

Centennial Review

Advances in Sleep-disordered Breathing

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Since the original clarification of the obstructive nature of obstructive sleep apnea (OSA) in 1965, much has been learned about the disorder. It is a condition with a high prevalence with obesity as a major risk factor. It aggregates in families, a relationship that is not simply explained by obesity. Premenopausal women are relatively protected from the disorder because OSA is uncommon in this group. Its prevalence in women rises after menopause. Although OSA is a risk factor for excessive sleepiness, there is developing evidence that it is also a risk factor for hypertension, acute cardiovascular events, and insulin resistance. The first line of therapy is nasal continuous positive airway pressure. Data as to the efficacy of continuous positive airway pressure in severe OSA have come from randomized, placebo-controlled clinical trials with the endpoints being sleepiness, quality of life, and 24-h ambulatory blood pressure. Data are currently less convincing for treatment outcomes in mild to moderate OSA, and new clinical trials to assess outcomes in this group are underway. Thus, even though this field only began toward the end of the first century of the American Thoracic Society, substantial progress has been made, and OSA has increasingly emerged as a major public health concern.

Keywords: hypertension; metabolic syndrome; obesity; obstructive sleep apnea; sleep

Much of what we have learned about sleep-disordered breathing has occurred in the very recent past. The first description of obstructive sleep apnea (OSA) that recognized that intermittent upper airway obstruction was the major pathogenetic mechanism was in 1965 (1). (For a comprehensive review of the history of development of knowledge about sleep-disordered breathing, see Reference 2.) The development of this area of medicine has been challenging since there was initially considerable skepticism, including a letter to the *Lancet* that suggested that OSA was a rarity (3). Much of what we have learned about sleep-disordered breathing has occurred in the last 20 years. The progress has been remarkable. It is arguable that the seminal work of Sullivan and colleagues (4), describing nasal continuous positive airway pressure (CPAP) as a therapy, drove development of this area, because CPAP provided a low-risk effective therapy, albeit with adherence issues (5). Also, the realization, based on population-based studies with robust epidemiologic methods, that OSA, far from being rare, was extremely common, as was the association with obesity, was also critical (6), because OSA was then recognized as a major public health issue (7). This

article reviews development of new knowledge in several aspects of sleep-disordered breathing but does not cite all relevant articles due to space constraints. It focuses primarily on the most common disorder—that is, OSA—but also briefly discusses other types of sleep-disordered breathing.

HISTORICAL PERSPECTIVE

That sleep-disordered breathing was not recognized earlier as a major, common clinical disorder is remarkable, as pointed out by Lavie (2). Initial descriptions of sleep-related breathing disorders were made by clinical observation, and first described the pattern of breathing that we now call Cheyne-Stokes' respiration after the physicians who described it (8, 9). (It turns out that it was described earlier by Hunter [see Reference 2]; for current definition of Cheyne-Stokes' respiration, see Reference 10.)

In the late 19th century, there were also clinical descriptions of cases of obesity with extreme excessive sleepiness (see Reference 2). These astute physicians recognized that these cases were similar to the description of the fat boy in the *Pickwick Papers* (first published in 1835). This led, in time, to use of the term "Pickwickian syndrome" to describe the combination of obesity and marked excessive sleepiness. Recently, however, the term Pickwickian syndrome has come to have a more specific meaning and is restricted to those obese individuals who also have hypoventilation during wakefulness, as described in the classic report of Burwell and colleagues (11).

Physiologic recordings of subjects with Pickwickian features were done in the early 1960s and individuals such as Gerardy and colleagues (12) and Drachman and Gummit (13) made important contributions. They recognized that with sleep came periodic cessation of respiration associated with marked fluctuations in heart rate. They did not, however, recognize that the reason for the cessation of respiration was obstruction of the upper airway. This was accomplished by more careful assessment of airflow at the nose and mouth, as well as of thoracic movement by Gastaut and coworkers (1).

Thus, obstructive apnea was recognized. The number of investigators of this new disorder at this time was small in number. Investigators from Europe and the United States were brought together at an important conference organized by Lugaresi and colleagues from the Bologna (Italy) group. The conference was entitled "Hypersomnia and Periodic Breathing" and was held in Rimini in 1972 (proceedings are published in the *Bulletin de Physiopathologie Respiratoire*). This served to further catalyze research in this area. At this time, there was also description of the first definitive treatment—that is, tracheostomy—in two individual case reports (14, 15).

Table 1 gives a historical perspective of key contributions in this area.

