ELSEVIER
SAUNDERS

Med Clin N Am 88 (2004) 679–703

THE MEDICAL
CLINICS
OF NORTH AMERICA

Sleep and medical disorders

Richard B. Berry, MD, D-ABSM[a,*],
Susan M. Harding, MD, D-ABSM[b]

[a]*Sleep Disorders Centers Shands at AGH, Malcom Randall Veterans Affairs Medical Center, University of Florida, Box 100225 HSC, Gainesville, FL 32610, USA*
[b]*Division of Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham Sleep–Wake Disorders Center, University of Alabama at Birmingham, 1900 University Boulevard, THT-215, Birmingham, AL 35294, USA*

Sleep disturbance is a common problem in many medical disorders. Impairment of sleep may worsen symptoms in these disorders or even worsen the prognosis. Sleep quality may be reduced in many ways. The total sleep time may be reduced or brief awakenings from sleep (arousals) may be frequent and prevent sleep from being restorative. Frequent arousals can also reduce the amount of stage 3 and 4 or rapid eye movement (REM) sleep. Primary sleep disorders, such as sleep apnea, may adversely affect patients with medical disorders [1–4]. Because obstructive sleep apnea (OSA) is very common (2% to 4% or more) in medical patients, the internist taking care of patients with medical problems should be well aware of the impact of sleep apnea on these disorders. One study of mortality in sleep apnea patients found an increased risk for death in men 30–35 years of age [3]. This highlights the importance of early intervention. Because nearly every medical disorder has an interaction with sleep, space limitations mandate that only selected topics can be addressed. This article reviews the effects of sleep and sleep disorders on selected medical disorders including hypertension, congestive heart failure, coronary artery disease, arrhythmias, asthma and chronic obstructive pulmonary disease (COPD), gastroesophageal reflux (GER), renal disease, infectious diseases, selected endocrine disorders, and the fibromyalgia syndrome.

Cardiovascular disease

Normal sleep is usually a time of rest for the cardiovascular system with a reduction in heart rate, arterial blood pressure, and cardiac output [1].

* Corresponding author.
E-mail address: sleep_doc@msn.com (R.B. Berry).

0025-7125/04/$ - see front matter
doi:10.1016/j.mcna.2004.01.006

Sympathetic tone decreases and parasympathetic tone increases. The presence of OSA or central sleep apnea (CSA) impairs this period of rest and some recent evidence suggests that clinical outcomes of patients with cardiovascular disease may be adversely affected by the sleep-disordered breathing (SDB).

Arterial hypertension

Hypertensive patients without sleep apnea have a nocturnal fall in blood pressure. Twenty percent to 40% of patients with OSA, however, fail to have the normal nocturnal fall in systemic blood pressure (nondippers) [5]. Blood pressure tends to rise slightly during apnea and then rise abruptly at apnea termination secondary to arousal from sleep and sympathetic activation. There is continued controversy about whether OSA can cause daytime (diurnal) hypertension. Animal models of simulated OSA suggest that it can [6] but the evidence in humans is less clear-cut. Several studies have found that OSA is very common in adult populations with hypertension (>30%) [7]. This association does not prove causality because patients with hypertension and OSA share common potentially causative factors, such as obesity. Carlson et al [8] found that age, obesity, and sleep apnea were independent and additive risk factors for the presence of hypertension. The Wisconsin cohort study has shown that the presence of even mild OSA increases the risk for the presence of hypertension after adjusting for confounding factors, such as obesity, age, and smoking [9]. The Sleep Heart Health Study also found a modest increased risk of having hypertension when even mild levels of OSA were present [2]. Even if sleep apnea does not cause hypertension, it may well worsen the physiologic impact of the disorder or impair treatment efficacy. For example, Verdecchia et al [10] found that hypertensive patients who failed to have a 10% nocturnal fall in blood pressure had greater left ventricular hypertrophy.

If sleep apnea is effectively treated, does hypertension improve? This question has been approached by a number of studies that have determined the effect of nasal continuous positive airway pressure (CPAP) on nocturnal and daytime blood pressure in patients with OSA. Becker et al [11] found that effective treatment of sleep apnea with nasal CPAP for 9 weeks or more lowered both nocturnal and daytime blood pressure by about 10 mm Hg using a placebo-controlled study (Fig. 1). Other investigations have shown smaller [12,13] or no effects on daytime blood pressure [14,15]. These conflicting results may reflect inadequate CPAP treatment (poor adherence); too short a treatment interval; or less severe sleep apnea populations. In general, most hypertensive patients with sleep apnea still continue to require antihypertensive medications when treated with CPAP. Twenty-four–hour control of blood pressure, however, may improve on CPAP treatment.

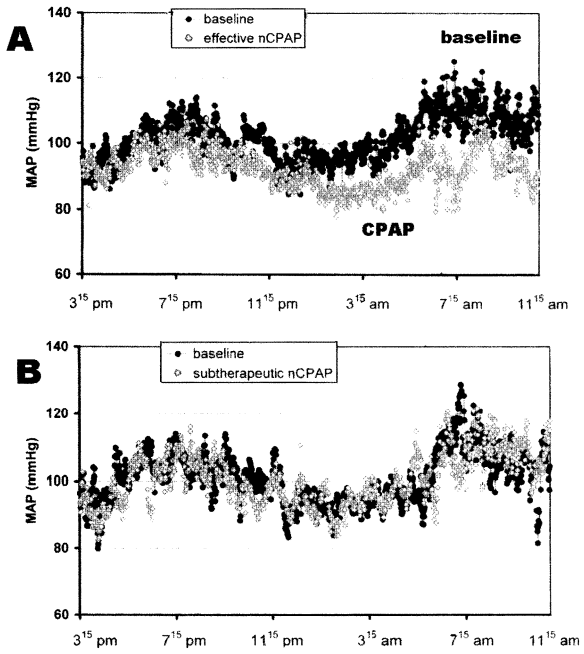

Fig. 1. (*A*) The 24-hour blood pressure at baseline (*black dots*) is reduced after CPAP treatment (*gray dots*). The greatest reductions are during the night and in the morning. (*B*) There is no difference between baseline and subtherapeutic CPAP. (*From* Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Sullivan CE, et al. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. Circulation 2003;107:68–73; with permission.)

Congestive heart failure

Clinicians may incorrectly dismiss complaints of frequent nocturnal awakenings, daytime sleepiness, or insomnia as simply reflecting the sleep disturbance associated with congestive heart failure (orthopnea, paroxysmal dyspnea). Recent evidence suggests, however, that occult SDB is common in patients with congestive heart failure [16,17]. OSA, CSA of the Cheyne-Stokes respiration type (CSA-CSR), and a mixture of OSA and CSA-CSR may be present in patients with heart failure. CSA-CSR refers to a crescendo-decrescendo pattern of respiration with central apnea at the nadir in effort (Fig. 2). Arousal usually occurs at the peak of the ventilatory phase. There is commonly a delay in the nadir in the arterial oxygen saturation (Sa_{O_2}) following the event reflecting an increased circulation time. Although a few patients may exhibit the CSR pattern of breathing during wakefulness, it is usually exhibited only during sleep. Sin et al [18] retrospectively evaluated a group of patients with significant left ventricular failure referred to the sleep laboratory and found that risk factors for CSA-CSR included the male gender, awake hypocapnia, age greater than 60 years, and the

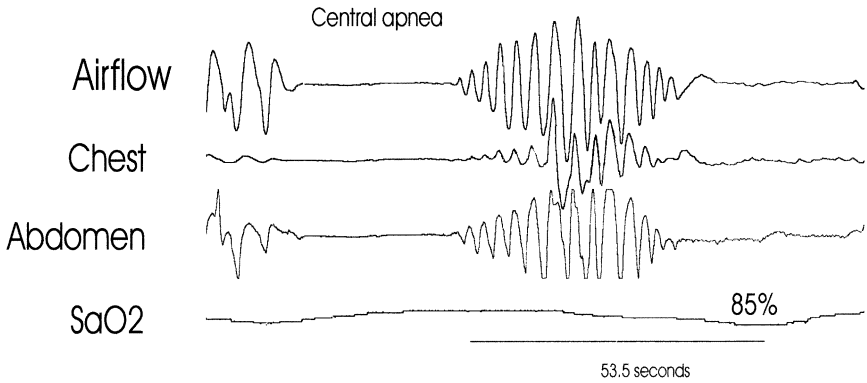

Fig. 2. A tracing of central apnea and Cheyne-Stokes respiration in a patient with congestive heart failure is shown. Note the crescendo-decrescendo pattern of respiration between apneas. The long delay in the nadir of the arterial oxygen saturation (53.5 seconds) is shown. This is caused by a prolonged circulation time.

presence of atrial fibrillation. The risk factors for OSA included an increased body mass index for men and increased age for women.

