes of obstructive sleep apnea may not exhibit the constellation of symptoms which were described. In fact, such patients may have none of the classic symptoms.\textsuperscript{17} Other investigative reports indicate that sleep apnea may exist to some extent in a completely normal asymptomatic control population.\textsuperscript{19} This poor relationship between episodes of obstructive sleep apnea and clinical signs and symptoms has retarded efforts to specifically define a syndrome. Our experience suggests that the most common symptom associated with obstructive sleep apnea is daytime sleepiness or fatigue and lethargy. In the symptomatic patient, obstructive sleep apnea and some alteration in daytime alertness are often noted; however, the presence of sonorous snoring with observations of respiratory pauses by the bed partner generally precedes the development of daytime hypersomnolence. Observations of daytime sleepiness by the spouse or other close friends and relatives are especially important, since many patients deny this symptom. Although snoring is commonly observed in these patients for years, and even decades, an exacerbation is generally noted prior to the patient's presentation to the physician.

We have seen myxedematous patients in whom the progressive development of profound hypothyroidism has been associated with an acute worsening of snoring and the development of severe daytime hypersomnolence. These patients were all documented to have severe obstructive sleep apnea, and the manifestations of this were subsequently totally reversed with appropriate thyroid replacement.\textsuperscript{19}

The association of obstruction of the airway and daytime lethargy and hypersomnolence has been noted in children who have undergone repair of a cleft palate;\textsuperscript{49} however, the resolution of this condition by anatomic reversal of the abnormality of the upper airway has not been demonstrated. These patients were generally treated with a tracheostomy. Similar observations have been made with the acute gain and loss of weight, but the actual anatomic alterations of the upper airway are more difficult to document. Although the classic association of obstructive sleep apnea with alterations in daytime alertness has been documented to occur in children with anatomic abnormalities such as cleft palate and adenotonsillar hypertrophy, in our experience, it is not nearly so common as in adults.\textsuperscript{40,41} It is of some interest that although the progressive exacerbation of snoring and the insidious development of daytime sleepiness suggest a condition which has been developing for many years, these symptoms can be reproduced within two to three days by plugging the tracheostomy tube in a patient with obstructive sleep apnea. These observations focus on the many as yet unanswered questions concerning the pathogenesis of this syndrome. In addition, it is abundantly clear that occlusion of the airway during sleep is common and can lead to severe behavioral and cardiopulmonary changes which can be extraordinarily
Evidence that moderate to severe obstructive sleep apnea (in excess of 120 episodes per night) exists in nonobese nonhypersomnolent individuals without evidence of cardiopulmonary dysfunction suggests that sleep-related obstruction of the upper airway is necessary but not sufficient to develop the commonly associated sequelae. Our study comparing a group of asymptomatic (nonhypersomnolent) individuals with those who had a similar number of episodes of obstructive sleep apnea revealed no significant difference in the number of arousals from sleep, or in their sleep pattern, and yet one group of patients remained essentially free of significant daytime sleepiness. We concluded, as Lugaresi et al have also noted, that arousals from sleep or sleep deprivation cannot explain the presence of profound daytime sleepiness in these patients. Thus, theories of pathogenesis must account not only for the simple observation of sleep-related dysfunction of the upper airway, but also for the development of the neurobehavioral sequelae, ie, sleepiness, hyperirritability, and impotence.

TREATMENT

Although numerous alternatives, both medical and surgical, have been recently proposed in the treatment of obstructive sleep apnea, the tracheostomy remains the most likely to succeed. In appropriately selected cases, this treatment is successful in nearly all instances. In this case, success in this case refers to a reversal of the symptom of daytime sleepiness and cardiopulmonary sequelae such as nocturnal hypoxemia, right ventricular failure, and systemic hypertension. Guillemainault and his colleagues have recently codified and reported on their extensive experience with tracheostomy for obstructive sleep apnea. An alternative surgical approach, the uvulopalatopharyngoplasty, has recently been described and in some cases obviates the need for a permanent tracheostomy.

Pharmacologic approaches to the treatment of this condition have met with only variable degrees of success. Medroxyprogesterone has been shown to enhance respiratory drive in patients with obstructive sleep apnea, but there is little convincing evidence that it is consistently successful in relieving obstructive sleep apnea. A recent study has shown that protriptyline decreases the number of obstructive apneic episodes, but this was determined to be secondary to a decrease in the percentage of REM sleep, a well-established effect of tricyclic antidepressant drugs.