EPIDEMIOLOGY OF OSA

Over the 1990s, a number of studies with robust designs from an epidemiologic standpoint examined the prevalence of

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TABLE 1. MILESTONES IN DEVELOPMENT OF KNOWLEDGE ABOUT OBSTRUCTIVE SLEEP APNEA

1818, 1854	Description by Cheyne (1818) (8) and Stokes (1854) (9) of Cheyne-Stokes' respiration
1956	Description of alveolar hypoventilation in obesity (Pickwickian syndrome) (11)
1960, 1962	Periodic cessation of respiration recognized in patients with Pickwickian features (12, 13)
1965	Recognition that cessation of respiration during sleep was due to airway obstruction (i.e., OSA) (1)
1971, 1974	Case reports describing effectiveness of tracheostomy in patients with OSA (14, 15)
1976	Case series of pediatric sleep apnea (94)
1978	Description of unifying concept re pathogenesis of OSA (40)
1981	Description of nasal CPAP (4); description of specific surgery for OSA (90)
1983	Identification of CO ₂ -dependent apnea threshold during sleep (102)
1988	Hypopneas have same consequences as apneas (17)
1992	Identification of neuromuscular compensation (39); intermittent cyclic hypoxia leads to hypertension (47)
1993	Study with robust epidemiologic methods reveals high prevalence of OSA (6)
1995	Family aggregation shown: Cleveland Family Study (30), in Israel (32), and in relatively nonobese Scots (31)
1997	Induced obstructive apneas in dogs leads to hypertension (71)
1998	Schoolchildren with poor academic performance have high prevalence of OSA. School performance improves after surgical treatment of OSA (97)
1999	Introduction of sham CPAP in clinical trials. Efficacy in severe sleep apnea syndrome identified (107)
2002	Improvement with nasal CPAP in blood pressure demonstrated in randomized, placebo-controlled trial (67)

Definition of abbreviations: CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea.

sleep-disordered breathing. These studies built on earlier studies of prevalence, one of which showed how a two-stage sampling strategy could be used to more accurately estimate prevalence (16). Hypopneas (decrements in breathing) were also shown to have the same clinical consequences as apnea (17). Disease severity was assessed by the apnea-hypopnea index (AHI; i.e., number of apneas plus hypopneas per hour of sleep). The largest studies in middle-aged adults were done in state employees in Wisconsin (the Wisconsin Sleep Cohort) (6); in the town of Busselton, Australia (18); and in Dauphin and Lebanon counties in Pennsylvania (19, 20). The studies give similar estimates of prevalence of the disorder at different degrees of severity (see Table 2 for data on males; see Table 3 for data on females). Prevalence increases with age in some studies (6, 19), but not all (18), and epidemiologic studies targeted to the elderly show even higher prevalence rates to those given in Tables 2 and 3 (21). Prevalence is higher in men than women but the male-to-female ratio is only of the order of 2–3:1 (compare Tables 2 and 3). Prevalence is particularly low in premenopausal women and increases after menopause (see Table 3) (20).

These data are for subjects with different degrees of sleep-disordered breathing (i.e., without considering whether they have complaints of excessive sleepiness). When the latter is added as part of the definition (i.e., the OSA syndrome; for definition, see Reference 10), the prevalence numbers drop dramatically (see Tables 2 and 3). Thus, sleepiness is not an inevitable consequence of OSA. By consensus (10), the following terms are used: mild sleep apnea, AHI > 5 and ≤ 15 episodes/hour; moderate sleep apnea, AHI > 15 and ≤ 30 episodes/hour; and

severe sleep apnea, AHI > 30 episodes/hour. These terms are used throughout this article.

RISK FACTORS FOR SLEEP-DISORDERED BREATHING

There are a number of risk factors for obstructive sleep apnea (see Table 4) (for review, see Reference 22). In the middle-aged adult population, the most important risk factor is obesity, and even moderate increases in weight increase the risk of OSA (6). Obesity increases the rate of progression of disease, and weight gain further accelerates disease progression (23). In the elderly, however, OSA is not as closely associated with obesity (24). In children, the major risk factor for OSA is adenoidal-tonsillar hypertrophy (25). OSA is common in patients with craniofacial disorders; however, even in individuals without a specific disorder, alterations in craniofacial structure confer risk for OSA. This is particularly significant in patients of Asian descent (26).

Women who are premenopausal are relatively protected from OSA even in the presence of other risk factors (Table 4). There is, however, a higher prevalence of sleep apnea in women with the polycystic ovarian syndrome (27). Cross-sectional prevalence studies show a fourfold higher prevalence of at least moderate OSA in postmenopausal women as compared with premenopausal women (see Table 3) (20), an effect that is not simply explained by age (28). In postmenopausal women taking hormone replacement therapy, the prevalence of OSA is similar to premenopausal women (see Table 3) (20), although given the increased risk of cardiovascular (CV) disease and uterine and breast cancer with hormone replacement therapy (29), this is currently not a viable therapy for postmenopausal women with

TABLE 2. PREVALENCE OF SLEEP-DISORDERED BREATHING AT DIFFERENT SEVERITIES AND SLEEP APNEA SYNDROME (RIGHT COLUMN) IN DIFFERENT LARGE-POPULATION STUDIES IN MIDDLE-AGED MEN

Name/Citation of Study	Prevalence of AHI ≥ 5/h (%)	Prevalence of AHI ≥ 15/h or 20/h (%)	Prevalence of AHI > 5/h and Symptoms of Sleepiness (%)
Young and colleagues (6) (n = 602; 353 M) studied in lab	24.0	9.1*	4.0
Bearpark and colleagues (18) (n = 486; all M); 294 studied in lab	25.9	3.4†	3.1
Bixler and colleagues (19) 4,364 (all M); 741 studied in lab	17.0	5.6†	3.3

Definition of abbreviations: AHI = apnea-hypopnea index; M = men.