In patients with congestive heart failure and OSA, the negative intrathoracic pressure, hypoxemia, and increased sympathetic tone associated with the apneas are believed to impact ventricular function negatively [1]. Treatment of OSA with nasal CPAP in patients with cardiomyopathy was found to improve the ejection fraction and symptoms [19,20]. This seems to occur because of a reduction in sympathetic tone and a decrease in ventricular afterload [1].

The primary cause of CSA-CSR in patients with congestive heart failure was once believed to be the long circulation time (delayed feedback to chemoreceptors) causing an overshoot in ventilation. During sleep if the P_{CO_2} falls below a critical level (apneic threshold), central apnea occurs [21]. Studies of groups of patients with congestive heart failure, however, have found equivalent circulation time (and ejection fraction) in congestive heart failure patients with and without CSA-CSR [22]. Patients with CSR tend to have daytime hypocapnia, higher ventilatory responses to C_{O_2}, and sleeping P_{CO_2} values nearer the apneic threshold [21]. These characteristics increase the likelihood of instability in ventilatory control and the presence of CSR. The etiology of the hypocapnia seems related at least in part to greater pulmonary congestion and stimulation of ventilation by J receptors in the lung [23].

Patients with congestive heart failure and CSA-CSR seem to have a worse prognosis than patients with equivalent ejection fractions but without CSR [24–26]. Lanfranchi et al [25] evaluated a cohort of patients with reduced left ventricular ejection fraction by portable monitoring. Patients with atrial fibrillation or an obstructive apnea-hypopnea index greater than 5 per hour were excluded. Echocardiography to assess chamber size and Holter EKG

monitoring to detect heart rate variability were also performed. After a mean follow-up of 28 months, characteristics of survivors and nonsurvivors were determined. As a group, nonsurvivors did have worse symptoms and a lower ejection fraction. Multivariate analysis showed, however, that an apnea-hypopnea index greater than 30 per hour (amount of CSR) and a large left atrial size were the only independent predictors of cardiac death.

Successful treatment of CSA-CSR in congestive heart failure patients seems to improve sleep quality, improve ejection fraction, and possibly improve survival (Fig. 3) [26]. The initial treatment of CSA-CSR is optimization of medical treatment for heart failure. The best secondary treatment of choice seems to be nasal CPAP. Studies have shown an improvement in sleep and daytime ejection fraction after 1 to 3 months of CPAP treatment [26,27]. CPAP often acutely reduces but does not eliminate central events. An empiric approach is to titrate CPAP up to levels of 10 to 12 cm H_2O if tolerated [1,26]. This may require several days of patient adjustment. Prospective controlled trials of the effects of CPAP in patients with heart failure are underway to document further that CPAP can improve survival in patients with CSA-CSR. Newer modes of adaptive positive pressure ventilation have been developed to reduce CSA-CSR more rapidly and improve patient acceptance of positive pressure therapy [28,29]. Supplemental oxygen has also been shown to decrease the apnea-hypopnea index and degree of nocturnal desaturation in patients with CSA-CSR and heart failure [30,31]. Oxygen has not been shown, however, to improve the ejection fraction or improve survival.

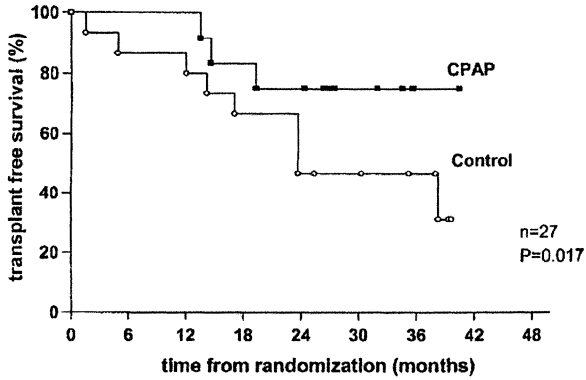

Fig. 3. In congestive heart failure patients with CSA-CSR, treatment analysis revealed that transplant-free survival was significantly greater in patients randomized to CPAP who complied with therapy, than in control subjects (standard medical care). An intention-to-treat analysis that included all patients randomized to CPAP showed a strong trend for increased survival ($P = .059$). (*From* Sin DD, Logan AG, Fitzgerald FS, Liu PP, Bradley TD. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. Circulation 2000;102:61–6; with permission.)

Arrhythmias and pacing

New information has also emerged concerning the effect of sleep disorders on arrhythmias. Patients with OSA typically have a slowing of the heart rate with the onset of apnea and an increase in heart rate following apnea termination. Although this has been called the brady-tachy pattern, many OSA patients have heart rates that actually remain between 50 and 100 beats per minute. The incidence of more significant rhythm disturbances in patients with OSA has varied between studies. A recent prospective study of 45 recently diagnosed OSA patients used Holter monitoring for 18 hours after diagnosis and again after 2 to 3 days of CPAP treatment [32]. Only 8 of the 45 had significant rhythm disturbances including ventricular tachycardia, atrial fibrillation, supraventricular tachycardia, and second- or third-degree heart block. In seven of these eight patients CPAP resulted in the abolition of the arrhythmia. Javaheri and Corbett [33] performed Holter monitoring, polysomnography, and arterial blood gas testing in 59 patients with stable congestive heart failure and an ejection fraction of 45% or less. Patients with hypocapnia were more likely to have CSA and the presence of ventricular tachycardia was 20 times as great in the hypocapnic patients.

Kanagala et al [34] found that patients with untreated OSA had a higher recurrence of atrial fibrillation after cardioversion than patients without a polysomnographic diagnosis of sleep apnea (Fig. 4). Appropriate treatment with CPAP in OSA was associated with a lower recurrence of atrial fibrillation. Decreased heart rate variability has been shown to be a poor

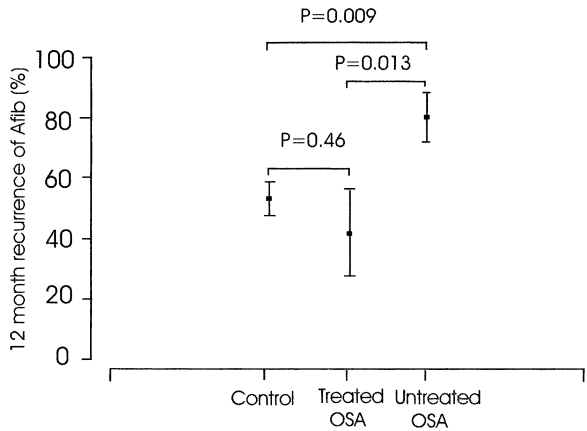

Fig. 4. The 12-month recurrence (means ± SD) of atrial fibrillation after cardioversion was higher in untreated OSA patients than controls (who did not have sleep studies). The recurrence did not differ between controls and treated OSA patients (including noncompliant patients). (*From* Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, Ballma KV, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation 2003;107:2589–94; with permission.)

prognostic sign in patients with cardiovascular disease. In many patients this may represent an increase in sympathetic predominance. Khoo et al [35] found that CPAP treatment of OSA improved vagal heart rate control and that the degree of improvement varied directly with the amount of adherence with CPAP use.

Because patients with OSA may have nocturnal bradycardia and paroxysmal tachyarrhythmias one group investigated the effects of atrial pacing. An unexpected finding was that atrial overdrive pacing actually reduced the number of CSAs and OSAs [36]. The mechanism for this action is unknown.

Coronary artery disease

There is a circadian peak in the onset of acute myocardial infarction at midmorning. One retrospective study of 3309 patients found that 26% had the onset of acute myocardial infarction during sleep [37]. The patients tended to have lower ejection fraction and older age. Sleep studies were not performed on the patients. The Sleep Heart Health Study, a large prospective cohort of patients, found evidence of a modest increase in risk of having self-reported coronary artery disease at even low levels of sleep apnea [2]. Peker et al [38] found an increase in mortality in patients with coronary artery disease who had untreated OSA.

There have also been a growing number of studies showing changes in blood components or indicators of inflammation in OSA that may be associated with an increased risk of atherosclerosis or thrombosis. In OSA there is an increase in the early morning hematocrit [39] and fibrinogen levels [40] that decreased after CPAP treatment. The levels of vascular endothelial growth factor [41], amount of neutrophil [42,43], and platelet activation [44] are also reduced with CPAP treatment of patients with OSA. Inflammation is now believed to play a role in atherosclerosis or plaque rupture. The level of C-reactive protein (a marker of inflammation) is reduced with CPAP treatment [45,46]. One study found a reduction in leptin (a hormone secreted by adipose tissue) and a reduction in visceral fat on CPAP treatment [47]. Increased visceral fat is associated with an increased risk of cardiac disease.

