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History and epidemiology of sleep-related breathing disorders

Robert D. Vorona, MD[a,b,*], J. Catesby Ware, PhD[c,d]

[a]*Division of Sleep Medicine, Department of Internal Medicine, Eastern Virginia Medical School, USA*
[b]*Sleep Disorders Center, Sentara Norfolk General Hospital, 600 Gresham Drive, Norfolk, VA 23507, USA*
[c]*Departments of Internal Medicine and Psychiatry, and Division of Sleep Medicine, Eastern Virginia Medical School, USA*
[d]*Sleep Disorders Center, Sentara Norfolk General Hospital, 600 Gresham Drive, Norfolk, VA 23507, USA*

By the late twentieth century, the medical community recognized that snoring and daytime sleepiness were signs of obstructive sleep apnea syndrome (OSAS). Parts of the sleep apnea syndrome complex were, however, known many years earlier by an insightful few. The 1965 polysomnographic study that described obstructive, central, and mixed sleep apnea events during sleep was the beginning of the objective study of what we now recognize as sleep apnea syndrome [1]. Less well known are some earlier descriptions of the problem. Symptoms of heavy snoring and excessive daytime sleepiness were reported in a patient with acromegaly in 1896 [2]. Lavie [3] identified what may have been the first reported case of sleep apnea in a patient who had components of both obstructive and central apnea events [4]. Lavie also described two other 1889 cases with daytime sleepiness and failed respiratory attempts during sleep [5,6]. The description of these patients leaves no doubt that the phenomenon of obstructive sleep apnea, although unnamed and not understood, was recognized well before the advent of polysomnography.

C.S. Burwell is often credited with first using the name Pickwickian syndrome when describing an obese patient with respiratory acidosis, heart failure, and sleepiness [7]. The term Pickwickian had actually been used, however, several times earlier to describe sleepy obese patients including the use by William Osler. In *The Principles and Practice of Medicine*, Osler wrote in his chapter on obesity, "A remarkable phenomenon associated with excessive fat in young persons is an uncontrollable tendency to sleep like the fat boy in Pickwick" [8]. But because of the lack of understanding of the various conditions that could cause sleepiness and the absence of techniques to study sleep, the term Pickwickian described a heterogeneous group of patients with little regard to specific etiology.

After Burwell's work, the term Pickwickian typically indicated obesity accompanied by somnolence and lethargy, hypoventilation, hypoxia, and secondary polycythemia, but not necessarily repetitive sleep apnea events. By including hypoventilation and polycythemia as part of the syndrome, most of the sleep apnea patients seen in sleep disorder centers today do not have Pickwickian syndrome. The development of basic polysomnographic tools and procedures in the 1950s and 1960s provided a method to study causes of daytime sleepiness. Polysomnography led to the understanding that daytime sleepiness often originated from intrinsic sleep disturbances in the patients' sleep. Prior to polysomnography, only secondary characteristics of OSAS were recognized and treated.

The growth spurt of the 1970s and 1980s

Perhaps the number of publications in the field best reflects the explosion in interest in OSAS. Publications addressing sleep apnea in some form

* Corresponding author.
E-mail address: voronard@evms.edu (R.D. Vorona).

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increased by nearly tenfold in the 1980s when compared with the 1970s (Fig. 1). At the same time, the reports on Pickwickian syndrome decreased. This decrease in part was from recognition of the heterogeneous population that the term Pickwickian encompassed.

An early champion of OSAS in the United States was a young Frenchman, Christian Guilleminault, at Stanford University. Despite a focus on insomnia and narcolepsy by the small community of those studying sleep and sleep disorders in the United States, Guilleminault forged ahead with his interest in sleep apnea, motivated by the idea that differences in the control of vital functions during sleep contributed to a number of medical disorders. Returning to Europe where there was considerable interest in the Pickwickian syndrome, Guilleminault recorded several hundred patients at a sleep medicine clinic at La Salpetriere Hospital in Paris. He realized that breathing irregularities and apnea occurred in a variety of patients, not necessarily obese ones (personal communications, March 2001). Later after his return to Stanford University, Guilleminault and associates helped to demonstrate that OSAS caused excessive daytime sleepiness more often than narcolepsy. They developed an objective definition of OSAS as five events per hour of sleep lasting at least 10 seconds each [9]. They extended the investigation of apnea to children [10–13]. Early on, they also hypothesized that sleep apnea might be related to sudden infant death syndrome [14]. The recognition of children and infants as possible at-risk populations along with his other work considerably increased the interest in and study of sleep apnea.