Other nonsurgical approaches have recently been described involving the use of positive pressure to the upper airway. Sullivan et al have reported the successful use of continuous positive airway pressure (CPAP) in the treatment of patients with symptomatic obstructive sleep apnea. This study documents a virtual ablation of episodes of obstructive sleep apnea, as well as impressive symptomatic improvement in all patients studied. The application of expiratory positive pressure has also been shown to reduce episodes of obstruction of the airway and affect a remission of symptoms in the majority of the patients studied in a preliminary report. Recently, the use of a tongue-retaining device has been reported to be successful in some patients. Of these mechanical devices, only the report by Sullivan et al using CPAP appears to be consistently successful in reducing episodes of obstructive sleep apnea to a clinically significant degree and producing consistent symptomatic improvement. All of these mechanical devices suffer from the disadvantage of being cumbersome, which presents a considerable problem with compliance. None of these procedures has yet been shown to be effective with long-term follow-up.

Loss of weight has been touted as an effective treatment for obstructive sleep apnea, since many of these patients are obese. In fact, nearly every clinician with any experience with this syndrome has noted examples of substantial improvement with loss of weight; however, it is the experience of most investigators in this area that weight loss is not consistently effective in resolving obstructive sleep apnea. Furthermore, compliance with weight loss programs is notoriously poor. Generally, our approach to treatment is to attempt weight loss in the obese, clearly symptomatic patient, whose sleep study does not reveal severe oxygen desaturation or malignant cardiac arrhythmias. Although this has not been particularly successful, we believe that the patient should be encouraged to take this option prior to a more aggressive surgical approach.

OTHER SLEEP-RELATED BREATHING DISORDERS

The dramatic description of sleep-related upper airway obstruction focused considerable attention on the investigation of other pulmonary diseases and the association of these with sleep-related respiratory disturbances. Wynne and his colleagues have described sleep-related breathing disorders resulting in severe oxygen desaturation (to approximately 50 percent arterial oxygen saturation) in patients with severe chronic obstructive pulmonary disease (COPD). There appears to be little doubt that in some patients, this may play an important role in the development of the pulmonary hypertension and consequent right ventricular failure associated with severe chronic obstructive pulmonary disease (COPD). Other investigators have pursued these observations in more depth by specifically identifying patients most likely to develop nocturnal hypoxemia. Douglas and his colleagues have noted that patients with COPD characterized as “blue bloaters” tend to exhibit sleep-related
oxygen desaturation more frequently than those described as "pink puffers." These observations have contributed greatly to understanding the pathogenesis of the cardiopulmonary complications of COPD and their appropriate treatment.

Other intrinsic pulmonary diseases have also been studied with regard to their possible association with sleep-related breathing disorders. A recent study with asthmatic subjects documented that although there is no specific tendency for nocturnal attacks to occur in any particular state of sleep, oxygen desaturation was proportionally more frequent and severe during REM sleep.

Other studies in patients with cystic fibrosis have shown that sleep-related spontaneous oxygen desaturation is sufficiently severe to play a prominent role in the development of the malignant pulmonary hypertension commonly encountered in these patients. These authors noted that the spontaneous episodes of oxygen desaturation most commonly occurred during REM sleep and inferred that this was due to decreases in pulmonary volume. Similar results have been noted in patients with kyphoscoliosis.

SUMMARY

The study of sleep-related breathing disorders has substantially advanced the practice of pulmonary medicine, both in terms of improving diagnostic accuracy and in defining more appropriate and specific treatments for a variety of respiratory disorders. Although a presumptive diagnosis of these disorders can be made with a good clinical history, an overnight sleep evaluation is generally necessary in order to determine the presence and severity of a specific disorder. Awareness of sleep-related breathing disorders has revolutionized the practice of pulmonary medicine and has dictated that it become a specialty equally concerned with sleeping and waking respiratory functions. The clinician who remains satisfied with an evaluation of the patient only during the waking state ignores the myriad of disorders of ventilation known to be induced or exacerbated by sleep. The knowledgeable physician must now embrace the full 24-hour spectrum of man's physiologic and pathophysiologic functioning.

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