Sleep and respiratory disease

Asthma

Nocturnal worsening of symptoms and sleep disturbance are significant problems for patients with asthma. In one study, up to 40% of asthmatics experienced symptoms every night [48]. The normal circadian variation in airway function, with the highest airflow in the late afternoon (4:00 PM) and the lowest in the early morning (4:00 AM), is exaggerated in patients with

obstructive airway diseases [49]. In patients with nocturnal asthma the forced expiratory volume in 1 second or peak flow can fall as much as 20% to 40% in the morning hours (morning dippers). The etiology of this variation is multifactorial and includes circadian changes in the amounts of circulating steroids and epinephrine, cholinergic tone, and possibly inflammatory mediators in the lungs [49,50]. Sleep also seems to have an adverse effect on asthma, independent of other factors. The easiest way to diagnose severe nocturnal worsening of asthma is to have the patient record peak flow measurements at bedtime and on awakening.

Treatment of patients with nocturnal asthma should begin with inhaled corticosteroids [51]. This medication has been shown to reduce the circadian fluctuation in airway tone. Patients with continued nocturnal symptoms despite an adequate dose of inhaled corticosteroids can then be treated with a long-acting bronchodilator. Theophylline has been proved effective despite the stimulatory effects of the medication [49,52,53]. In dosing theophylline, the goal should be to obtain the highest levels during the time of greatest airflow obstruction (at night and early morning). Long-acting inhaled beta agonists (salmeterol and formoterol) are also useful for control of symptoms in nocturnal asthma and potentially might cause less sleep disruption than theophylline. Selby et al [52], however, found only a slight advantage for salmeterol compared with theophylline in sleep quality (fewer arousals). The falls in morning flow rates were similar but awakenings were less frequent on salmeterol. Weigand et al [53] found salmeterol to be more effective than theophylline at preventing the morning drop in flow rates. The drugs did not differ in polysomnographic findings but patients perceived better sleep with salmeterol than theophylline. If OSA is also present, nocturnal asthma may improve with effective treatment [54].

Sleep and chronic obstructive pulmonary disease

Patients with COPD often have multiple sleep complaints, such as insomnia (difficulty initiating or maintaining sleep) and frequent awakenings with shortness of breath or cough. The sleep of patients with COPD is poor, with low total sleep times, and reduced amounts of slow wave and REM sleep. Airflow obstruction typically worsens in the early morning hours similar to asthmatics [55]. Those with moderate to severe COPD may also exhibit significant falls in the oxygen saturation during sleep. COPD patients with an awake Po_2 of 50 to 60 mm Hg have desaturation during sleep as even normal persons have a fall in Po_2 of 8 to 10 mm Hg during non-REM (NREM) sleep. The most severe desaturations occur during REM sleep, however, when there is skeletal muscle hypotonia and periods of hypoventilation characterized by irregular breathing, reduced respiratory effort, and small tidal volumes (Fig. 5) [56,57]. Of note, REM-associated nonapneic hypoventilation may result in severe hypoxemia even if the daytime Po_2 is greater than or equal to 60 mm Hg. NREM and REM sleep

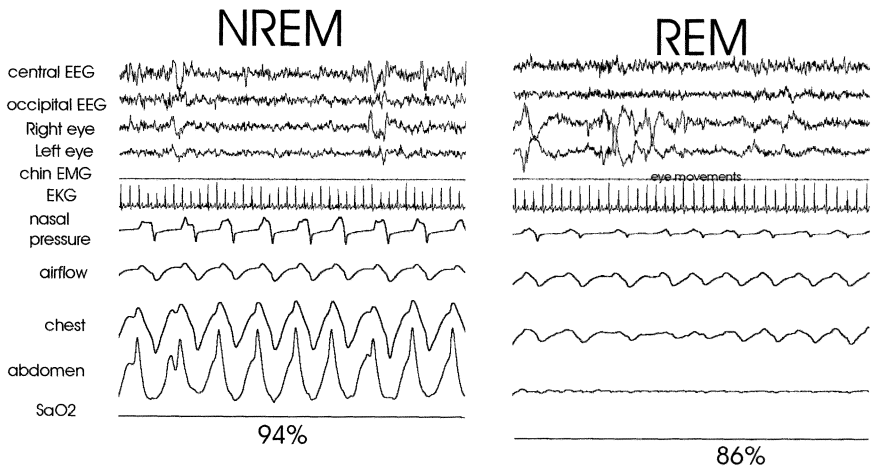

Fig. 5. Tracings of NREM and REM in the same patient in the supine sleeping position. REM sleep is associated with a reduction in tidal volume, hypoventilation, and nonapneic arterial oxygen desaturation. This patient had a daytime Po_2 of 65 mm Hg. Because the arterial oxygen saturation (Sao_2) was below 85% for only 10 minutes of the night, oxygen therapy was not prescribed.

normally occupy about 80% and 20% of the total sleep time, respectively. In general, patients with lower Sao_2 and higher Pco_2 are more likely to have significant nocturnal desaturation; however, there is considerable individual variation.

Low-flow oxygen by nasal cannula can prevent the typical, nonapneic arterial oxygen desaturation manifested by patients with COPD, without substantially increasing the nocturnal Pco_2 [58]. The benefits of chronic 24-hour oxygen therapy in patients with COPD have been well documented by the Nocturnal Oxygen Treatment Trial [59] and other studies of patients meeting the standard criteria of a daytime Po_2 less than 55 mm Hg breathing room air. The value of 55 mm Hg was chosen because below this point pulmonary arterial pressure starts to increase significantly secondary to hypoxic vasoconstriction. In the Nocturnal Oxygen Treatment Trial study, patients also received oxygen if the Po_2 was 55 to 59 mm Hg and evidence of end organ damage was present (pedal edema, hematocrit >55%, or P pulmonale on EKG). Today most physicians consider evidence of significant cor pulmonale or neurologic dysfunction an indication for oxygen treatment in this group with borderline oxygenation. The indication for nocturnal oxygen in patients with a daytime Po_2 greater than or equal to 60 mm Hg but with nocturnal arterial oxygen desaturation is not established [60]. Brief periods of mild REM hypoxemia probably should not be treated. One could make a case for nocturnal oxygen if there is severe REM-associated desaturation or prolonged desaturation to less than 85% during NREM sleep. Of note, patients with the overlap syndrome (sleep apnea plus COPD)

are best treated with positive airway pressure (CPAP or bilevel positive airway pressure) with the addition of supplemental oxygen if needed. Giving such patients oxygen alone may increase apnea duration, incompletely reverse desaturation, and may result in large increases in nocturnal P_{CO_2} [58].

Treatment of nocturnal symptoms in patients with COPD includes theophylline and long-acting beta agonists. Sustained-action theophylline improves morning pulmonary function compared with short-acting beta agonists without negatively impacting sleep [61]. Theophylline and long-acting beta agonists have not been compared in COPD subjects. In asthma, however, some studies showed a possible slight advantage for long-acting beta agonists [52]. Ipratropium bromide at bedtime has also been shown to be useful in COPD [62] and the only problem with this medication is the relatively short duration of action. Many COPD patients complain of insomnia despite bronchodilator treatment. Studies have found that benzodiazepine receptor agonists are generally safe [63]. COPD patients with hypoventilation or those with coexistent sleep apnea, however, should not be prescribed hypnotics.

Sleep and gastroesophageal reflux

Important physiologic changes in esophageal function occur during sleep and following arousal from sleep [64,65]. The upper esophageal sphincter pressure decreases from 40 to 20 mm Hg with sleep onset and further decreases to 8 mm Hg during stable sleep. This increases the possibility that esophageal contents can reach the upper airway or be aspirated into the lung [65]. The lower esophageal sphincter (LES) is the primary antireflux barrier. The LES normally relaxes with swallowing. When the LES relaxes without a swallow, a transient LES relaxation is said to occur. Although one might assume that gastroesophageal reflux (GER) occurs because of inadequate LES pressure, most patients with GER have normal LES pressure. Transient LES relaxations are the primary GER mechanism, accounting for 63% to 100% of GER episodes [66,67]. Other reflux episodes are secondary to stress reflux (increases in gastric pressure) or free reflux (sustained reduction in LES pressure). In normal subjects, nearly all episodes of GER are caused by transient LES relaxations. Transient LES relaxations are confined to wake time and following brief arousals from sleep [68]. Sleep also affects esophageal acid clearance mechanisms. Production of saliva (neutralizes acid) and swallowing rapidly clear acid from the esophagus during wakefulness. Saliva production ceases during sleep, however, impeding the ability to neutralize refluxate [69]. Furthermore, swallowing frequency is almost nonexistent during stable sleep, with swallowing occurring only during brief arousals [70]. For these reasons, esophageal acid clearance is markedly prolonged during sleep, and requires arousal from sleep [70]. If reflux does occur during sleep, acid migrates further upward in the esophagus [71].