Researchers employed a variety of techniques to better understand what occurs during sleep apnea events. Lateral imaging of the upper airway using Xerography in a small number of severe OSAS patients revealed no specific pathology when awake but a clear collapse of airway space at the base of the tongue during sleep [15]. Compared with controls, fluoroscopy and computed tomography indicated a more narrow section of the airway in patients in the region posterior to the soft palate [16]. Direct observation with fiberoptic endoscopy of the sudden dramatic closure of the airway suggested the possibility of an active process; an alternative explanation was that muscle relaxation and a negative pharyngeal airway pressure accounted for the rapid airway collapse and apnea events [17,18].

In the late 1970s, the recognition that OSAS can occur in families added another dimension to the

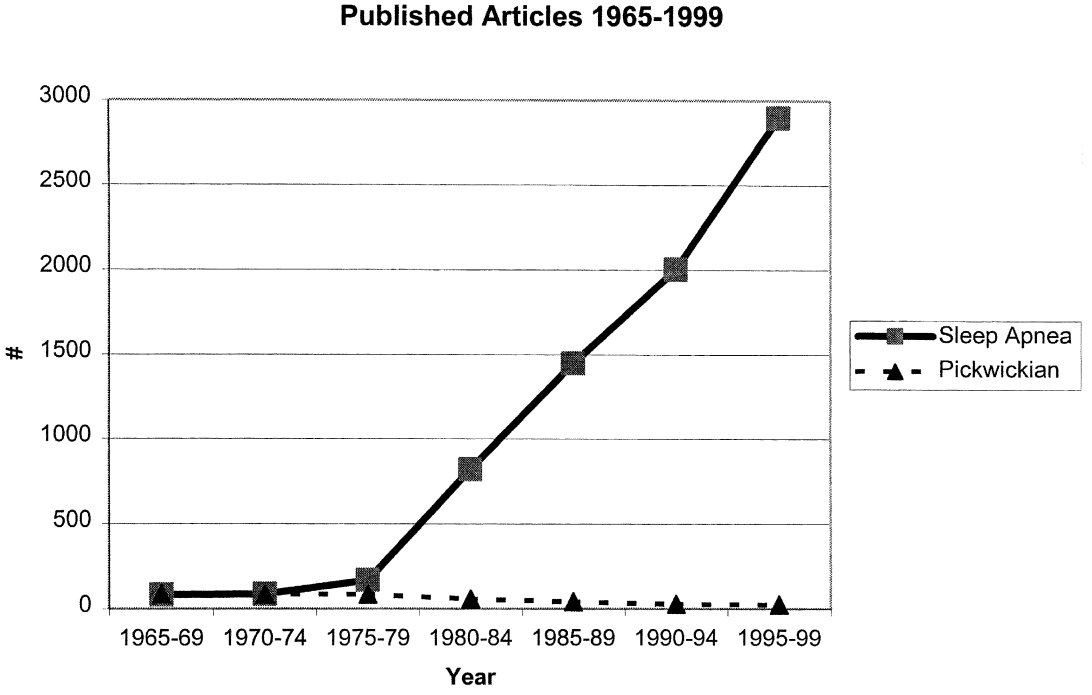

Fig. 1. The number of publications listed in PubMed (National Library of Medicine, Rockville Pike, MD) generated by the search terms "sleep apnea" and "Pickwickian" for 5-year blocks, 1965–1999.

problem and further emphasized the complexity without clarifying the etiology [19,20]. For example, the apnea-potentiating trait of a small or retrognathic mandible can have both genetic and environmental contributing factors. Analysis of lateral cephalometric radiographs did help identify those with mandibular deficiencies and a shallow posterior airway space (PAS), although no imaging technique or other test when patients were awake was able to identify all sleep apnea cases [21].