* AHI ≥ 15 episodes/h (reported by Young and colleagues [6]).

† AHI ≥ 20 episodes/h (reported by Bearpark and colleagues [18] and Bixler and colleagues [19]).

TABLE 3. PREVALENCE OF SLEEP APNEA AND SLEEP APNEA SYNDROME IN WOMEN AND EFFECTS OF MENOPAUSE

Study	Prevalence of AHI > 15 episodes/h (%)	Sleep Apnea Syndrome* (%)
Young and coworkers (6) (n = 602, 249 females)	4.0	2.0
Bixler and coworkers (20) (12,219 females, 1,000 studied in lab)		
All women	2.2	1.2
Premenopausal	0.6	0.6
Postmenopausal (overall)	3.9	1.9
On HRT	1.1	0.5
Not on HRT	5.5	2.7

Definition of abbreviations: AHI = apnea-hypopnea index; HRT = hormone replacement therapy.

* In Young and coworkers, defined as AHI > 5 with sleepiness. In Bixler and coworkers, defined as AHI > 10 with reason to treat (e.g., sleepiness and/or hypertension).

OSA. Nevertheless, understanding why premenopausal women are protected from OSA is likely to be a fruitful area of inquiry.

GENETICS OF OSA

As in many common conditions, genetics also play a role. Family aggregation of OSA has been shown in several populations: an outbred population in Cleveland, Ohio (30); in Scotland (31); in Israel (32); it was also demonstrated using the unique genealogy approach in the founder population of Iceland (33). In these studies, having a first degree relative with OSA increases the relative risk of OSA by the order of 1.5–2.0.

Because obesity is a risk factor for OSA, and itself aggregates in families (for review, *see* Reference 34), it is reasonable to ask whether familial aggregation of OSA is simply related to the genetics of obesity. Family aggregation is found, however, even after controlling for body mass index (BMI) as a covariate (30), and also when the probands selected for study were relatively nonobese patients with OSA (i.e., BMI < 30 kg/m²) (31).

Although familial aggregation has been shown, little is currently known about the genes conferring risk. The genetic association studies that have been conducted have had apolipoprotein E (APOE) as their major focus. APOE4 is particularly associated with OSA in younger subjects (35). The increased risk in individuals with this allele who are younger than 65 years of having an AHI of more than 15 episodes/hour is 3.1, whereas there is no increase in risk in subjects 65 years and older (35).

PATHOGENESIS OF OSA AND ITS CONSEQUENCES

There are certain aspects about the pathogenesis that are known. Patients with OSA have narrowed upper airways even during

TABLE 4. RISK FACTORS FOR OBSTRUCTIVE SLEEP APNEA

Obesity
Specific craniofacial disorders (e.g., Treacher-Collins, Pierre-Robin syndromes)
Retroposed mandible/maxillae
Adenotonsillar hypertrophy
Nasal problems: septal deviation, allergic rhinitis
Endocrine abnormalities: hypothyroidism/acromegaly
Polycystic ovarian syndrome
Postmenopause
Down syndrome
Family aggregation
APOE4 allele (in subjects < 65 yr)

For risk factors, *see also* Reference 22.

wakefulness as revealed by many imaging studies using multiple imaging modalities (for review of imaging studies, *see* Reference 36). This is true for both adults and children with OSA, with the airway in the latter being narrowest in the region of overlap between tonsils and adenoids (37). The airway in patients with OSA is not only smaller but is also more collapsible (38).

Despite these abnormalities, during wakefulness the upper airway is patent. Subjects with OSA protect themselves while awake by increased activation of their airway dilator muscles, at least the genioglossus (39). Thus, in the balance of forces model (40)—that is, negative intraluminal pressure promoting collapse of the airway with activation of airway dilator muscles promoting patency—the net effect during wakefulness is for patency.

During sleep, there is reduction of activity of upper airway dilator muscles, thereby shifting the balance of forces toward collapse. Neural control of upper airway motoneurons is complex, involving many different neurotransmitters, several of which are affected by sleep. One important neurotransmitter is likely to be serotonin (5-HT); during sleep there is reduced firing of serotonin raphe cells in the brainstem (for review of evidence, *see* Reference 41). Serotonin is an excitatory neurotransmitter to upper airway motoneurons. This excitatory effect is largely mediated by serotonin subtype 2A (5-HT_{2A}) receptors (42). Unfortunately, these receptors do not represent an appealing target for pharmaceutical intervention, since agonists of 5-HT_{2A} produce undesired effects due to activation of other neuronal pathways.