Sleep-related gastroesophageal reflux

Gastroesophageal reflux during sleep is common with up to 10% of the population reporting symptoms of nocturnal reflux in surveys studies [72]. In a recent Gallup poll of heartburn patients, 79% reported nighttime heartburn, of which 75% noted that heartburn negatively affected their sleep. Despite medical therapy for GER, only 49% had adequate control of their nocturnal symptoms [73]. Nocturnal GER is potentially more injurious than diurnal GER because acid clearance mechanisms are impaired during sleep. Freidin et al [68] compared normal subjects and patients with reflux esophagitis with nocturnal monitoring of pH, esophageal manometry, and sleep stage. The LES pressures were similar in normal subjects and patients. Both groups had similar LES pressure during both wakefulness and sleep. The patients had many more reflux episodes, however, with most nocturnal reflux episodes occurring during wake periods and some occurring following brief arousals from sleep. Transient LES relaxations accounted for most of these episodes.

Because symptomatic reflux is a risk factor for the development of Barrett's esophagus (a precursor for carcinoma) [74], nocturnal GER could pose a significant role in the development of Barrett's esophagus. One study of GER patients found that a history of nocturnal reflux increased the risk of having Barrett's esophagus [75]. Another study, however, did not replicate this finding [76].

Symptoms of nocturnal GER include multiple awakenings, substernal burning or chest discomfort, indigestion, and heartburn. Other symptoms include a sour or bitter taste in the mouth, regurgitation, water brash, coughing, and choking. Diagnostic methods for detecting nocturnal GER include esophageal pH testing that has a sensitivity and specificity of approximately 90% [77]. It can be integrated with polysomnography (sleep monitoring) for temporal correlation of sleep-related events, such as arousals. Esophageal pH testing is performed by placing a pH probe in the distal esophagus (5 cm above the LES). Many laboratories include dual pH probes, where a proximal pH probe is also placed at the upper esophageal sphincter or in the pharynx. A GER episode is defined by the presence of material that has a pH of less than 4. Fig. 6 shows a GER event following an arousal from sleep. GER episodes should be suspected on routine polysomnography if there is an arousal followed by a prolonged period of increased chin electromyogram (manifestation of swallowing).

Nocturnal asthma and gastroesophageal reflux

Recently there has been considerable interest in the relationship between nocturnal GER and asthma. Gislason et al [78] noted that 5% of randomly selected subjects had nocturnal GER more than once a week, and that asthma was more frequent in those with nocturnal GER. There is some experimental evidence to suggest that GER can worsen airway function with

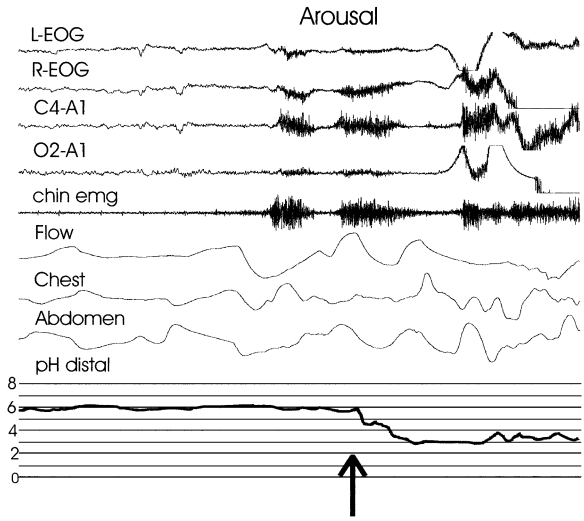

Fig. 6. An episode of GER is documented by pH monitoring of the distal esophagus during a sleep study. The episode (*arrow*) occurs during an arousal and is manifested by a sudden drop in pH to less than 4. This patient complained of frequent symptoms of heartburn at night. L-EOG and R-EOG, left and right eye movement tracings; C4-A1 and O2-A1, right central and occipital EEG tracings.

or without aspiration into the lungs. Jack et al [79] monitored both tracheal and esophageal pH in four nocturnal asthmatics with GER. There were 37 episodes of esophageal reflux of which 5 episodes were associated with a fall in tracheal pH. Tracheal acid episodes were associated with prolonged reflux episodes, nocturnal awakenings, and bronchospasm during the night. Aspiration, however, may not be required to trigger changes in bronchial tone. Afferent vagal fibers are present in the lower esophagus and could trigger changes in bronchial tone when stimulated by gastric contents. Cuttitta et al [80] evaluated spontaneous reflux episodes and airway patency during the night in seven asthmatics with GER. Multiple stepwise linear regression analysis revealed that the most important predictor of change in lower respiratory resistance was the duration of esophageal acid exposure. Both long and short GER episodes (those less than 5 minutes and those longer than 5 minutes) were associated with higher respiratory resistance compared with baseline. These data collectively suggest that esophageal acid is able to elicit nocturnal bronchoconstriction.

Given these findings an important question is whether or not treatment of nocturnal GER can improve asthma. Some uncontrolled studies have shown a benefit in asthma with aggressive treatment of GER [81]. A systematic review of published studies, however, did not find enough evidence to conclude that treatment of GER definitely improves asthma in unselected patients [82]. A 2- to 3-month trial, however, of aggressive treatment of GER

in individual symptomatic patients with uncontrolled nocturnal asthma and GER should be considered.

Sleep-related laryngospasm

Gastroesophageal reflux also has a role in sleep-related laryngospasm. Patients abruptly awaken with an intense feeling of suffocation often accompanied with stridor and choking sensations [83]. Other features include intense anxiety, rapid heart rate, sensation of impending death, and residual hoarseness. Differential diagnosis for sleep-related laryngospasm includes OSA, epilepsy, sleep choking syndrome, sleep terrors, vocal cord dysfunction, and other upper airway pathologies. Thurnheer et al [83] noted that 9 of 10 patients with sleep-related laryngospasm had GER documented by esophageal pH testing [83]. Six patients responded to antireflux therapy, showing that GER may be associated with sleep-related laryngospasm.

Gastroesophageal reflux and obstructive sleep apnea

Given the negative intrathoracic pressure during obstructive apnea and the frequent arousals from sleep, one would suspect that nocturnal GER is common in patients with OSA. Green et al [84] prospectively examined 331 OSA patients. Significant nighttime GER was found in 62% of subjects before OSA treatment. Patients compliant with CPAP had a 48% improvement in their nocturnal GER symptoms. There was no change in nighttime reflux symptoms if patients did not use CPAP. Furthermore, there was a strong correlation between higher CPAP pressures and improvement in nocturnal GER symptom scores. This study shows that nocturnal reflux is common in OSA patients and that nasal CPAP decreases the frequency of nocturnal GER symptoms. Of note, the fact that nocturnal GER is common in OSA patients and that CPAP reduces GER does not necessarily prove that OSA causes GER. In some studies episodes of GER were not correlated with apneic events [85]. CPAP by increasing the pressure gradient between the thorax and the stomach may also reduce GER independent of the effects of CPAP on OSA.

Therapy of sleep-related gastroesophageal reflux

Adequate treatment of GER requires a comprehensive approach including lifestyle modifications and medications [86]. Patients should not eat for at least 2 hours before bedtime and avoid foods that promote GER, including high fat–containing foods, caffeine, chocolate, mint, alcohol, tomato products, citrus, and sodas. Medications that promote reflux should be avoided, including calcium channel blockers, theophylline, prostaglandins, and bisphosphonates. Smoking significantly decreases LES pressure, so all patients should be encouraged to stop smoking. Patients should loose weight if they are obese and sleep in loose-fitting clothing. Positional

therapy can also be used. Sleeping with the head of the bed elevated 6 inches with a full-length wedge or placing blocks under the head of the bed may be useful. The right lateral decubitus position worsens GER, whereas the left lateral decubitus posture seems to be the best sleep position for sleep-related GER [87].

Medications to treat sleep-related GER include antacids for acute symptom control, H_2 receptor antagonists, proton pump inhibitors, and prokinetic agents. H_2 receptor antagonists provide heartburn relief in 60% of patients and can be given before sleep onset. Proton pump inhibitors provide superior gastric acid suppression. One study found that that 40 mg of omeprazole with dinner, or omeprazole, 20 mg, before breakfast and with dinner, resulted in better gastric acid suppression than giving 40 mg before breakfast only [88]. Recent data suggest there may be nocturnal acid breakthrough despite proton pump inhibitor therapy [89]. Whether nocturnal gastric acid breakthrough is clinically important in GER is not known. Metoclopramide is the only prokinetic agent available in the United States and has a high prevalence (20% to 50%) of central nervous system side effects. Prokinetic agents can be used concomitantly with gastric acid suppressive agents. Antireflux surgery, primarily fundoplication (both open and laparoscopic methods), is successful in 80% to 90% of patients. Long-term results, however, show that many surgically treated patients use antireflux medications regularly [90]. Nasal CPAP therapy has also been shown to reduce sleep-related GER symptoms [91].

Sleep disturbances in patients with renal disease

Sleep disturbances are also very common in renal disease patients [92]. Most investigations examine patients with end-stage renal disease who are on chronic hemodialysis or continuous ambulatory peritoneal dialysis. Sleep complaints occur in up to 80% of dialysis patients [92]. Holley et al [93] reported that the most common sleep complaints were nighttime awakenings in 67%, early morning awakenings in 80%, restless legs in 72%, jerking legs in 83%, and daytime sleepiness in 28% of patients. Dialysis patients also have alterations in their objectively recorded sleep architecture. Polysomnographic features include reduced total sleep times, sleep efficiencies as low as 66%, and large amounts of wake time [92].