Treatment

Surgery

The difficulty in treating OSAS patients tempered the excitement of recognizing the problem of OSAS as a primary cause of excessive daytime sleepiness. The standard treatment of tracheostomy was traumatic but successful in relieving OSAS [22,23]. A tracheostomy with its accompanying improvement in areas other than daytime sleepiness gave hints of the complexity of the sleep apnea problem. For example, this surgical procedure not only relieved the apnea events but also reduced cardiac arrhythmias [24] and improved the ventilatory response to CO_2 [25]. This helped foster the realization that intermittent obstruction during sleep had pervasive effects on neurological, cardiac, and respiratory functioning. It also helped to emphasize the importance of normal sleep and raised the problematic question of "How many apnea events during sleep are too many?"

Even with the threat of a tracheostomy, most obese apnea patients could not lose weight by dieting. Treating OSAS patients with a weight loss prescription, although often beneficial when a patient could lose weight [26], succeeded only in a minority of patients. In addition, there was a high recidivism rate for those who initially lost weight. Therefore, bariatric surgery to induce weight loss and treat obstructive sleep apnea was introduced in the late 1970s [27] and continues to be used successfully in selected cases [28].

Following the recognition that retrognathia could contribute to apnea events, mandibular surgery was used successfully to treat retrognathic OSAS patients [29,30]. In addition, mandibular surgery was successfully used to treat OSAS in an obese patient [31].

The treatment with the greatest impact on OSAS, although unfortunately not the greatest success rate, was that of the uvulopalatopharyngoplasty (UPPP), [32]. The UPPP was a less drastic but less effective procedure than tracheostomy. Because a tracheostomy was used primarily for end-stage OSAS patients, the development of a surgical technique with the potential of treating less severe cases was welcomed. The UPPP allowed some patients to avoid a tracheostomy. In addition, the UPPP fit well into the conceptualization of the etiology of OSAS. Specific upper airway obstructions, for example, large tonsils and adenoids [33,34], nasal obstruction [35], and supraglottic edema [36], were understood to cause the obstruction and apnea. Evidence suggested, however, that other factors also played a role.

A second UPPP benefit was its high failure rate. Because the UPPP was far from 100% successful and was not free of morbidity and mortality, documentation of both the presence and severity of OSAS was necessary before performing an UPPP. Therefore, the availability of the UPPP as a treatment option resulted in the consistent polysomnographic study of a large number of patients with symptoms of OSAS. These clinical studies raised the awareness of the prevalence of OSAS and allowed the development of an appreciation of the range of severities of OSAS (from 0 to 100+ events per hour of sleep). This quantification of the frequency of apnea events also provided a baseline for comparing different techniques for treating OSAS patients. Pre- and postoperative polysomnographic studies of OSAS patients also led to an early awareness that subjective reporting of improvement by the patient often was not congruent with polysomnographic findings [37]. The approximate 50% success of the UPPP [38], recognized early on from those doing postsurgical sleep studies, spurred the search for other treatments. Treatment failures also reinforced the idea that for some OSAS patients, more than a mechanical obstruction of the upper airway was involved. The differences between men and women [39], the effects of aging [40], and the effects of sleep stage on apnea frequency [41] indicated that OSAS involved both physiological and pathophysiological (as well as anatomical) factors. A number of nonanatomical factors may play a role in OSAS. The tone of the pharyngeal dilating muscles, pharyngeal extramural pressure, and pharyngeal compliance all may contribute to OSAS [42], and treatment without regard to the specific etiology is likely to have a significant failure rate.

Oral appliances

Despite the logic of pulling the mandible forward to open the airway, the sleep community greeted the first reports of using an oral appliance to treat OSAS with considerable skepticism. As is usually the case

for new procedures, the early reports were not controlled trials [43,44]. But persistence on the part of the dental community, more rigorous studies showing polysomnographic efficacy (rather than self report), and the developing need to treat patients intolerant or nonresponsive to other treatments gained the oral appliances wider use and the opportunity to improve and become an important treatment option.

Pharmacological treatment

Early pharmacological treatment attempts included use of medroxyprogesterone [45,46] and even strychnine in a "Don't do this at home study" [47]. The motivation to use strychnine was to correct upper airway hypotonicity. More recently, researchers have attempted to stimulate electrically the upper airway musculature [48]. One of the problems inherent in this technique is the arousal from sleep produced by the electrical stimulation. Thus, it is difficult to separate the specific effects of stimulating the muscle from the more general effects of an arousal from sleep.