Sleep apnea is a progressive disorder, although it progresses at a slow rate (23). There are changes in the upper airway that are likely secondary to the vibration produced by snoring and/or the large swings in intraluminal pressure during sleep. There is evidence of denervation of palatal muscle in subjects with OSA (43, 44) and inflammatory cells infiltrate both the mucosal and muscle layers of the soft palate (44). This has led to the concept of OSA being the progressive snorer's disorder (43). If this concept is correct, then the disorder should be recognized earlier, with intervention occurring at an earlier age (i.e., a prevention strategy).

OSA produces its consequences by a number of mechanisms. There is sleep fragmentation with arousals occurring at the end of the apnea-hypopnea episodes. This fragmentation plays a major role in the excessive sleepiness that occurs in patients with OSA (for review, *see* Reference 45). There are oscillations of sympathetic output with apnea-hypopnea events (46), and the respiratory disturbances in this disorder produce a unique pattern of repetitive deoxygenation followed by reoxygenation. This is like repetitive episodes of ischemia/reperfusion and results in free radical production and oxidative change. Fletcher and colleagues (47), in seminal studies, developed technology to produce repetitive cycles of deoxygenation/reoxygenation in rodents over weeks. Studies using this strategy have identified damage to hippocampal neurons (48) and to neurons promoting wakefulness (49). The former will likely contribute to the learning problems found in OSA, whereas the latter may be the basis of the residual sleepiness that is found even in well-treated patients with OSA.

DIAGNOSIS OF OSA

Tools have been developed to assess likelihood of apnea. These include questionnaires about symptoms (50) and the multivariable apnea prediction that combines frequency of relevant symptoms with age, sex, and BMI (51). The latter tool has been used as part of a two-stage screening strategy (52). It would seem in the future that screening for OSA in relevant high-risk populations, such as commercial drivers, will become routine.

Definitive diagnosis of OSA still depends on in-laboratory polysomnography. This involves recording of multiple variables during sleep, including the electroencephalogram. Newer technologies are available that allow studies of sleep in the home, in particular all of the relevant respiratory variables. But currently, evidence to support use of these for diagnosis in routine clinical practice is lacking (53). This is likely not because of inadequacy of the technology *per se* but rather the quality of studies to assess the effectiveness of these alternative strategies. Despite lack of definitive evidence, these ambulatory studies are used frequently to diagnose OSA around the globe, particularly outside the United States (54). There is a rapidly growing demand for diagnosis and treatment of OSA, as it gets increasingly recognized, and infrastructure for diagnosis of treatment is lacking in many countries (54).

OSA/EXCESSIVE SLEEPINESS AND QUALITY OF LIFE

OSA is a risk factor for excessive sleepiness. Thus, many patients who seek help clinically complain of falling asleep inappropriately during the day. This results in declines in quality of life, as revealed by general instruments such as the Short Form-36 (55). Three disease-specific quality-of-life instruments have also been developed; they show impairments in patients with sleep apnea syndrome and are now used widely in clinical trials. Sleepiness in OSA leads to excessive pressure for sleep (i.e., short sleep latency), as well as performance decrements, such as frequent lapses due to sleep intruding into wakefulness for brief periods (for review, *see* Reference 45). Wakefulness in OSA is much less stable (45). These performance decrements put subjects with OSA at increased risk for crashes while driving, as shown originally by George and colleagues (56). A recent meta-analysis puts the average odds ratio for subjects with sleep apnea syndrome for having a crash at 2.5 (57). The latter raises interesting questions for practitioners in deciding about driving privileges.

OSA AND INSULIN RESISTANCE

There are a number of metabolic and endocrine consequences of OSA, with insulin resistance being particularly important. Sleep-disordered breathing is an independent risk factor for insulin resistance. This has been shown in three relatively large studies: (1) a sleep center population in Hong Kong (58); (2) a community-based sample in the Baltimore area (59); and (3) most recently, in a large sample from the Sleep Heart Health Study (60). The increased risk of insulin resistance with sleep-disordered breathing is found after controlling for BMI and, where data were available, for visceral obesity as assessed by waist-to-hip ratio.

Intervention data are, however, quite limited. In the largest study to date (61), improvements in insulin sensitivity were found when OSA was treated with CPAP, although the improvements were largely limited to relatively nonobese subjects. There are also some data, albeit in a small sample, of improvement in glucose control in obese patients with type 2 diabetes who had OSA and were treated with CPAP (62). These studies support the notion that OSA is an integral component of the metabolic syndrome, together with visceral obesity, hypertension, hyperlipidemia, and insulin resistance. The data call for randomized trials assessing efficacy of CPAP therapy on glucose control in obese patients with type 2 diabetes.

