Adult Obstructive Sleep Apnea/ Hypopnea Syndrome: Definitions, Risk Factors, and Pathogenesis

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KEYWORDS

• Epidemiology • Obstructive sleep apnea syndrome
• Pathogenesis • Risk factors

DEFINITIONS

The *International Classification of Sleep Disorders, Second Edition (ICSD-2)* classifies sleep-related breathing disorders into 3 basic categories: central sleep apnea syndrome, obstructive sleep apnea (OSA) syndrome, and sleep-related hypoventilation/hypoxic syndrome. In this classification, the term ''upper airway resistance syndrome'' is subsumed under the diagnosis of OSA because the pathophysiology is so similar to that of OSA. Sleep apnea is termed ''obstructive'' when respiratory effort is present and ''central'' or ''nonobstructive'' when this effort is absent. OSA, which is the focus of this article, is decidedly more prevalent and amenable to treatments that are directed at increasing the size of the upper airway. Clinical disease is characterized by repetitive airflow cessation (apnea) or reduction (hypopnea). The onset of an obstructive apnea occurs when forces promoting airway collapse overcome mechanisms that maintain airway patency.

An apnea is defined as the cessation of airflow for 10 seconds or longer using a valid measure of airflow; this time criteria represents approximately 2.5 cycles of normal respiration. Unlike the definition of apnea that has remained consistent over time, the definition of hypopnea has shifted over time to represent the measurable features of partial upper airway obstruction. This, in part, is a reflection of the fact that this event involves identification of a subtle reduction in airflow. A consensus conference (Chicago Criteria) provided a definition of hypopnea as including 1 of 3 features: a substantial reduction in airflow (>50%), a moderate reduction in airflow (<50%) with desaturation (>3%), or a moderate reduction in airflow (<50%) with electroencephalographic evidence of arousal.[1] Subsequently, population studies addressed various operational definitions of hypopnea. The Sleep Heart Health Study (SHHS), a large cohort study designed to relate cardiovascular disease with polysomnographic findings, defined hypopnea as a 30% decrease (from baseline) in airflow or chest wall movement for at least 10 seconds, accompanied by an oxygen desaturation of 4% or greater.[2] This definition is accompanied by a high degree of

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Clin Chest Med 31 (2010) 179–186
doi:10.1016/j.ccm.2010.02.011
0272-5231/10/$ – see front matter

interscorer reliability and pathophysiologic consequences.

An analysis of more than 5000 records from the SHHS underscores the effect of various hypopnea definitions. This analysis showed that the magnitude of the median apnea-hypopnea index (AHI) could vary 10 fold (ie, 29.3 when the AHI was based on events identified on the basis of flow or volume amplitude alone vs 2 for an AHI that required an associated 5% desaturation with events).[3] Varying thresholds for polysomnographic summary data also resulted in marked differences in the percentage of subjects classified as diseased. For example, using an AHI cutoff value of greater than 15 and requiring a 5% level of desaturation resulted in a prevalence estimate of 10.8. In contrast, almost the entire cohort was affected when sleep-disordered breathing (SDB) was defined using an AHI threshold value of 5 and when all hypopneas were scored regardless of associated corroborative physiologic changes. To add to the complexity of scoring clinical records, there are events called respiratory effort–related arousals (RERAs), whereby arousals are identified in the setting of heavy snoring without hypoxemia or discernible reductions in airflow; these events contribute to clinical presentations because their elimination improves symptoms.[1] Thus, there is a need for standardization across laboratories and research protocols, not necessarily to determine an individual severity but to facilitate multicenter trials and recommendations for therapy as determined by laboratory-based disease severity.

The most widely used severity criteria use ''cutoffs'' based on the frequency of apnea and hypopnea events. By consensus, mild sleep apnea has been defined as an AHI (number of apneas and hypopneas/hour of sleep) of 5 to 15 events per hour, moderate as greater than 15 to 30 events per hour, and severe as greater than 30 events per hour.[1] A similar measure called respiratory disturbance index (RDI) not only is based on flow, desaturations, and arousals but also uses RERAs. Most epidemiologic studies have used the AHI or RDI almost interchangeably as the single polysomnographic-derived measurement when testing the association between OSA and cardiovascular complications. However, other unidimensional indices, such as (among others) the severity of oxygen desaturation or arousal index (number of arousals per hour), are not captured by AHI. The current severity criteria based on AHI or RDI also correlate only loosely with symptom or clinical severity.[4] Furthermore, investigators have questioned whether the AHI alone is the best predictor for outcomes such as survival, cardiovascular events, or incident hypertension and metabolic dysfunction.[5,6] Available evidence supports a need to standardize these other dimensions; for example, recurrence of atrial fibrillation among OSAs may not be best predicted by the AHI but rather by the severity of nocturnal hypoxemia.[7]