One of the successful early pharmacological treatments was the use of protriptyline [49,50]. Although protriptyline, an alerting tricyclic antidepressant, may have helped because of improved alertness and mood, it also reduced apnea events possibly by increasing muscle tone. One of the most pronounced effects of protriptyline is the suppression of REM sleep, the sleep stage accompanied by loss of antigravity muscle tone. The stage of REM sleep can have the longest apnea events with the most severe oxygen desaturations. To what degree REM sleep and apnea would return after long-term use is unknown. One study indicated that apnea returns after a year, but patients continued to report feeling better and had slightly higher O2 saturation baseline [51].

Continuous positive airway pressure

The technique of using continuous positive airway pressure (CPAP) in the upper airway essentially became the nonsurgical tracheostomy [52] and transformed the field of sleep disorders medicine by providing a low morbidity treatment with a high success rate. If used by the patient, it keeps the upper airway patent. A significant number of patients ($>30\%$), however, do not continue to use CPAP over the long term [53]. Practical problems of administering positive air pressure to the upper airway comfortably were difficult to overcome. But FDA approval in the United States in the mid-1980s and product commercialization led to continued refinements in mask fit, material, and humidification. Once the most common treatments for OSAS was nonsurgical; patients with milder symptoms of OSAS were evaluated and treated. This led to an explosion in the number of sleep disorder facilities and patients studied. This growth also reinforced the need for a credentialing body for clinicians (American Board of Sleep Medicine) and an accreditation body for sleep disorders centers (American Academy of Sleep Medicine). The availability of CPAP allowed for a change in location to nonhospital based centers. Treating less severe patients also opened the possibility for the investigation and use of portable diagnostic equipment and self-titrating CPAP devices. Thus, moving some of the diagnostic and treatment procedures to the home is now under investigation.

Epidemiology of OSAS

The problem of OSAS spans all age groups and both sexes and is found throughout the globe. Obesity is often but not always a critical determinant of OSAS. An enlarging body of work reveals the cardiovascular and cerebrovascular links and consequences of OSAS.

Classically, OSAS was thought to be a syndrome of the middle-aged. All age groups may have apneic events during sleep, however. In over 1000 healthy full-term infants who ranged in age from 2 to 28 weeks, the absolute numbers of obstructive or mixed apneas in these infants were quite low [54]. Of interest, males between 8 and 11 weeks of age were more apt to have obstructive apneic events and more events per hour than females. The apnea events tended to decline in length with age. Apneas do not always connote disease in infants. Central apneas (apneas without respiratory effort) may occur in normal infants, and even protracted central apneas with desaturation may not be of import [55,56].

Older children are not exempt from OSAS. Redline and associates found 1.6% of their children or teens (2–18 years old) had sleep disordered breathing (SDB) as defined by a respiratory disturbance index of greater than or equal to 10 events per hour [57]. Between the ages of 2 and 8 years, children are most apt to have OSAS [58]. The tonsils and adenoids are of great importance in putting these children at risk for sleep disordered breathing events. In contrast with adults in whom tonsillectomy and adenoidectomy are rarely curative for OSAS, in children the same operative procedure is often but not always effective [59]. Frank anatomic abnormalities in children are not, however, the only reason for obstruction of the

upper airway [58]. Neuromuscular function alteration can also be of import. Cerebral palsy and muscular dystrophy put children at risk for OSAS [60,61]. Skeletal abnormalities also put children at risk for sleep-disordered breathing [59]. Children with OSAS may like their adult counterparts be obese. Redline et al found what they described as a moderate linkage with an odds ratio for obesity and SDB of 4.6 [57]. They also linked respiratory disease of both the upper and lower tract. In contrast with data in adults, they did not, however, find a clear relationship between sex and SDB in children.

Work from Spain has investigated sleep disordered breathing in children 12–16 years old. This study of 101 teens, buttressed by the use of limited polysomnography, found that 29% snored and 17.8% had a respiratory disturbance index of greater than or equal to 10 [62]. Only 1.9%, however, also had symptoms indicative of the diagnosis of OSAS. The authors noted that this frequency was akin to that found in younger children.