There is also a higher prevalence of OSA in renal disease patients compared with the general population. Kimmel et al [94], performing polysomnography in 30 patients with chronic renal failure, found that 73% of patients had sleep apnea. Continuous ambulatory peritoneal dialysis patients had increased sleep fragmentation and lower oxygen saturations from apneas on nights when fluid was present in their abdomens.

Patients with renal disease also have a high prevalence of restless legs syndrome and periodic limb movement of sleep disorder [95]. The restless legs syndrome is characterized by unpleasant sensations in the legs or an

irresistible urge to move the limbs during wakefulness that is temporarily improved by movement and is present only or worse in the evening. Uremia is considered a secondary cause of restless legs syndrome. Periodic limb movement of sleep disorder is defined as complaints of disturbed sleep, insomnia, or daytime sleepiness secondary to periodic movements of the legs during sleep. Up to 80% of patients with restless legs syndrome also have periodic limb movement of sleep disorder. The restless legs syndrome is extremely distressing to many renal patients, and occurs in approximately 80% of dialysis patients. Renal transplantation can often result in cure of this problem. Treatments of restless legs syndrome include treatment of iron deficiency (if present); dopaminergic agents; narcotics; selected antiepileptic medications; and benzodiazepines [96].

Patients with end-stage renal disease often complain of daytime sleepiness and objective testing has confirmed this [97]. Daytime sleepiness is often multifactorial. Possible causes include sleep disorders such as insufficient sleep caused by dialysis schedules, OSA, restless legs syndrome or periodic limb movement of sleep disorder, and direct effects of renal failure. Other potential causes of daytime sleepiness include uremic encephalopathy, parathyroid hormone excess (which could have neurotoxic effects), and alterations in neurotransmitter levels. Dialysis may also release cytokines that have somnogenic properties, including interleukin-1 and tumor necrosis factor-α. Rapid changes in the acid-base balance and serum osmolality may also affect alertness.

Sleep in infectious disease patients

Most of us notice an increased propensity to sleep when we have an infection. Infectious products induce release of somnogenic cytokines including interleukin-1 [98]. These immune responses are partially responsible for sleep alterations. This section briefly discusses sleep alterations in HIV patients and other infections. This section does not discuss central nervous system infections including African sleeping sickness (*Trypanosoma brucei*), meningeal encephalitis, and prion diseases.

HIV infection

Patients with HIV infection report many sleep-related symptoms including daytime sleepiness, difficulty in initiating and maintaining sleep, and multiple nocturnal arousals (Table 1) [99]. HIV infection alters cytokines and other immune regulators that may impact sleep. Also, secondary infectious processes or medications used to treat HIV infection may disrupt sleep. For instance, some patients report insomnia with the use of zidovudine (AZT). Vivid dreams have been reported in patients taking the nonnucleoside reverse transcriptase inhibitors nevirapine and efavirenz [100].

Table 1
Symptoms and signs of sleep symptoms in patients with HIV infection

Stage of disease	Symptoms	Sleep study findings
Early CD4 >400/mm^3	Mild insomnia	Increased SWS
	Mild daytime fatigue	Alpha intrusion may occur
400/mm3> CD4 >200	Significant insomnia	Decreased SWS
	Moderate daytime fatigue	
CD4 <200/mm^3	Severe insomnia	Absent SWS
	Severe fatigue	Fragmented sleep architecture

Abbreviation: SWS, slow wave sleep (stage 3, 4 NREM sleep).

Many investigators have examined sleep architecture in HIV patients. Norman et al [99] found an increase in delta sleep that was more prevalent during the later part of the sleep time. The effects of HIV infection on sleep vary with the stage of the disease [101]. During the early stages of HIV infection (CD4 counts >400/mm^3), there is mild difficulty in initiating and maintaining sleep associated with mild and intermittent periods of daytime fatigue. Polysomnographic findings in these patients include an increase in total slow wave sleep percentage with more slow wave sleep occurring during the later sleep cycles. Alpha intrusion may also be noted along with mild alterations in the REM-NREM sleep cycles. In patients with moderate HIV infection (CD4 count greater than 200/mm^3 but less than 400/mm^3), there is more difficulty in maintaining sleep and patients note increasing fatigue. Polysomnographic findings include a decrease in sleep efficiency with lesser amounts of delta sleep and more difficultly discriminating the NREM-REM sleep cycles. In the terminal stages of HIV infection (CD4 counts less than 200/mm^3), patients have more difficulty with daytime fatigue and severe difficulty in maintaining sleep. Polysomnographic findings include further decreases and sometimes even the absence of delta sleep, poor sleep efficiency, and difficulty in recognizing NREM-REM sleep cycles with many spontaneous arousals. It has been postulated that the decrease in delta sleep as the disease progresses may be related to fluctuations in cytokines and neurologic involvement from the infection [101,102].

Therapy of sleep disturbances in HIV-positive individuals includes good sleep hygiene practices; avoidance of alcohol, caffeine, and other sleep disruptive substances; and screening for treatable sleep disorders. For instance, lipodystrophy may predispose patients to OSA development. Patients with HIV also have a high prevalence of depression, so this should be screened for and treated if present. Some practitioners use intermittent sedatives and hypnotics for insomnia, which may be helpful in selected patients. As more aggressive therapeutic modalities are available to treat HIV infection, clinical outcomes may be improved, and further attention to sleep disturbances may improve the patient's overall quality of life.

Other infectious disease and immunization effects

Patients with infectious mononucleosis experience malaise and fatigue during active infection. Some patients develop chronic sleepiness and fatigue and have prolonged sleep periods and nap throughout the day. Other chronic infections that may potentially cause fatigue include cytomegalovirus, hepatitis B and C, Lyme disease [103], and brucellosis. There has also been some interesting evidence showing that sleep deprivation can impair immune function. For example, preceding sleep deprivation can impair the response to vaccination [104].

Sleep in endocrine disorders

Hypothyroidism has been associated with sleep apnea [105]. There are no large cohort studies evaluating the prevalence of sleep apnea in hypothyroid subjects. Obesity may be a significant confounding factor. Pelttari et al [106] examined 26 patients with hypothyroidism and 188 euthyroid control subjects finding that 50% of hypothyroid patients and 29% of control subjects had significant respiratory events [106]. Whereas some physicians order thyroid function tests on all OSA patients, this may not be not cost effective [107]. Postmenopausal women with OSA (who are at higher risk for hypothyroidism) or OSA patients without predisposing OSA risk factors, might warrant thyroid studies. There are case reports showing resolution of OSA after attaining normal thyroid function; however, it takes an extended period of time. Hypothyroid sleep apnea should be treated as usual (nasal CPAP), while the euthyroid state is being restored, and until a repeat sleep study off treatment shows the absence of OSA. Hypothyroidism has differing effects on sleep in patients without OSA, including complaints of excessive daytime sleepiness and a reduction in delta sleep percentage. Hyperthyroidism has been associated with insomnia. There are conflicting data concerning hyperthyroidism's effect on sleep architecture.

Growth hormone excess resulting in acromegaly is also associated with sleep apnea. Grunstein et al [108] noted that 60% of unselected acromegaly patients have sleep apnea. Potential pathophysiologic mechanisms of this association include macroglossia and increased muscle mass of the upper airway. Because CSA is also noted in acromegalic patients, alterations in central ventilatory control may also play a role [108]. Acromegalic patients without OSA may also have excessive daytime sleepiness with an increase in REM sleep [109]. There are limited data examining sleep characteristics with growth hormone deficiency. One study showed a reduction in delta sleep, although more research is needed to make any conclusions.

Adrenocorticosteroid excess, as seen in Cushing's disease, is associated with sleep apnea in approximately 30% of patients [110]. Other investigations have shown shortened REM latencies and poor sleep efficiencies, although more data are needed to draw further conclusions.

Studies have suggested that patients with OSA have impaired glucose tolerance, but unfortunately obesity is a major confounding factor. Some studies have suggested that OSA impairs glucose tolerance independent of the associated obesity [111,112]. A large cohort study, however, did not document that SDB was an independent risk factor for diabetes [113]. Diabetic patients did seem to have more central apnea or periodic breathing. OSA patients with smaller degrees of obesity had a more clear-cut impairment of glucose control secondary to SDB. The impaired glucose control in OSA patients that is independent of obesity is thought secondary to increased sympathetic activity. Harsch et al [114] found that CPAP treatment rapidly improves insulin sensitivity in OSA patients. The improvement was greater in patients with lower body mass. Significant improvement in glucose control with long-term CPAP has yet to be demonstrated.

Mild to moderate chronic sleep deprivation is a chronic behavior in many industrialized societies. Spiegel et al [115] found sleep restriction to 4 hours of sleep at night impaired glucose tolerance, increased the evening cortisol, and increased sympathetic activation in normal subjects. The authors hypothesized that sleep debt may increase the severity of age-related chronic disorders.