PREVALENCE

According to the first major US population-based study conducted about 15 years ago, when AHI criteria based on thermistor measures of airflow are applied to a general population of middle-aged adults, 24% of men and 9% of women meet criteria for OSA.[8] These prevalence figures are based on a cutoff AHI of 5 or higher. Most of these patients (>50%) had mild sleep apnea according to current criteria. If the symptom of sleepiness is included as part of a syndromic definition (OSA syndrome), 4% of men and 2% of women meet criteria in this 1993 study. From this study and subsequent studies, more than 75% of patients with OSA are undiagnosed or untreated.[8] In view of the epidemic increase of obesity (an important determinant of OSA) in the US population since 1993, these numbers are an underestimate that the current prevalence figures. Recent results from the National Sleep Foundation *Sleep in America 2005 Poll* containing a validated instrument used to identify individuals at risk for sleep apnea, using a composite score from self-reports (the Berlin Questionnaire), indicated that as many as 1 in 4 American adults met criteria for a high pretest probability risk for OSA.[9] Not all of these individuals need definitive testing or direct therapy; however, the pool of people who could be considered at risk for OSA from a population perspective is large and perhaps more importantly at risk for its behavioral and cardiovascular consequences.

Risk Factors in Clinical Assessments

Despite the numerous advancements in the understanding and the pathogenesis and clinical consequences of OSA, great majority of patients (approximately 70%–80%) remain undiagnosed.[10] Case identification is confounded in part by the fact that patients are often unaware of the importance of associated symptoms even if they can frequently be identified by a bed partner or family member. Public knowledge of risk factors along with physician awareness needs to be addressed to inform appropriate diagnostic attention and case finding in the future.

Sex

Men are at higher risk for the development of sleep apnea; however, the effect is modest. Some of the

early (largely clinic-based) studies suggested that there was a 5- to 8-fold increased risk for sleep apnea among men compared with women.[11] Subsequent population-based studies have shown this magnitude of risk to be closer to 2 to 3 fold higher among men.[8,12] These studies indicate that one does not have to be a man to have sleep apnea, but it helps. This difference between early clinic-based and population-based estimates not only relates in part to patient presentations but also may reflect differences in how women and men perceive and report symptoms of SDB. Although a prototypical male patient with sleep apnea tends to present with excessive daytime sleepiness, unrefreshing sleep, and loud snoring, community-based studies of women (which included women with significant sleep apnea) suggest that women are less likely to endorse these classic symptoms of sleep apnea and more likely to report symptoms of daytime fatigue, morning headache, and mood disturbance.[13,14] If women are less likely to report classic symptoms of sleep apnea, they are less likely to be referred to sleep clinics for evaluation and, therefore, may be underrepresented in clinic-based studies and lead down alternative diagnostic pathways.[13] Alternatively, the disease process may be different, requiring alternative case funding and assessments for risk and response to therapy.

Well-designed population-based studies confirm a clear increased expression of objectively measured SDB among men compared with women. Studies examining this difference have focused on hormonal differences. In women, a strong predictor of sleep apnea is menopausal status. Bixler and colleagues[12] found a nearly 4-fold increased risk of sleep apnea (AHI $\geq$ 5) among postmenopausal women compared with premenopausal women. Similar results were seen in the Wisconsin Sleep Cohort Study in which such an increased risk was seen even after adjusting for the confounding effects of age and body fat distribution.[15] In addition, the SHHS demonstrated a lower prevalence of sleep apnea among postmenopausal women who were taking hormone replacement therapy (HRT), compared with those who were not, implicating a potential protective effect of HRT.