Middle school children with poorer performance are more likely to snore [63]. It appears that even medical students who snore are more likely to fail examinations [64]. Potential complications of untreated OSAS in children include failure to thrive, pulmonary hypertension, cor pulmonale, and arterial hypertension [13,59,65]. As OSAS usually has been associated with older patients, the clinician may not be as quick to think of OSAS in the child as in the adult. Nevertheless, the potential complications, though serious, are remediable [59,66] and therefore warrant that clinicians be cognizant of OSAS in children.

OSAS, with its complications including daytime sleepiness and difficulties with memory and concentration, obviously can impair school performance. Teens already are at risk for difficulties functioning in the morning because of a tendency to delayed sleep phase (they tend to go to sleep later and wake up later), coupled with high school hours that prod them to start the day early. Concomitant OSAS could only exacerbate this situation and hence deserves consideration. In addition, sleep loss suffered by teens may exacerbate existing sleep apnea [67].

A study at the Chinese University of Hong Kong used a questionnaire to study some 1910 students followed by limited polysomnographic recordings in some [68]. They found by questionnaire that some 25.7% had snoring. In the small subgroup who underwent a limited sleep study, only 2.3% had a respiratory disturbance index of greater than 5. Hence, once again the prevalence of OSAS was relatively low.

Young et al performed a critical study to assess the impact of sleep disordered breathing in middle-aged adults [69]. In this study of middle-aged Wisconsin state employees aged 30–60 years, some 9% of women and 24% of men had a Respiratory Disturbance Index (RDI) of greater than or equal to 5 per hour. When coupled with complaints of excessive daytime sleepiness, 2% of women and 4% of men manifested OSAS. This study is perhaps the best measure of the prevalence of OSAS in the US adult population to date.

A study in Spain examining the prevalence of SDB and OSAS in a 50–70-year-old population found that 29% of the patients (28% men, 30% women) had an RDI of greater than or equal to 5 per hour. Although there was no sex difference for number of sleep disordered breathing events, only men were symptomatic, and therefore only the men were diagnosed with OSAS as defined both by sleep disordered breathing and symptoms [70]. Another study used oxygen desaturation events of greater than or equal to 4% as a surrogate to screen for OSAS in a 40–64-year-old group; the authors projected from their sample that an apnea occurrence of more than or equal to 15 per hour occurred in 20.3% of the men and 7.6% of the women [71].

Some data suggest even higher rates of sleep disordered breathing in the elderly. In one study investigating the frequency of respiratory disturbances in those greater than or equal to 65 years of age, 24% of their sample had greater than or equal to 5 apneas per hour, and 62% had an RDI greater than or equal to 10 per hour [72]. Over the next 8.5 years, however, there was no progression in sleep related respiratory events [73].

The importance of these respiratory events in the elderly is controversial. For example, Ancoli-Israel et al in 1989 showed that elderly women with sleep disordered breathing had an increased mortality [74]. Mant et al [75] in a study of the elderly did not find such increased mortality associated with OSAS as defined by an RDI greater than or equal to 15. Additionally, when Phillips et al. looked at elderly subjects who were ostensibly healthy, those with an RDI over or equal to 5 per hour showed no alteration in daytime performance [76].

Early evidence indicated that OSAS was overwhelmingly a male phenomenon [39]. The more recent information above reveals, however, the male to female ratio more closely approximates 2–3: 1. Bixler et al [40] showed that 3.9% of men and 1.2% of women had OSAS. But premenopausal women and postmenopausal women on hormone replacement therapy had much lower prevalences (0.6% and 0.5%,

respectively) than postmenopausal women (2.7%). They therefore postulated that the premenopausal status and hormone replacement therapy were protective. Those apneic females who were premenopausal or postmenopausal and taking hormones were all obese, thus defining the essential role of obesity in these subgroups. In addition, Pickett et al found that the combination of estrogens and progesterone decreased respiratory events in nine women postovariectomy and hysterectomy [77].

In a large population of Italian women aged 40–65 years, 19.7% "always snored" and 10.7% had a respiratory disturbance index from 5 to 9 per hour [78]. Nearly 8% had more severe SDB with a respiratory index between 10 and 19. Interestingly, in contrast with Bixler et al, this study could not correlate menopausal status and sleep disordered breathing. In a study comparing Body Mass Index (BMI) matched men and women presenting to a sleep disorders center, men had significantly more apnea in the young and middle-aged groups but were similar to women in the older age group, presumably when the women were postmenopausal [79].