Fibromyalgia syndrome

Fibromyalgia syndrome is defined by the American College of Rheumatology as the presence of widespread musculoskeletal pain for at least 3 months, which is bilateral above and below the waist, including axial pain and the presence of 11 of 18 tender points [116]. Fibromyalgia syndrome should be considered a syndrome rather than a disease process. Fibromyalgia affects about 3% of the population aged 30 to 50 years and 70% to 90% of patients are women [117]. Depression is common in the disorder. The pathophysiology of fibromyalgia syndrome is very complex [118–121]. The main mechanism is thought to be central sensitization of nociceptive neurons in the dorsal horn of the spinal cord with activation of *N*-methyl-D-aspartate receptors [121]. This central sensitization results in generalized heightened pain sensitivity caused by pathologic nociceptive processing within the central nervous system. There is a threefold increase in substance P and a decrease in serotonin levels in the cerebrospinal fluid [120].

Sleep complaints are common and include nonrestorative sleep, fragmented sleep, and insomnia. Poor sleep seems to worsen pain symptoms in 67% of the patients [118]. Sleep studies in fibromyalgia syndrome patients have shown decreased total sleep time, decreased slow wave and REM sleep, and increased arousals [117]. An interesting EEG pattern (alpha sleep or alpha-NREM anomaly) was first described in fibromyalgia syndrome patients by Moldofsky [122,123]. This is characterized by prominent alpha activity (8–13 Hz) persisting into NREM sleep (alpha intrusion). Alpha

activity is normally present during relaxed wake and following brief awakenings (arousals) but is normally virtually absent during stages 2 to 4 of NREM sleep. Alpha intrusion into slow wave (delta) sleep is called alpha-delta sleep. Since that time it has been recognized that the alpha-NREM sleep anomaly is not specific for fibromyalgia and is not present in all patients with this syndrome. Other groups in which the alpha-NREM sleep anomaly can be found include patients with chronic pain syndromes, depression, and diverse causes of nonrestorative sleep. Indeed, alpha sleep has been seen in up to 15% of normal subjects [124]. A variant of alpha sleep (phasic alpha activity) in which alpha intrusion is seen mainly during slow wave sleep rather than being present diffusely in NREM sleep seemed to be present in fibromyalgia syndrome patients with prominent sleep disturbance, subjective feeling of superficial sleep, and more pain and stiffness [125].

Treatments for fibromyalgia include antidepressants, hypnotics, muscle relaxers, cognitive therapy, exercise, biofeedback, and hypnosis [123]. Patients should incorporate good sleep hygiene habits. Furthermore, screening for primary sleep disorders is also indicated. Of note, fibromyalgia patients have a higher prevalence of restless legs syndrome than controls [126]. Some fibromyalgia syndrome patients have clinical improvement with low doses of antidepressants, whereas others require the usual doses needed for an antidepressant effect. Antidepressants that have been used include trazodone, fluoxetine, amitriptyline, and venlafaxine, sometimes in combination [127]. Recently sodium oxybate (γ-hydroxybutyrate) was found to be effective in improving subjective and objective sleep quality (assessed by polysomnography) and daytime symptoms using a placebo-controlled design [128]. This medication is currently approved by the Food and Drug Administration only for treatment of cataplexy in narcolepsy. The 5HT3 receptor antagonist tropisetron was also found to be effective [129]. The role of these new treatments in the routine treatment of fibromyalgia remains to be determined.

References

[1] Leung RST, Bradley TD. Sleep apnea and cardiovascular disease. State of the art. Am J Respir Crit Care Med 2001;164:2147–65.

[2] Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier Nieto F, et al. Sleep disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001;163:19–25.

[3] Lavie P, Herer P, Peled R, Berger I, Yoffe N, Zomer J, et al. Mortality in sleep apnea patients: a multivariate analysis of risk factors. Sleep 1997;20:377–80.

[4] Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea. Am J Respir Crit Care Med 2002;166:159–65.

[5] Suzuki M, Guilleminault G, Otsuka K, Shimomi T. Blood pressure ''dipping'' and ''non-dipping'' in obstructive sleep apnea syndrome patients. Sleep 1996;19:382–7.

[6] Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnea as a cause of systemic hypertension: evidence from a canine model. J Clin Invest 1997;99:106–9.
[7] Kales A, Bixler EO, Cadieux RJ, Schneck DW, Shaw LC III, Locke TW, et al. Sleep apnea in a hypertensive population. Lancet 1984;3:1005–8.
[8] Carlson JT, Hedner JA, Ejnell H, Peterson LE. High prevalence of hypertension in sleep apnea patients independent of obesity. Am J Respir Crit Care Med 1994;150:72–7.
[9] Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep- disordered breathing and hypertension. N Engl J Med 2000;342:1378–84.
[10] Verdecchia P, Schillaci G, Guerrieri M, Gatteschi C, Benemio G, Boldrini F, et al. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. Circulation 1990;81:528–36.
[11] Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Sullivan CE, et al. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. Circulation 2003;107:68–73.
[12] Pepperell JCT, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnea: a randomized parallel trial. Lancet 2002;359:204–10.
[13] Faccendia J, Mackay TW, Bood NA, Douglas NJ. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med 2001;163:344–8.
[14] Engleman HM, Gough K, Martin SE, Kingshott RN, Padfiled PL, Douglas NJ. Ambulatory blood pressure on and off continuous positive airway pressure therapy for the sleep apnea-hypopnea syndrome: effects in ''non-dippers. Sleep 1996;19:378–81.
[15] Dimsdale JE, Loredo JS, Profant J. Effect of continuous positive pressure on blood pressure placebo trial. Hypertension 2000;35:144–7.
[16] Javaheri S, Parker TJ, Wexler L, Michaels SE, Stanberry E, Nishyama H, et al. Occult sleep- disordered breathing in stable congestion heart failure. Ann Intern Med 1995;122: 487–92.
[17] Lanfranchi PA, Somers VK, Braghiroli A, Corra U, Eleuteri E, Giannuzzi P. Central sleep apnea in left ventricular dysfunction: prevalence and implications for arrhythmic risk. Circulation 2003;107:727–32.
[18] Sin D, Fitzgerald F, Parker J. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med 1999;160: 1101–6.
[19] Malone S, Liu PP, Holloway R, Rutherford R, Xie A, Bradley TD. Obstructive sleep apnea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. Lancet 1991;33:1480–4.
[20] Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med 2003;348:1233–41.
[21] Xie A, Skatrud JB, Puleo S, Rahko PS, Dempsey JA. Apnea-hypopnea threshold for CO_2 in patients with congestive heart failure. Am J Respir Crit Care Med 2002;165:1245–50.
[22] Naughton M, Benard D, Tam A, Rutherford R, Bradley TD. Role of hyperventilation in the pathogenesis of central sleep apnea in patients with congestive heart failure. Am Rev Respir Dis 1993;148:330–8.
[23] Solin P, Bergin P, Richardson M, Kaye DM, Walters EH, Naughton MT. Influence of pulmonary capillary wedge pressure on central apnea in heart failure. Circulation 1999; 99:1574–9.
[24] Hanly PJ, Zuberi-Khokhar N. Increased mortality associated with Cheyne-Stokes respiration in patients with congestive heart failure. Am J Respir Crit Care Med 1996;153: 272–6.