In addition to the differences in event prevalence, the severity of sleep apnea and its occurrence in sleep stages may differ between men and women. There seems to be, on average, a decrease in number and shorter duration of apneic events in women compared with men.[16] Women tend to have a higher percentage of rapid eye movement (REM)–related apneas and hypopneas and are more likely to have sleep apnea that occurs entirely during REM sleep, an effect more prominent in younger populations.[17] In addition, one study suggests that women may be more symptomatic at a lower severity of sleep apnea,[18] and a proposed mechanism is the clustering of events within and hence disruption of REM sleep.

Other hypotheses for the gender differences in sleep apnea have included differences in airway caliber and compliance,[19] soft tissue structure,[20] genioglossal activity,[21] and regional fat distribution[22] (with men more likely to have upper body fat distribution and women more likely to have lower body fat deposition).

Excess weight and measures of obesity

Epidemiologic studies in the United States and Europe have consistently identified body weight as the strongest risk factor for OSA, and there seems to be little controversy regarding the causal associations seen in observational studies. In the Wisconsin Cohort Study, a 10% weight gain was associated with a 6-fold increased risk of OSA.[23] Longitudinal data from the Cleveland Family Study show that an increase in bodyweight over time increases the risk for and accelerates the progression of OSA,[24] suggesting that the incidence of sleep apnea increases as the incidence of obesity continues to increase. In the Asian population, obesity is less prevalent, but sleep apnea is not proportionately reduced, indicating an effect of craniofacial features perhaps interacting with body habitus (see later discussion).

The close link with features of obesity is a strong factor in the clinical identification of patients who have a high likelihood of sleep apnea, at least in the US population. Neck circumference (a measure of upper body obesity strongly correlated with body measures) is a strong predictor of sleep apnea.[25] Fatty tissue amounts in the neck cause narrowing of the airway, thus increasing the chances of airway closure during sleep. Imaging studies of the neck and upper airway among patients with sleep apnea show larger lateral parapharyngeal fat pads and pharyngeal walls compared with nonobese controls.[26] With weight reduction, the volume of the parapharyngeal walls and lateral paraphyngeal fat pads decreases, accompanied by an increase in airway caliber.

Weight reduction (by any means) can improve severity of sleep apnea in many patients and may be completely curative in some. Extrapolating from pooled surgical and medical weight loss studies, a 10% to 20% weight reduction is associated with an approximately 50% reduction in AHI.[27]

Age

With advancing age, sleep-related difficulties are more common, often manifested by complaints

of difficulty falling asleep, increased number of and duration of night-time awakenings, and a decreased amount of night-time sleep. This age-related variability in sleep stability contributes in some way to an increasing prevalence of OSA with advancing age.

In one of the first large population-based studies of sleep apnea among older people, Ancoli-Israel and colleagues[28] examined 427 community-dwelling men and women of ages between 65 and 95 years. They found that 70% of men and 56% of women had OSA objectively defined as AHI greater than or equal to 10. This value is several folds higher than the prevalence estimates among middle-aged adults.[8] Subsequent studies from several population-based samples confirmed this higher prevalence of SDB among older individuals.[29–31] This higher prevalence with older age raises some important questions: how does aging itself have an etiologic role in the development of SDB and what is the significance of the high prevalence of OSA in the elderly?

If aging has an etiologic role in sleep apnea, then authors would expect the prevalence to continue to increase over the older-age range, but this does not seem to be the case. Most of the age-related increases in OSA occur before the age of 65 years and then plateaus subsequently.[29,31] This is not what would be expected with continued accumulation of cases and suggests several possibilities: the incidence may decrease with age older than 65 years, a cohort effect, or perhaps an increased mortality rate among older-aged patients with sleep apnea.[27]

The question arises whether OSA among older adults represents a different clinical entity compared with that seen in middle-aged adults. In particular, age-related attributable morbidity and mortality is an area of controversy. Some of the studies have shown increased risk of adverse outcomes,[32] whereas others have reported little or no association.[33] Additional samples with adequate control for confounding covariates are needed to investigate whether OSA portends excess medical risk among older people.