Sleep disturbances during pregnancy have been frequently noted with snoring and nocturnal choking among the complaints possibly linked to OSAS. Of 127 pregnant women in an outpatient setting, it was determined that 29.8% snored during pregnancy [80]. The majority of these women did not snore prior to pregnancy. By the last quarter of pregnancy, approximately 31% reported awakening choking, a symptom the authors attempted to relate to OSAS. This information achieves greater import when one reviews the data from Franklin et al [81]. In their study of 502 pregnant women, there was a 23% incidence of nightly snoring in the last week of pregnancy. Those who snored were more than two times as likely to develop hypertension during pregnancy and preeclampsia, and to deliver children with growth retardation. A low Apgar score also occurred more frequently in children born to mothers who snored habitually. Treating preeclamptic women with CPAP demonstrated improved upper airway flow mechanics and blood pressure control [82].

Racial differences also occur in OSAS patients. Much of the above information is related to Caucasians from North America and Western Europe. Kripke et al [71] found that 16.3% of the Hispanics and other minority patients had 20 or more events per hour. This was in contrast with only 4.9% of their Caucasian patients. In children, Redline et al [57] showed that African-Americans were at increased risk for OSAS. Elderly African-Americans appear to have twice the risk of severe sleep disordered breathing when compared with Caucasians [83]. Brachycephaly appears to put Caucasians at risk, whereas soft tissue abnormalities may be of more importance in African Americans [84].

Differences in OSAS between Caucasians and Far East Asians also occur. Ip et al [85] reported that 4.1% of middle-aged Chinese men have OSAS (roughly comparable with Young's data). Obesity, however, was a less important exacerbating factor for OSAS in Chinese than in Caucasians as found by Young. Caucasian apneics are more obese than Asian apneics [86]. If matched for BMI, the Asians with OSAS had more severe disease than Caucasians with OSAS. The Far East Asians had "a significantly shorter anterior cranial base and more acute cranial base flexure"(58). Caucasians and Asians with OSAS also differed on some soft tissue measures (eg, PAS and mandibular plane to hyoid distances). Liu et al compared cephalometrics in Chinese and Caucasians with OSAS and found skeletal differences that they described as "steeper and shorter anterior cranial bases" [87]. Many but not all of the soft tissue structures were similar between Chinese and Caucasians. These differences may have import in planning either treatment approaches with surgery or mandibular repositioning devices. Further, OSAS should not be approached as a monolithic syndrome in these different groups.

Although anatomic differences may exist between races with OSAS, obesity is prevalent in its role as a risk factor. Some 60–70% of patients with OSAS are obese [88]. Alternatively, more than 50% of obese patients with a BMI of greater than 40 kg/m^2 have OSAS [89]. Obesity, although a risk factor for SDB in children and adults, may not be as important in children [57]. Young's study of the middle-aged noted, "An increase of 1 SD in any measure of body habitus was related to a threefold increase in the risk of an apnea-hypopnea score of 5 or higher" [69]. Grunstein et al showed that increasing central obesity correlated with worsened sleep apnea [90]. As would be expected, weight loss does reduce OSAS. In a study of 690 patients, a 10% weight gain lead to a 32% worsening in RDI and a 10% weight loss lead to a 26% improvement [91]. Of interest, obesity may have differential effects by gender. Upper body obesity worsened OSAS in men more than in women [92]. Although there is controversy, some evidence suggests that BMI may be the best predictor of RDI in women, whereas neck circumference may be the best predictor in men [89].

In addition to the above demographics, the oral surgeon interested in OSAS must appreciate the importance of family history. Pillar and Lavie [93]

studied the adult children of 45 patients diagnosed with OSAS. Remarkably, 47% of these children had OSAS. They also found that an additional 21.9% of the remaining patients studied had simple snoring.

Finally, no discussion of the epidemiology of OSAS would be complete without discussing some of the recent important information concerning mortality and cardiovascular and cerebrovascular complications. He et al [94] noted that an apnea index of greater than 20 per hour was associated with 0.63 eight-year survival. This is compared with 0.96 eight-year survival in those patients with an index less than 20 per hour. As opposed to tracheostomy and CPAP, uvulopalatopharyngoplasty had no impact in decreasing this increased mortality rate. Interestingly, there was a large range in causes of death, a number of which were not obviously related to OSAS. Lavie et al [95] also found an increased death rate in individuals with OSAS. This increased risk of death was in those in the fourth and fifth decades of life. They postulated that the major risk factor for death was hypertension.