OSA AND CV DISEASE

One of the most exciting current areas of inquiry is the role of OSA as an independent risk factor for CV disease. This has been a challenging area since obesity is a risk factor for OSA

and also for CV disease. Thus, it has been essential to show that the CV risk from OSA is not simply the result of confounding by obesity. This has been done using sufficiently large samples in cohort studies to allow for control for obesity (BMI and/or measures of visceral obesity) as a covariate or by appropriate selection of obese controls in case-control studies. Interestingly, the converse has not occurred and, to date, obesity researchers have largely ignored the possibility that results attributed to obesity might be due to OSA. It is conceivable that OSA is an important part of the mechanism by which obesity leads to CV disease. If so, this is of fundamental significance since it would open an alternative strategy to address the growing epidemic of CV disease related to obesity. Thus, this is a question with major public health significance that needs to be vigorously pursued.

OSA as a Risk Factor for Hypertension

Data for the CV risk of OSA are most convincing for hypertension. Early studies showed that OSA was more prevalent in patients with hypertension and that hypertension was more common in OSA. This association between presence of hypertension and degree of sleep-disordered breathing was then confirmed in large cross-sectional studies (63, 64). Likewise, an association with incident hypertension has been demonstrated in follow-up studies of untreated subjects with sleep-disordered breathing in the Wisconsin Sleep Cohort Study (65). In these studies, the association is found even at low levels of sleep-disordered breathing (i.e., AHI between 5 and 15 episodes/hour), and is present after controlling for BMI as a covariate.

For hypertension, however, current evidence is not only an association but there are also data showing improvements in blood pressure in randomized trials with CPAP (66–68), with the placebo being one of the following: an oral medication that subjects are told might improve sleep apnea (66), use of sham CPAP (i.e., CPAP at an ineffective pressure of 0.5–1.0 cm H₂O) (67), or CPAP at its lowest setting on conventional machines (i.e., 4.0 cm H₂O) (68). There is substantial variation in the reduction of blood pressure in these trials in patients with severe sleep apnea syndrome (*see* Table 5). Although there was a difference in the degree of sleep-disordered breathing in these studies, probably more important is the percentage of subjects included who had known hypertension (*see* Table 5). The study with the least effect on blood pressure had, by design, no subjects with known hypertension (66). (This was to avoid the issue of medication use affecting results.) In contrast, the study with the highest percentage of subjects with known hypertension had the largest fall in mean blood pressure (*see* Table 5) (68). This suggests that those who will benefit from treatment of OSA with respect to reduction in blood pressure are subjects who are hypertensive, a conclusion supported by a secondary analysis of the data collected by Pepperell and colleagues (67). Thus, sleep apnea seems to confer resistance to antihypertensive medications, a conclusion compatible with the observed high prevalence of OSA in subjects with refractory hypertension (69) and the marked reductions in blood pressure when such patients are treated with CPAP (69).

There is, however, an apparent discrepancy between results of association studies and intervention studies. Specifically, association studies show a relationship to hypertension with even mild to moderate sleep apnea (63–65). However, secondary analysis of intervention data (67) shows effects in only the most severe cases. Moreover, studies specifically targeting mild to moderate apnea in randomized trials show no improvements in blood pressure (70). Further trials of CPAP use are needed in patients with mild to moderate sleep apnea who have hypertension to address benefit in this group.

TABLE 5. COMPARISON OF ESTIMATES OF DIFFERENT RANDOMIZED TRIALS ASSESSING 24-h BLOOD PRESSURE AS OUTCOME OF TREATMENT OF SEVERE SLEEP APNEA

Study	Change in Mean BP (mm Hg) Across 24 h	AHI Episodes/h	Taking Antihypertensive Medications (%)
Faccenda and colleagues (66) (cross-over study)	-1.0 (NS)	35 (median)	0.0
Pepperell and colleagues (67) (parallel group study)	-2.5 (p = 0.0013)	35.9–38.0 (mean in two groups)	18.6
Becker and colleagues (68) (parallel group study)	-9.9 (p = 0.01)	62.5–65.0 (mean in two groups)	42.8

Definition of abbreviations: AHI = apnea-hypopnea index; BP = blood pressure.

Evidence for the role of OSA as being causative for hypertension also comes from animal studies. Administration of chronic intermittent hypoxia to rats for 8 hours/day simulating the pattern found in OSA increases mean arterial blood pressure by 13.7 mm Hg after 35 days (47). Moreover, inducing OSA in dogs by an ingenious methodology that involves an electronically controlled valve intermittently occluding their trachea results in elevation of systemic blood pressure, which returns to normal when obstructive apneas are no longer produced (71).