Ethnicity

Most population-based studies examining the prevalence of OSA have largely focused on characterizing disease prevalence in North America, Australia, and Europe. Compared with the literature on cardiac disease, there are no studies using similar methods that have examined racially, ethnically, and geographically diverse samples. In the data involving African American samples, population-based samples suggest that the prevalence of sleep apnea is as high or higher and potentially more severe among African Americans (particularly among older and younger age groups as compared with middle-aged groups). For example, Ancoli-Israel and colleagues[34] studied a random sample of persons older than 65 years of age from the community with home overnight monitoring. The overall prevalence of SDB, defined as an RDI greater than 15 per hour, was approximately the same in whites (30%) and African Americans (32%), but more African Americans had severe SDB than whites, with an RDI greater than 30 (17 vs 8%). Logistic regression showed that African American race as well as male sex, older age, and increased body mass index (BMI) were independent risk factors for an RDI greater than 30. The odds ratio for severe SDB for African Americans was 2.55 compared with whites, even after adjustment for BMI, sex, and age. A case-control study that also included family members of patients with OSA showed that African Americans with SDB tended to be younger than their white counterparts.[35] Among subjects younger than 25 years of age, African Americans had significantly higher RDIs than their white counterparts, even after adjustment for obesity, sex, familial clustering, and proband sampling. A limitation of the data that links race with an increased risk for OSA has a strong potential for confounding by pathophysiologic, cultural, and socioeconomic factors. Minority samples may have a higher prevalence of comorbid medical conditions, including obesity. These factors in conjunction with systemic factors such as economic status or access to or knowledge of health care may all contribute to a higher risk for OSA. Thus, race may, in part, be a surrogate for other predisposing factors, and this heightened risk in minority samples may disappear if confounding is adequately addressed.

In support of such ethnic and population differences, Asian samples seem to have a similar prevalence rate compared with the West (approximately 5%) despite lower levels of obesity (approximately 3%).[36] And for a given age, sex, and BMI, Asians have greater disease severity compared with whites. One explanation for such differences is in craniofacial morphology.[37]

Craniofacial morphology

The critical element in determining the onset of an obstructive apnea or hypopneas or snoring is the structure and functional control of the nasopharyngeal and pharyngeal airway. Both soft tissue and bone structure may play a role in determining the initial, passive set point of the air channel and muscle act and interact to affect airway size and wall stiffness.[38] US and European patients with

obstructive sleep apnea-hypopnea syndrome (OSAHS) tend to have smaller upper airways related to a variety of structural features, including reduction in the length of the mandible, retroposition of the hyoid bone and maxilla, increased tongue volume, elongated soft palate, and increased parapharyngeal fat pads.[39] Many of these features are likely to have an inherited basis and thus play a role in the familial aggregation of OSAHS. These features could contribute to racial/population differences in sleep apnea. In one study, Asians and Caucasians with OSAHS had a more crowded posterior oropharynx (judged by Mallampati Score) and a steeper thyromental plane (line through soft tissue mentum and thyroid prominence) than the controls. Asians tended to have more severe airway narrowing by these measures and more severe OSA after accounting for BMI and neck circumference.[37] Brachycephaly, a head form associated with reduced anterior-posterior cranial dimensions, also seems to be associated with a risk for an AHI of greater than or equal to 15 in whites but not in African Americans.[40] These studies involve limited numbers of subjects, measured in a cross-sectional manner. These issues being raised begin to address predisposing and childhood risk factors for adult disease.

Thus, craniofacial abnormality may be an important risk factor for SDB independent from BMI, and its importance varies among different ethnic groups. Whether such measures are useful in individual assessments or in making decisions about therapy remains an open question. One could imagine that a comprehensive risk assessment in the future would include craniofacial profiling.

Familial/genetic factors

Familial aggregation was first recognized in the 1970s among a family with several affected members.[41] Subsequent studies indicate that first-degree relatives are at increased risk, and this increases with the number of affected family members. This effect is modest and would not drive testing for sleep apnea in unaffected members of the family of a patient. Segregation analysis models suggest that 35% of the variance of OSA severity (ie, AHI) may be attributed to genetic factors that are independent of BMI.[42] Twin studies have also demonstrated that concordance rates for snoring were significantly higher in monozygotic twins than in dizygotic twins.[43,44]

So what is the genetic substrate and what is the likelihood that studies of genetic factors might lead to therapy and individualized therapy in particular? Sleep apnea in adult disease from this perspective is similar to diabetes and hypertension in that they are "complex diseases." A complex disease is one in which no one gene or risk factor is sufficient or required to produce the disease.[45] Each of the risk factors listed earlier are also "complex" traits, and risk factors can operate either alone or in combination to result in the initiation and propagation of apneas over time not only over years but also over the course of a sleep study. In addition to the complexity of those systems affecting obesity, body fat distribution, craniofacial morphology, and self-reported sleepiness, other factors (eg, ventilatory control and sleep cycles/architecture) operating during sleep are in part the result of various genetic and environmental factors that act and interact to produce disease.

