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Sleep Disturbances and their Relationship to Cardiovascular Disease

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Abstract

Sleep disturbances are a common problem with chronic insomnia occurring in 10% of the general adult population and obstructive sleep apnea present in 4% and 2% of middle-aged men and women respectively. In addition, Americans are sleeping fewer hours per night than they did 20 years ago. There is now increasing evidence that reductions and increases in sleep duration, and various sleep disorders including obstructive sleep apnea and insomnia may be causal factors in the development of cardiovascular disease. Some of the evidence linking disturbances of sleep with cardiovascular disease is described in this review.

Keywords

Cardiovascular disease; Sleep; Insomnia; Sleep Apnea

The ancient physician Hippocrates once wrote “Both sleep and insomnolency, when immoderate, are bad” (*Aphorisms. Hippocrates, 400 B.C.*). This quote is evidence that the impact of perturbations in normal sleep have been known for thousands of years. However, only recently has research demonstrated that sleep disturbances are associated with a number of medical conditions including diabetes mellitus,1 cancer,[2] and very importantly, cardiovascular disease (CVD).[3] This review will outline some of the linkages between sleep disturbances and CVD. Before presenting this evidence, however, it is important to understand some of the basics of normal sleep and some theories concerning why sleep is a biologic imperative, as well as the overall prevalence of sleep problems in the population.

Normal Sleep

A number of well known authors have provided literary descriptions of sleep. For example, Shakespere in Macbeth described sleep as the “balm of hurt minds, great natures second course, chief nourisher in lifes feast” (*Macbeth. William Shakespere, 1604*), and Cervantes in Don Quixote wrote that sleep was “the food that cures all hunger, the water that quenches all thirst” (*Don Quixote, Miguel de Cervantes, 1602*). However, from a behavioral perspective there are 4 attributes that define sleep:[4]

1. reduction in physical activity;
2. typical body posture such as recumbent with eyes closed;
3. decreased responsiveness to external stimuli;

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4. reversibility in contrast to other states of reduced consciousness such as coma.

From a physiologic perspective, sleep in contradistinction to wakefulness is defined by characteristic findings on the electroencephalogram, electrooculogram and chin electromyogram. From the patterning of these findings, sleep is divided into 2 primary stages, rapid eye movement (REM) and non rapid eye movement (NREM) sleep. REM sleep is the stage during which dreaming most commonly occurs. Stages of NREM and REM sleep are bundled together and occur in cycles throughout the sleep period with approximately 4 of these cycles occurring per night. In general, sleep occupies approximately 1/3 of our lives.

Sleep is a biologic imperative. Sleep is universally found in mammalian species, and rest/activity periods are observed in many lower order animals as well.[5] Prolonged sleep deprivation in experimental animals results in death.[6] However, why we sleep remains a mystery although there are several theories.[4] The “inactivity” theory proposes that the inactivity of sleep at night keeps an animal out of harms way. A counter-argument to this theory is that being alert at night is a better defense mechanism than sleep. Related is the “energy conservation” theory which argues that sleep reduces energy consumption at a time when searching for food is less productive. However, there are some animals that are awake at night to hunt. A more popular is the “restorative” theory which proposes that sleep is a time when the body repairs and restores itself from damage occurring during wakefulness. In its favor are data indicating that some restorative functions in the body are more active during sleep. Finally, sleep may be necessary for changes in the structure and organization of the brain, or “brain plasticity”. This may be especially important in infants and children who spend more of their day asleep than adults. Even in adults sleep deprivation is associated with impairment in memory and cognition.[4] Although these theories are unproven, they do provide some context to the age old question of “Why do we sleep?”.

Prevalence of Sleep Disturbances

Sleep disturbances are a common problem in the general population. Over 30% of all adults have a current symptom of insomnia, and chronic insomnia occurs in 10% of the general adult population.[7, 8] In addition, symptoms of sleep disturbances are observed more frequently in women, and increase with age.[8] In persons older than 65 years, almost 50% will have a complaint of disturbed sleep.[7] It is now recognized that sleep disturbances are associated with reduced quality of life, man made catastrophes, and billions of dollars in damages and lost productivity.[8]

Sleep Duration

It is now established that amount of time that Americans spend asleep has been decreasing with the percentage of men and women sleeping less than 6 hours increasing markedly over the past 2 decades.[8,9] Of particular relevance in this regard are several large studies demonstrating that both short and long sleep durations are associated with increased mortality.[10, 11,12-14] In one such study using the Cancer Prevention Study II database,[10] over 1.1 million adults were queried in 1982 regarding their sleep duration and followed up 6 years later for vital status. A “U” shaped distribution for both men and women was observed with the best survival experienced at a usual sleep duration of 7 hours. Adjusted hazard ratios indicating higher mortality rates progressively increased with decreasing usual sleep duration so that at 3 hours, they were 1.33 for women and 1.19 for men. Adjusted hazard ratios also increased with increasing sleep duration. At a sleep duration exceeding 10 hours, they were 1.41 for women and 1.34 for men. Similar data have been reported in other large cohorts including the Nurses Health Study and the Japan Collaborative Study on Evaluation of Cancer Risk.[13, 14] Additional evidence indicates that short sleep durations are associated with an increased incidence of cardiovascular mortality.[12] However, other causes of death also are possible.