[25] Lanfrachi PA, Braghiroli A, Bosimini E, Mazzuero G, Colombo R, et al. Prognostic values of Cheyne-Stokes respiration in chronic heart failure. Circulation 1999;99:1435–40.
[26] Sin DD, Logan AG, Fitzgerald FS, Liu PP, Bradley TD. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. Circulation 2000;102:61–6.
[27] Naughton MW, Liu P, Benard DC, Goldstein RS, Bradley TD. Treatment of congestive heart failure and Cheyne-Stokes respiration during sleep by continuous positive airway pressure. Am J Respir Crit Care Med 1995;151:92–7.
[28] Teschler H, Dohring J, Wang YM, Berthon-Jones M. Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. Am J Respir Crit Care Med 2001;164:614–9.
[29] Pepperell JCT, Maskell NA, Jones DR, Lanford-Wiley BA, Crosthwaite N, Stradling JR, et al. A randomized controlled trial of adaptive ventilation for Cheyne-Stokes breathing in heart failure. Am J Respir Crit Care Med 2003;168:1109–14.
[30] Javaheri S. Pembrey's dream: the time has come for a long term trial of nocturnal supplemental oxygen to treat central sleep apnea in congestive heart failure. Chest 2003; 123:322–5.
[31] Krachman SL, D'Alonzo GE, Berger TJ, Eisen HJ. Comparison of oxygen therapy with nasal continuous positive airway pressure on Cheyne-Stokes respiration during sleep in congestive heart failure. Chest 1999;116:1550–7.
[32] Harbison J, O'Reilly P, McNicholas WT. Cardiac rhythm disturbances in obstructive sleep apnea syndrome: effects of nasal continuous positive airway pressure therapy. Chest 2000;118:591–5.
[33] Javaheri S, Corbett WS. Association of low P_{CO_2} with central sleep apnea and ventricular arrhythmias in ambulatory patients with stable heart failure. Ann Intern Med 1998;28: 204–7.
[34] Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, Ballma KV, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation 2003;107: 2589–94.
[35] Khoo MC, Belozeroff V, Berry RB, Sassoon CSH. Cardiac autonomic control in obstructive sleep apnea: effects of long term CPAP therapy. Am J Respir Crit Care Med 2001;164:807–12.
[36] Garrigue S, Bordier P, Jais P, Shah DC, Hocini M, Raherison C, et al. Benefit of atrial pacing in sleep apnea syndrome. N Engl J Med 2002;346:404–12.
[37] Peters RW, Zoble RG, Brooks MM. Onset of myocardial infarction during sleep. Clin Cardiol 2002;25:237–41.
[38] Peker Y, Hender J, Kraiczi H, Loth S. Respiratory disturbance index: an independent predictor of mortality in coronary artery disease. Am J Respir Crit Care Med 2000;162: 81–6.
[39] Kreiger J, Sforza E, Barthelmebs M, et al. Overnight decreases in hematocrit after nasal CPAP with patients with OSA. Chest 1990;97:729–30.
[40] Chin K, Ohi M, Kita H, et al. Effects of NCPAP therapy on fibrinogen levels in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 1996;153:1972–6.
[41] Lavie L, Kraiczi H, Hefetz A, Ghandour H, Perelman A, Hedner J, et al. Plasma vascular endothelial growth factor in sleep apnea syndrome: effects of nasal continuous positive air pressure treatment. Am J Respir Crit Care Med 2002;165:1624–8.
[42] Dyugovskaya L, Lavie P, Lavie L. Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. Am J Respir Crit Care Med 2002;165:934–9.
[43] Schulz R, Mahmoudi S, Hattar K, Sibelius U, Olschewski H, Mayer K, et al. Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea: impact of continuous positive airway pressure therapy. Am J Respir Crit Care Med 2000; 162:566–70.

[44] Bokinsky G, Miller M, Ault K, Husband P, Mitchell J. Spontaneous platelet activation and aggregation during obstructive sleep apnea and its response to therapy with nasal continuous positive airway pressure: a preliminary investigation. Chest 1995;108:625–30.
[45] Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation 2002;105: 2462–4.
[46] Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, et al. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation 2003; 107:1129–34.
[47] Shimizu K, Chin K, Nakamura T, Masuzaki H, Ogawa Y, Hosokawa R, et al. Plasma leptin levels and cardiac sympathetic function in patients with obstructive sleep apnoea-hypopnoea syndrome. Thorax 2002;57:429–34.
[48] Turner Warwick. Epidemiology of nocturnal asthma. Am J Med 1988;85:6–8.
[49] Martin RJ. Nocturnal asthma: circadian rhythms and therapeutic interventions. Am Rev Respir Dis 1993;147:525–8.
[50] Beam WR, Weiner DE, Martin RJ. Timing of prednisone and alterations of airways inflammation in nocturnal asthma. Am Rev Respir Dis 1992;146:1524–30.
[51] Weersink EJM, Douma RR, Postma DS, Koeter GH. Fluticasone propionate, salmeterol xinafoate, and their combination in the treatment of nocturnal asthma. Am J Respir Crit Care Med 1997;155:1241–6.
[52] Selby C, Engleman HM, Fitzpatrick MF, Sime PM, Mackay TW, Douglas NJ. Inhaled salmeterol or oral theophylline in nocturnal asthma? Am J Respir Crit Care Med 1997; 155:104–8.
[53] Wiegand L, Mende CN, Zaidel G, Zwillich CW, Petrocella VJ, Yancey S, et al. Salmeterol vs Theophylline: sleep and efficacy outcomes in patients with nocturnal asthma. Chest 1999;115:1525–32.
[54] Chan CS, Woolcock AJ, Sullivan CE. Nocturnal asthma: role of snoring and obstructive sleep apnea. Am Rev Respir Dis 1988;137:1502–4.
[55] Douglas NJ, Flenley DC. Breathing during sleep in patients with obstructive lung disease. Am Rev Respir Dis 1990;141:1055–69.
[56] Fletcher EC, Gray BA, Levin DC. Nonapneic mechanisms of arterial oxygen desaturation during rapid-eye-movement sleep. J Appl Physiol 1983;54:632–9.
[57] Hudgel DW, Martin RJ, Capehart M, et al. Contribution of hypoventilation to sleep oxygen desaturation in chronic obstructive pulmonary disease. J Appl Physiol 1983;55: 669–77.
[58] Goldstein RS, Ramcharan V, Bowes G, et al. Effect of supplemental nocturnal oxygen on gas exchange in patients with severe obstructive lung disease. N Engl J Med 1984;310: 425–9.
[59] Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. Ann Intern Med 1980;93:391–8.
[60] Chaouat A, Weitzenblum E, Kessler R, et al. Outcome of COPD patients with mild daytime hypoxemia with or without sleep-related oxygen desaturation. Eur Respir J 2001; 17:848–55.
[61] Berry RB, Desa MM, Branum JP, Light RW. Effect of theophylline on sleep and sleep-disordered breathing in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1991;143:245–50.
[62] Martin RJ, Bartelson BL, Smith P, Hudgel DW, Lewis D, Pohl G, et al. Effect of ipratropium bromide treatment on oxygen saturation and sleep quality in COPD. Chest 1999;115:1338–45.
[63] Girault C, Muir JF, Mihaltan F, et al. Effects of repeated administration of zolpidem on sleep, diurnal and nocturnal respiratory function, vigilance, and physical performance in patients with COPD. Chest 1996;110:1203–11.

[64] Orr WC, Johnson LF, Robinson MG. The effect of sleep on swallowing, esophageal peristalsis, and acid clearance. Gastroenterology 1984;86:814–9.
[65] Kahrilas PJ, Dodds WJ, Dent J, Haeberle B, Hogan WJ, Arndorfer RC. Effect of sleep, spontaneous gastroesophageal reflux, and a meal on upper esophageal sphincter pressure in normal human volunteers. Gastroenterology 1987;92:466–71.
[66] Mittal RK, Holloway RH, Panagini R, Blackshaw A, Dent J. Transient lower esophageal sphincter relaxation. Gastroenterology 1995;109:601–10.
[67] Mittal R, Balaban DH. The esophageal junction. N Engl J Med 1997;336:924–32.
[68] Freidin N, Fisher MJ, Taylor W, Boyd D, Surratt P, McCallum RW, et al. Sleep and nocturnal acid reflux in normal subjects and patients with reflux oesophagitis. Gut 1991; 32:1275–9.
[69] Schneyer LH, Pigman W, Hanahan L, et al. Rate of flow of human parotid, sublingual, and submaxillary secretion during sleep. J Dent Res 1956;35:109–14.
[70] Orr WC, Johnson LF. Responses to different levels of esophageal acidification during waking and sleep. Dig Dis Sci 1998;43:241–5.
[71] Orr WC, Elsenbruch S, Harnish MJ, et al. Proximal migration of esophageal acid perfusions during waking and sleep. Am J Gastroenterol 2000;95:37–42.
[72] Farup C, Kleinman L, Sloan S, Ganoczy D, Chee D, Lee C, et al. The impact of nocturnal symptoms associated with gastroesophageal reflux disease on health-related quality of life. Arch Intern Med 2001;161:45–70.
[73] Shaker R, Castell DO, Schoenfeld PS, Spechler SJ. Nighttime heartburn is an under-appreciated clinical problem that impacts sleep and daytime function: the results of a Gallup Survey conducted on behalf of the American Gastroenterological Association. Am J Gastroenterol 2003;98:1487–93.
[74] Lagergren J, Bergstrom R, Lindgren A, Nuyren O. Symptomatic gastroesophageal reflux as a risk factor or esophageal adenocarcinoma. N Engl J Med 1999;340:825–31.
[75] Gerson LB, Edson R, Lavori PW, Triadafilopoulos G. Use of a simple symptom questionnaire to predict Barrett's esophagus in patients with symptoms of gastroesophageal reflux. Am J Gastroenterol 2001;96:2005–12.
[76] Eloubeidi MA, Provenzale D. Clinical and demographic predictors of Barrett's esophagus among patients with gastroesophageal reflux disease: a multivariable analysis in veterans. J Clin Gastroenterol 2001;33:306–9.
[77] Kahrilas PJ, Quigley EMM. Clinical esophageal pH recording: a technical review for practice guideline development. Gastroenterology 1996;110:1982–96.
[78] Gislason T, Janson C, Vermeire P, Plaschke P, Bjornsson E, Gislason D, et al. Respiratory symptoms and nocturnal gastroesophageal reflux: a population-based study of young adults in three European countries. Chest 2002;121:158–63.
[79] Jack CIA, Calverley PMA, Donnelly RJ, Tran J, Russell G, Hind CRK, et al. Simultaneous tracheal and oesophageal pH measurement in asthmatic patients with gastro-oesophageal reflux. Thorax 1995;50:201–4.
[80] Cuttitta G, Cibella F, Visconti A. Spontaneous gastroesophageal reflux and airway patency during the night in adult asthmatics. Am J Respir Crit Care Med 2000;151:177–81.
[81] Harding SM, Richter JE, Guzzo MR, Schan CA, et al. Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. Am J Med 1996;100:395–405.
[82] Gibson PG, Henry RL, Coughlan JL. Gastro-oesophageal reflux treatment for asthma in adults and children. Cochran Database Syst Rev 2003;2:CD001496.
[83] Thurnheer R, Henz S, Knoblauch A. Sleep-related laryngospasm. Eur Respir J 1997;10: 2084–6.
[84] Green BT, Broughton WA, O'Connor JB. Marked improvement in nocturnal gastroesophageal reflux in a large cohort of patients with obstructive sleep apnea. Arch Intern Med 2003;163:41–5.
[85] Graf KI, Karaus M, Heinemann S, et al. Gastroesophageal reflux in patients with sleep apnea syndrome. Z Gastroenterol 1995;33:689–93.