OSA and Atherogenesis, CV Events, and Mortality

The level of evidence for the role of OSA in causing other types of CV disease is suggestive but not as complete as for hypertension.

There is evidence of an association from the Sleep Heart Health Study for stroke and myocardial infarctions (72). Case-control studies also show that OSA is a risk factor for myocardial infarction/unstable angina even when control subjects have similar levels of obesity (73). Untreated patients with severe sleep apnea have an increased risk of CV events over a 10-year period when compared with control subjects with similar degrees of obesity (see Figure 1) (74). Treatment with CPAP in severe OSA reduces the risk to the control level (see Figure 1). In mild to moderate disease, the risk is elevated, but not significantly (see Figure 1). This may be an issue of statistical power. Although suggestive that untreated, severe OSA leads to elevated CV events, one cannot rule out the possibility that patients with

severe OSA who did not use CPAP were different in other ways and were, for example, also noncompliant with medications to reduce CV risk.

This increased risk of CV events in untreated OSA suggests that OSA might lead to mortality. That OSA can result in fatal outcomes was indicated initially by retrospective studies both in North America and Israel. This has now been shown in the prospective cohort study just described, because patients with severe, untreated OSA had a significant increase in CV deaths (74). When such patients were treated with CPAP, there was no increase in mortality (74).

There is, moreover, a plausible biology whereby sleep apnea could directly contribute to atherogenesis. As discussed earlier, the cyclic deoxygenation/reoxygenation that occurs in OSA leads to free radical production. Thus, OSA is increasingly seen as an oxidative stress disorder (75). The mechanisms involved are summarized in Figure 2 (modified from Reference 75). Changes in many of these steps in OSA have been demonstrated, albeit in small studies. One of the particular advantages of studying OSA is that there is a highly effective treatment (i.e., nasal CPAP), and one can therefore determine whether when OSA is effectively treated there is alteration in these processes, including relevant biomarkers. Studies have shown the following changes with CPAP: reduction in free radical production from white cells

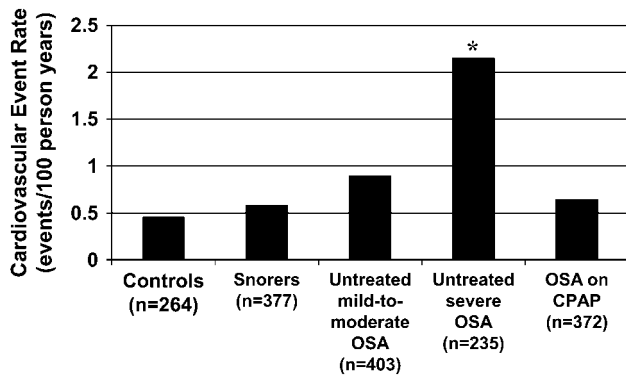


Figure 1. Incidence of acute cardiovascular events over 10 yr of follow-up in different groups. The groups are as follows: normal groups (controls), snorers without obstructive sleep apnea (OSA), mild to moderate untreated OSA, untreated severe OSA, and OSA on continuous positive airway pressure (CPAP). * Rate of acute cardiovascular events in untreated severe OSA is significantly higher than in other groups (p = 0.0012). Event rate is the same as control levels in individuals with severe OSA treated with CPAP. Data from Reference 74.

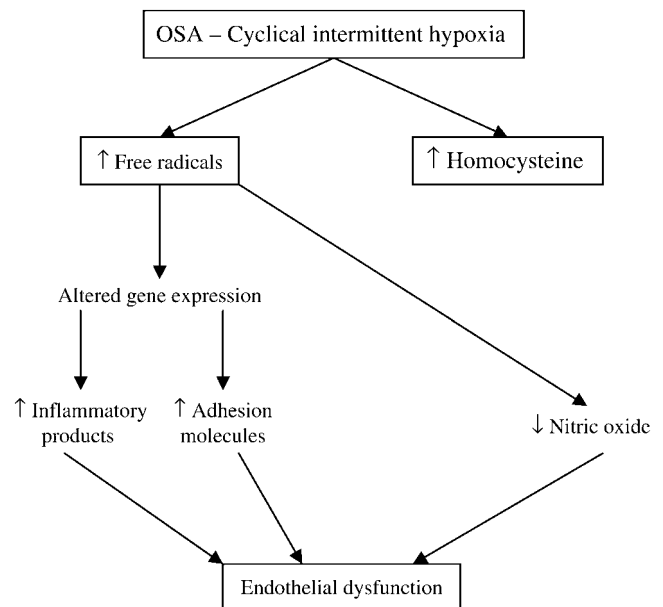


Figure 2. Proposed pathways affected by cyclic changes in oxygen that occur in OSA and their downstream effects. Modified from Reference 75.

(76); reduction in circulating adhesion molecules, specifically intercellular adhesion molecule (77); reduction in high-sensitivity C-reactive protein and interleukin 6 (78); and improvement in endothelial function (79).