Whether reduced sleep duration is a primary risk factor for early mortality or whether it is just a marker for various co-morbid medical conditions is still unclear. Nevertheless, it is less clear why an increase in sleep duration is linked to increased mortality.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a condition caused by repetitive episodes of complete or partial upper airway obstruction during sleep, thus producing repetitive episodes of arousal from sleep and hypoxemia.[15] Common symptoms include daytime hypersomnolence and loud snoring.15 It is estimated from the Wisconsin Sleep Cohort, a large population study, that the prevalence of symptomatic OSA is 4% and 2% in middle-aged men and women respectively, 16 but is even higher in the elderly. 17 Evidence from both clinical populations and the general populace have demonstrated that there is an increased prevalence of hypertension in persons with OSA independent of other conditions such as obesity.[1819,] 20 Furthermore, longitudinal studies suggest that OSA is an independent risk factor for the incident hypertension.21, 22 In one study there was almost a 3 fold greater risk of developing hypertension over a 4-8 year period in persons with OSA compared to those without OSA.[21] Moreover, the risk increases with increasing severity of OSA. Additional evidence supporting a causal role for OSA in the development of hypertension are studies demonstrating that treatment of OSA with continuous positive airway pressure (CPAP) can lead to an improvement in blood pressure.[18] Because hypertension is an important risk factor for CVD, it follows that OSA should be a risk for CVD as well.

There is considerable evidence indicating that OSA is an independent risk factor for the development of CVD. Cross-sectional analyses of data from both clinical and general population cohorts demonstrate that increasing severity of OSA is associated with a greater likelihood of having CVD.23-[26] For example, in the Sleep Heart Health Study (SHHS), a population-based cohort of 6,441 adults over the age of 40 years, the prevalence of CVD was 23% in those in the highest quartile of OSA severity versus 11% in the lowest quartile.[23] Recent data from a large clinically derived population demonstrate a greater risk for an incident CVD event in persons with severe OSA.27 Furthermore, treatment of OSA with continuous positive airway pressure reduced the risk to a level observed in those without OSA.27

In addition to a greater risk of CVD, OSA appears to be a risk factor for the occurrence of various arrhythmias. In a recent analysis of data from the SHHS, persons with severe OSA were approximately twice as likely to have ventricular ectopy and 6 times as likely to have atrial fibrillation.[28]

The underlying mechanisms responsible for the increased risk of CVD in those with OSA remain to be precisely defined. However, it does appear that OSA is associated with the presence of atherosclerosis in large blood vessels,[29, 30] as well as in the coronary arteries.[31] One recent study found angiographic luminal narrowing of the coronary arteries to have progressed over a 3 year period in a cohort of snoring women, many of whom presumptively had OSA.[31] Obviously, because hypertension appears to be a risk factor for both OSA and CVD, it is possible that CVD attributable to OSA could be mediated by hypertension. Notwithstanding this obvious linkage, evidence suggests that other factors can be contributing as well. Repetitive episodes of airway obstruction from OSA are associated with recurrent transient hypoxemia and hypercapnia. This may lead to increased sympathetic activity.[32] Obstructive sleep apnea also has been linked to endothelial dysfunction and increased levels of inflammatory mediators such as IL8,[33] which could promote the development of both hypertension and coronary heart disease. Recently, the relationship between OSA and diabetes mellitus has been emphasized. In cross-sectional analyses in a large population cohort, increasing severity of OSA was found to be associated with a greater likelihood of having an

impaired or frankly diabetic fasting glucose.[34] In addition, in those with OSA, diabetic control as measured by HgA1c levels is improved after treatment with CPAP providing additional evidence that OSA impairs glucose control.[35] Therefore, because diabetes mellitus is a major risk factor for the occurrence of CVD, it is possible that some of the impact on OSA on increasing the likelihood of CVD is mediated through diabetes.