PATHOGENESIS

The upper airway in humans has a complex anatomic structure characterized by an elongated posterior pharyngeal space, a 90 degree bend in airflow, and lack of rigidity. This is in part due to its multipurpose function of phonation, swallowing, and breathing. With respect to breathing and the underlying pathogenesis of sleep apnea, the patency of the upper airway depends on a balance of forces: forces that promote airway collapse and opposing forces that maintain upper airway patency. Forces promoting airway collapse include the negative pressure of ventilation and extraluminal positive pressure imposed by factors such as adipose deposition in the soft tissues of the upper airway, fluid, obstructive lesions of the upper airway (eg, tonsillar hypertrophy), and small mandibular size. Upper airway lumen cross-sectional area also decreases somewhat during sleep because of loss of a "tracheal tug"when lung volume falls on assuming the recumbent position.[46]

With inspiration, the negative intraluminal pressure predisposes to collapse of the airway and the activity of the pharyngeal dilator muscles (eg, genioglossus) of the upper airway increases in a phasic manner to oppose these collapsing forces and maintain patency. This activity is usually maintained during sleep. The tensor palli-tine dilator muscles are tonically active and help to provide some upper airway stiffness to resist collapse, however this activity falls during sleep. This, in addition to inadequate compensatory increase in phasic dilator muscle activity predisposes to collapse. Furthermore, vibratory damage to the upper airway musculature from snoring may predispose to worsen (or indeed induce) sleep apnea. Friberg and colleagues[47] studied biopsy samples of the upper airway in control subjects, snorers, and patients with OSA. Biopsy specimens

were taken from other muscles (eg, anterior tibialis) as control sites. All patients had abnormalities in the upper airway biopsy findings, and 71% had morphometric signs, such as fascicular atrophy and grouped atrophy consistent with neurogenic lesions. Only 20% of control individuals had slight changes of these types. The tibialis muscle biopsies were normal in 20 of the 21 patients, indicating that no generalized muscle or neurologic abnormality was present. The degree of abnormality in the upper airway biopsy specimens was correlated with the percentage of time spent in periodic breathing on an overnight monitoring study. The authors concluded that trauma from snoring may contribute to neurogenic lesions of the upper airway, leading to increased collapsibility, and increased risk for SDB.

Recent data suggests that rostral shifts of fluid may also play an important role in the underlying pathogenesis of sleep-disordered breathing. It has previously been demonstrated that fluid displacement from the legs by inflation of antishock trousers increases neck circumference, narrows the pharynx, and increases collapsibility in awake healthy subjects.[48–50] The amount of fluid displaced correlates with overnight increase in neck circumference and frequency of obstructive apnea and hypopneas per hour of sleep. These findings have obvious implications for patients with conditions characterized by dependent fluid retention in the legs such as congestive heart failure and chronic renal failure. Indeed recent data suggests that nocturnal fluid shift may be directly related to the pathogenesis of sleep apnea in these conditions.[51,52]

Finally, in some patients with OSAHS, an unstable respiratory control system appears to promote cycling of respiratory effort. This produces varying levels of upper airway intraluminal negative pressure, and the inadequate compensatory increase in phasic dilator muscle activity predisposes the airway to collapse. Brief microarousals following apneas cause an increase in respiratory effort and accentuate the changes in ventilation. Resulting fluctuations in the level of Pao_2 and $Paco_2$ give feedback to neural respiratory control centers, augmenting and perpetuating respiratory cycling. Thus, upper airway patency is determined by the interaction of a number of structural and functional factors. OSAHS patients appear to have varying degrees of anatomic narrowing combined with reduced neuromuscular dilatory compensatory mechanisms during sleep. Ventilatory controller instability may also contribute to a propensity for periodic breathing and partial or complete airway closure in some patients.

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