[86] DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. The Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol 1999;94:1434–42.
[87] Khoury RM, Camacho-Lobato L, Katz PO, Mohiuddin MA, Castell DO. Influence of spontaneous sleep positions on nighttime recumbent reflux in patients with gastroesophageal reflux disease. Am J Gastroenterol 1999;94:2069–73.
[88] Kuo B, Castell DO. Optimal dosing of omeprazole 40 mg daily: effects on gastric and esophageal pH and serum gastrin in healthy controls. Am J Gastroenterol 1996;91:1532–8.
[89] Peghini PL, Katz PO, Bracy NA, et al. Nocturnal recovery of gastric acid secretion with twice-daily dosing of proton pump inhibitors. Am J Gastroenterol 1998;93:763–7.
[90] Spechler SJ, Lee E, Ahnen D, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. JAMA 2001;285:2331–8.
[91] Kerr P, Shoenut JP, Steens RD, Millar T, Miclfliker AB, Kryger MH. Nasal continuous positive airway pressure: a new treatment for nocturnal gastroesophageal reflux? J Clin Gastroenterol 1993;17:276–80.
[92] Parker KP. Sleep disturbances in dialysis patients. Sleep Med Rev 2003;7:131–43.
[93] Holley JL, Nespor S, Rault R. Characterizing sleep disorders in chronic hemodialysis patients. ASAIO Trans 1991;37:M456–7.
[94] Kimmel PL, Miller G, Mendelson WB. Sleep apnea syndrome in chronic renal disease. Am J Med 1989;86:308–14.
[95] Winkelman JW, Chertow GM, Lazarus JM. Restless legs syndrome in end-stage renal disease. Am J Kidney Dis 1996;28:372–8.
[96] Earley CJ. Clinical practice: restless legs syndrome. N Engl J Med 2003;348:2103–9.
[97] Stepanski E, Faber M, Zorick F, et al. Sleep disorders in patients on continuous ambulatory peritoneal dialysis. J Am Soc Nephrol 1995;6:192–7.
[98] Krueger JM, Majde JA, Obale F. Sleep in host defense. Brain Behav Immun 2003;17(Suppl 1):S41–7.
[99] Norman SE, Chediak AD, Freeman C, et al. Sleep disturbances in HIV infected men. AIDS 1996;4:775–81.
[100] Morlese JF, Qazi NA, Gazzard BG, et al. Nevirapine-induced neuropsychiatric complications, a class effect of non-nucleoside reverse transcriptase inhibitors? AIDS 2002;16:1840–1.
[101] Darko DF, McCutchan J, Kripke D, Gillin JC, Golshan S. Fatigue, sleep disturbances, disability and indices of progression in HIV infection. Am J Psychiatry 1992;149:514–20.
[102] Norman SE, Chediak AD, Freeman C, Kiel M, Mendez A, Duncan R, et al. Sleep disturbances in men with asymptomatic human immunodeficiency virus (HIV) infection. Sleep 1992;15:150–5.
[103] Greenberg HE, Ney G, Scharf SM, Ravdin L, Hilton E. Sleep quality in Lyme disease. Sleep 1995;18:912–6.
[104] Spiegel K, Sheridan JF, Van Cauter E. Effect of sleep deprivation on response to immunization. JAMA 2002;288:1471–2.
[105] Grunstein RR, Sullivan CE. Sleep apnea and hypothyroidism: mechanisms and management. Am J Med 1988;85:775–9.
[106] Pelttari L, Rauhala E, Polo O, et al. Upper airway obstruction in hypothyroidism. J Intern Med 1994;236:177–81.
[107] Winkelman JW, Goldman H, Piscatelli N, et al. Are thyroid function tests necessary in patients with suspected sleep apnea? Sleep 1996;19:790–3.
[108] Grunstein RR, Ho KY, Sullivan CE. Sleep apnea in acromegaly. Ann Intern Med 1991;115:527–32.
[109] Astrom C, Christensen L, Gjerris F, et al. Sleep in acromegaly before and after treatment with adrenalectomy. Neuroendocrinology 1991;53:328–31.

[110] Shipley JE, Schteingart DE, Tandon R, et al. Sleep architecture and sleep apnea in patients with Cushing's disease. Sleep 1992;15:514–8.
[111] Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle aged and overweight men. Am J Respir Crit Care Med 2002;165:677–82.
[112] Meslier N, Gagnadoux F, Giraud P, Person C, Ouksel H, Urban T, et al. Impaired glucose-insulin metabolism in males with obstructive sleep apnea syndrome. Eur Respir J 2003;22:156–60.
[113] Sanders MH, Givelber R. Sleep disordered breathing may not be an independent risk factor for diabetes, but diabetes may contribute to the occurrence of periodic breathing in sleep. Sleep Med 2003;4:349–50.
[114] Harsch IA, Pour Schahin S, Radespiel-Troger M, Weintz O, Jahreiss H, Fuchs FS, et al. CPAP treatment rapidly improves insulin sensitivity in patients with OSAS. Am J Respir Crit Care Med 2004;169:159–62.
[115] Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet 1999;354:1435–9.
[116] Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombadier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the classification of fibromyalgia: report of the multi-center criteria committee. Arthritis Rheum 1990;33:160–72.
[117] Harding SM. Sleep in fibromyalgia patients: subjective and objective findings. Am J Med Sci 1998;315:367–76.
[118] Okifugi A, Turk DC. Stress and psychophysiological dysregulation in patients with fibromyalgia syndrome. Appl Psychophysiol Biofeedback 2002;27:129–41.
[119] Neeck G. Pathogenic mechanisms of fibromyalgia. Ageing Res Rev 2002;1:243–55.
[120] Pillemer SR, Bradley LA, Crofford LJ, Moldofsky H, Chrousos GP. The neuroscience and endocrinology of fibromyalgia. Arthritis Rheum 1997;40:1928–39.
[121] Neeck G, Crofford LJ. Neuroendocrine perturbations in fibromyalgia and chronic fatigue syndrome. Rheum Dis Clin North Am 2000;26:989–1002.
[122] Branco J, Atalaia A, Paiva T. Sleep cycles and alpha-delta sleep in fibromyalgia syndrome. J Rheumatol 1994;21:1113–7.
[123] Moldofsky H. Management of sleep disorders in fibromyalgia. Rheum Dis Clin North Am 2002;28:353–68.
[124] Mahowald ML, Mahowald MW. Nighttime sleep and daytime functioning (sleepiness and fatigue) in less well-defined chronic rheumatic diseases with particular reference to the "alpha-delta NREM sleep anomaly." Sleep Med 2000;1:195–207.
[125] Roizenblatt S, Moldofsky H, Benedito-Silva AA, Tufik S. Alpha sleep characteristics in fibromyalgia. Arthritis Rheum 2001;44:222–30.
[126] Yunus MB, Aldag J. Restless legs syndrome and leg cramps in fibromyalgia syndrome: a controlled study. BMJ 1996;312:1339.
[127] Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arthritis Rheum 1996;39:1852–9.
[128] Scharf MB, Baumann M, Berkowitz DV. The effects of sodium oxybate on clinical symptoms and sleep patterns in patients with fibromyalgia. J Rheumatol 2003;30:1070–4.
[129] Farber L, Stratz TH, Bruckle W, Spath M, Pongratz D, Lautenschlager J, et al. Short-term treatment of primary fibromyalgia with the 5–HT3-receptor antagonist tropisetron: results of a randomized, double-blind, placebo-controlled multicenter trial in 418 patients. Int J Clin Pharmacol Res 2001;21:1–13.