Although all of this is highly suggestive for a role of OSA in atherogenesis, we lack, as pointed out by Stradling (80), the definitive proof (i.e., showing reduction in CV events in large-scale randomized trials of treatment of OSA). This is an important question that we need to address.

TREATMENT OF OSA IN ADULTS

Although treatment of sleep apnea before nasal CPAP being available was by tracheostomy (14, 15), CPAP quickly became the treatment of choice and remains the mainstay of treatment. Definitive evidence for its efficacy is recent, coming in the last few years. Studies to address efficacy in randomized placebo-controlled trials were stimulated by the provocative article of Wright and colleagues in the *British Medical Journal* (81), who argued that there is a paucity of robust evidence for the effectiveness of CPAP therapy. The article of Wright and colleagues did lead to a very positive outcome as it stimulated new approaches and studies.

Using the placebo-controlled strategies described above, randomized trials have shown benefit in severe sleep apnea syndrome (i.e., with sleepiness) in many outcomes: for example, subjective sleepiness, objective tests of sleepiness, quality of life, driving performance, and depression scores (for meta-analysis, see Reference 82). Hypertension is also improved (see above). But no benefits of therapy are found in severe sleep apnea if subjects are not sleepy (83). Studies to date have all, however, used short-term outcomes, typically 1 month. A large multicenter National Institutes of Health (NIH)-funded study is currently underway to look at outcomes after 6 months of therapy.

Although the data for severe sleep apnea with sleepiness are convincing, as even Wright and Sheldon now acknowledge (84), data for mild to moderate sleep apnea are less so. The results of these studies are summarized in Table 6 (70, 85–88). The only outcome that changes in all studies in which it was assessed is nighttime symptoms (e.g., snoring). Some studies show no change in subjective sleepiness and none in objective measures of sleepiness. With mild to moderate disease, many subjects are not excessively sleepy. Thus, inclusion of such subjects in the studies summarized in Table 6 will reduce the effect of therapy when excessive sleepiness is used as an outcome. Currently, another NIH-funded multicenter study—is assessing efficacy of therapy in mild to moderate sleep apnea in patients who are excessively sleepy before therapy. Given the very high preva-

lence of mild to moderate OSA in the general population (see Tables 2 and 3), determining who with this level of the disorder will benefit from therapy is a key question.

Although evidence for CPAP use is developing, so too is that for an alternative therapy (i.e., use of intraoral devices that reposition the mandible forward during sleep). Randomized trials using a crossover design with a “placebo” (i.e., wearing a device that does not reposition the mandible) have shown efficacy (89). The reduction in AHI is, however, not as great as with CPAP. Moreover, although CPAP is efficacious in everybody, the intraoral device is not. There are subjects whose AHI does not improve with use of the intraoral device. The reasons for this are unclear, but do necessitate careful follow-up assessment with sleep studies. Thus, the intraoral device is a second-line therapy.

Surgical treatments are also used. One of the main surgical therapies, uvulopalatopharyngoplasty (UPPP), was described in the same year as CPAP (90). Its efficacy has never been assessed in rigorous trials. Rather, there are multiple publications of case series. These series were summarized in an article in 1996 (91) that gave quite a negative view of the outcomes of this surgery. Since then, new surgical approaches to perform UPPP in a less invasive fashion have evolved, as have a number of other surgical approaches (for review, see Reference 92). Unfortunately, however, the studies still tend to be case series and progress in this area has been limited. It seems that surgery does have a role and this role needs to be defined by more robust studies. One view is that surgery has two potential roles: first as an adjunct to nasal CPAP in individuals with nasal obstruction, and second, in patients who fail CPAP due to inability to use the therapy. In this group, surgery is to improve the degree of sleep-disordered breathing but not to cure it (93). It is hoped that we will see development of randomized trials in this area in the future.

PEDIATRIC SLEEP APNEA

The initial description of pediatric sleep apnea was based on a small case series (94). Sleep-disordered breathing is common in children, although, to date, we do not have the population-based epidemiologic studies with complete technology to assess breathing disturbances in sleep to provide accurate estimates of prevalence. Such studies are in progress. Although, as pointed out earlier, adenotonsillar hypertrophy is the major risk factor (25), other aspects of the pathogenesis are similar—for example, smaller airway awake (37) and more collapsible airway (95). What is different is that children do not commonly show the frank arousals in the electroencephalogram at the end of respiratory events that are found in adult subjects (96). Children may

TABLE 6. RESULTS OF RANDOMIZED TRIALS TO DATE ON OUTCOMES OF TREATMENT OF MILD TO MODERATE SLEEP APNEA

Study	Subjective Sleepiness	Functional Outcomes†	OSA Symptoms	Objective Sleepiness
Redline and colleagues, 1998 (85)	+	+	N/A	–
Engleman and colleagues, 1997 (86)	–	–	+	–
Engleman and colleagues, 1999 (87)	+	+	+	–
Monasterio and colleagues, 2001 (88)	–	–	+	–
Barnes and colleagues, 2002 (70)*	–	–	+	–

Definition of abbreviations: N/A = not assessed; OSA = obstructive sleep apnea.