Recent data clearly associate OSAS and hypertension. The Sleep Heart Health Study evaluated sleep disordered breathing and hypertension in 6132 patients who were either middle-aged or elderly [96]. Despite aggressive attempts at controlling for confounding factors, a moderate relationship occurred between SDB and hypertension. This relationship between SDB and hypertension was dose-dependent (although not linear), thus giving further credence to the relationship. Peppard et al [97] in the Wisconsin Sleep Cohort also discovered a dose-dependent relationship between sleep disordered breathing and blood pressure level four years later. A large study by Ohayon et al [98] comprising 13,057 subjects also linked OSAS and hypertension. An earlier study by Carlson et al linked OSAS and hypertension as well as age and BMI [99]. These associations between OSAS and hypertension are not solely limited to the adult population. Marcus et al [100] have compared blood pressure readings in children with OSAS and children with primary snoring. Diastolic blood pressure was more elevated in the group with OSAS. Conversely, the presence of hypertension in a patient should make the clinician think of OSAS. Worsnop et al [101] found that 34% of untreated and 38% of treated hypertensive patients had OSAS.

Hypertension is a major risk factor for coronary heart disease and cerebrovascular disease. OSAS and these two major killers have been investigated. Hung et al [102] used polysomnography to study patients shortly postmyocardial infarction but outside the hospital. OSAS was associated with an increased risk of coronary heart disease. The Sleep Heart Health Study revealed what the authors called "modest to moderate effects of sleep-disordered breathing on heterogeneous manifestations of CVD" [103]. They found a more marked relationship for OSAS and congestive heart failure than coronary heart disease. One daunting aspect of the study was that seemingly rather trivial numbers of respiratory disturbances seemed to put one at risk for cardiovascular consequences. A study in Sweden prospectively tracked patients with coronary heart disease and OSAS and found that untreated OSAS was linked with an increased death rate from cardiovascular causes [104].

OSAS and stroke have also been associated in the sleep literature. The Sleep Heart Health Study not only linked OSAS and heart disease but also linked OSAS with stroke. In fact, the association with stroke in this large study was stronger than with coronary heart disease. A study of transient ischemic attack (TIA) and stroke with OSAS found a high frequency of OSAS in both patients with TIA and stroke [105]. The authors pointed out the interesting fact that TIA also was clearly linked to OSAS, making it less likely that the OSAS was a consequence of the cerebral event.

A number of reasons have been postulated for the increased risk of cardiovascular and cerebrovascular events. Several investigators have demonstrated increased sympathetic activity in OSAS patients. Somers et al [106] showed that patients with OSAS had increased sympathetic nervous system activity both awake and asleep. In contrast with the norm, these patients showed elevations in blood pressure during sleep. When CPAP was applied to these patients, both sympathetic activity and blood pressure were reduced. Hedner et al [107] interrogated the response of sympathetic activity in OSAS treated by CPAP by measuring norepinephrine, vanilmandelic acid, and metanephrines. They found decreases in catecholamines but change neither in cardiac structure nor in blood pressure.

Directions in the twenty first century

In addition to refinements in surgical techniques for treating OSAS, we expect that there will be considerable advances in the understanding of sleepiness and other OSAS symptomatology. Although some details are missing, we now know that repeated disturbances in respiration during sleep play a major role in the typical symptoms of OSAS. In addition, we are beginning to understand how sleep arousals,

hypoxic and hypercapnic insults, and accompanying autonomic liability contribute to OSAS symptomology. These events may not account, however, for the complete picture. Obesity itself may contribute to the sleepiness [89,108]. The question "Are obese apnea patients of similar-frequency apnea more sleepy than less heavy patients?" is still one that needs to be clearly answered along with the question, "Why are all sleep apnea patients not sleepy?" [109]. Defects in the recently recognized hypocretin neurotransmitter system appear to be the key pathology in narcolepsy [110]. The hypocretin system that also appears to be involved with the regulation of normal sleep-wake behaviors and energy metabolism [111] probably contributes to the symptomatology in OSAS. Learning more about the underlying pathophysiology will allow us to apply our treatment armamentarium better and develop new and improved treatment methods.

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