Inasmuch as OSA appears to be a risk factor for CVD, it is not surprising that there is emerging evidence that both all cause mortality and mortality attributable to CVD is higher among those with OSA. In one large study from a clinic-derived population, mortality from CVD among OSA patients was higher over a 10 year follow-up than in those without OSA after controlling for a number of confounding factors.[27] In another study using a clinic-derived population, there was a greater likelihood of a composite endpoint of stroke or death among those with OSA over a median follow-up of 3.4 years.[36] Very recently, compelling data from the Wisconsin Sleep Cohort demonstrate that both all cause and CVD mortality were higher over a follow up period of 18 years in those with OSA.[37]

Insomnia

Insomnia is defined as the inability to fall asleep, inability to maintain sleep or the perception of disturbed sleep.[38, 39] It is subjective. Therefore, even if objective testing fails to demonstrate a sleep disturbance, a person is considered insomnic if they complain that they have disturbed sleep. Insomnia commonly is a chronic condition. In one study, 40.8% of individuals who had endorsed “Frequent” insomnia had similar symptoms 12 years later.[40] Insomnia is highly prevalent. As noted previously, over 30% of the general adult populace at any time will have at least one symptom consistent with insomnia, and 10% of the general population will report chronic insomnia.[7]

Linkages between the presence of insomnia and CVD have been sought for a number of years. 41 Some, but not all studies, have found that there is a higher prevalence of CVD in those with insomnia.41 More recently, cross-sectional data from a large cohort in Tennessee observed that the prevalence of both heart disease and hypertension were higher in those with insomnia. [42] In addition, a 6 year follow-up of approximately 13,000 persons from the Atherosclerosis Risk in Communities Study observed that there was a slightly higher risk of developing CVD (OR=1.5) in those with symptoms consistent with insomnia or subjectively poor sleep.[43]

If insomnia is a risk factor for CVD, the underlying mechanism is unclear. Insomnia is associated with an increased in sympathetic nervous system activity,[44] and this could be responsible for more cardiovascular morbidity. There also could be an increase in stress-related hormones or other mediators. Alternatively, insomnia could just be a marker for other CVD risk factors or serious co-morbid conditions.

Restless Legs Syndrome

Restless Legs Syndrome is a disorder characterized by an almost irresistible urge to move, usually associated with disagreeable leg sensations, worse during inactivity, and often interfering with sleep. It is a clinical diagnosis confirmed by the presence of 4 criteria outlined by the International Restless Legs Syndrome Study Group:[45]

1. An urge to move the legs, usually accompanied or caused by uncomfortable or unpleasant sensations in the legs.
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.

3. The urge to move or unpleasant sensations are partially or totally relieved by movement such as walking or stretching, at least as long as the activity continues.
4. The urge to move or unpleasant sensations are worse in the evening or at night than during the day, or only occur in the evening or night.

Recently, data from 2 large cohort studies have found a significant cross-sectional association between RLS and CVD. In the Wisconsin Sleep Cohort, the risk of CVD associated with daily symptoms of RLS was 2.58 times the risk of those without RLS symptoms.[46] Subsequently, the SHHS observed that persons with severe bothersome RLS were 2.32 times more likely to have coronary artery disease than those without RLS.[47] However, because these data cross-sectional, it is not clear whether RLS is a risk factor for incident CVD. In addition, mechanisms responsible for these observations have not yet been identified.

Parasomnias

Parasomnias are conditions which are associated with sleep, but are not primary sleep disorders. Commonly observed parasomnias are sleep terrors, nightmares and sleep walking. Data linking parasomnias to cardiovascular disease are sparse. In one study of the elderly, chest pain and palpitations were more commonly noted in those with nightmares.[48] However, chest pain and palpitations are not perfect surrogates for the presence of CVD, and these symptoms might be manifestations of other conditions in some of the affected individuals.

Reverse Causality

Although it is tempting to infer that sleep disorders play a causal role in the pathogenesis of CVD, this hypothesis in most cases is not proven. The data linking sleep duration, insomnia and restless legs syndrome to CVD is primarily cross-sectional. Thus, it is entirely possible that CVD is a causal factor in producing these sleep disturbances (i.e., reverse causality). For example, it has been demonstrated that insomnia symptoms are more prevalent in patients with congestive heart failure.[49] Moreover, incident insomnia has been shown to occur more frequently in those with a number of other chronic medical conditions.40 Thus, it is likely that for some persons, sleep disturbances are exacerbated or caused by co-morbid medical conditions.

Summary

There is substantial evidence linking abnormalities in sleep duration and several sleep disorders with CVD. With respect to OSA, recent data indicate that this condition may be an important risk factor for the development of hypertension, CVD and subsequent earlier mortality. For other conditions such as insomnia and restless legs syndrome, strong associations are present, but verification that they are primary risk factors can only be determined in longitudinal cohort studies. Whether or not they are primary risk factors for CVD, it also is likely that sleep disturbances occur more commonly in those with some types of CVD.

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