No trial in mild to moderate sleep apnea has used sham continuous positive airway pressure (CPAP). Two studies (85, 88) are parallel group comparison to weight loss, etc., and three are studies with a cross-over design with use of an oral tablet as a placebo (70, 86, 87). + = greater improvement with CPAP; – = no difference between CPAP and control groups.

* No effect on blood pressure in Barnes and coworkers (70).

† Functional outcomes refers to general quality-of-life instruments (either Short Form-36 or Nottingham Health Profile).

have clinical sequelae even in the absence of many respiratory events. Children can have persistent upper airway obstruction leading to sustained hypercapnia and hypoxia. This has been called “obstructive hypoventilation.” This means that criteria for abnormality based on a sleep study are different in children than adults (25). Sleep apnea can have unique consequences in children, such as failure to thrive and learning difficulties (97). A seminal study showed that children in the first grade in the lowest 10th percentile of academic scores had a high prevalence of sleep apnea, and, in those treated with adenotonsillectomy, scores improved after surgery (97). In general, however, there have been limited studies of outcomes of surgical therapy for childhood OSA despite the large number of children having the therapy.

OTHER FORMS OF SLEEP-DISORDERED BREATHING

Although this article has primarily focused on the common condition—OSA—there are other forms of sleep-disordered breathing. First, in some patients, there is alveolar hypoventilation that occurs during wakefulness (i.e., the Pickwickian syndrome) (11). This obesity–hypoventilation syndrome can occur in the absence of chronic obstructive pulmonary disease (98). Such patients will typically also have obstructive apneas during sleep but obesity–hypoventilation can occur even in the absence of obvious OSA (99). Obesity–hypoventilation can be effectively treated by nasal intermittent positive pressure ventilation (98). It is currently a condition less well studied than OSA; a recent study indicates that it is common in obese subjects and often unrecognized (100).

Central apnea, where there is episodic loss of neural output to the diaphragm and other respiratory pump muscles, can also occur but is much less common than OSA. It occurs in the periodic breathing at high altitude primarily related to unstable operation of the respiratory control system with hypoxic ventilatory stimulation. There is also an uncommon idiopathic version (101). Subjects with this have high sensitivity to CO₂ and low arterial Pco₂ awake (typically around 35.0 mm Hg) (101). Thus, they are much closer to the CO₂-dependent apnea threshold that is found during sleep (102). Hypocapnia is a risk factor for central sleep apnea. The most common form of central apnea that is found clinically is that described by Cheyne-Stokes’ respiration (8, 9). This is found both in patients with stroke (103) and with congestive heart failure (for review, see Reference 104). Initial data, albeit in a small study, indicated that treatment of Cheyne-Stokes’ respiration with nasal CPAP in patients with systolic dysfunction improved cardiac outcomes (105). This led to a large randomized multicenter treatment trial conducted in Canada that showed, however, no benefit from CPAP in patients with congestive failure and Cheyne-Stokes’ respiration on the endpoints of death or time to heart transplantation (106). This negative result might be related to the change that has occurred recently in medical management of patients with congestive heart failure, in particular the widespread use of β -blockers based on recently reported randomized trials. β -Blockers can affect ventilatory response to hypoxia and hence might directly affect the pathogenesis of Cheyne-Stokes’ respiration, as well as its consequences because such patients have increased sympathetic activity (104). Given these changes in medical management of heart failure, there is a need to reassess the prevalence and consequences of Cheyne-Stokes’ respiration in such patients.

CONCLUSIONS

This area of research is obviously a vibrant one. Much has been learned about sleep apnea, sleep, and other sleep disorders, all in the very recent past. There have been major new discoveries

and growing sophistication in the nature of clinical research studies and the level of evidence. There remain, however, major unanswered questions that we are well positioned to answer: for example, (1) what are the functions of sleep both for brain and other organs, (2) does sleep apnea play an important role in the CV consequences of obesity, (3) who with sleep apnea benefits from therapy, and (4) can we develop a new pharmacologic approach to therapy? With the recognition that sleep medicine is a unique discipline, and the enormous impact of sleep disturbance on many aspects of our life, one can anticipate that the rate of progress in gaining new knowledge will further accelerate as we move into the next century of the American Thoracic Society.

Conflict of Interest Statement: A.I.P. received royalties from Marcel Dekker Publishers for a book he edited entitled *Sleep Apnea: Pathogenesis, Diagnosis and Treatment*. He has acted as a consultant to Cypress Bioscience and has given a paid lecture at Merck Pharmaceuticals.

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