CHAPTER

24

Sleep and Cardiovascular Disorders

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Introduction

Sleep is essential for life and for physical, mental and emotional well being. Sleep must be of good quantity and quality. There is a close association between sleep and cardiovascular system. Cardiac functions in sleep are under control of autonomic nervous system activity, which in turn is dictated by brain states. NREM sleep is associated with relative cardiac and autonomic stability. There is also a functional co-ordinated activity between cardiac and respiratory variables. However in REM sleep there is cardiac bound sympathetic and parasympathetic activity which results in significant surges and pauses in heart rhythm. It is expected that these changes have a potential to affect cardiac function particularly coronary blood flow and cardiac stability. Sleep is not a protected state in subjects suffering from cardiac and respiratory disease.

Cardiovascular disease contribution has increased from 25.5% in 1990 to 30.2% for all causes of mortality in India.[1] There has been a steady increase in the prevalence of coronary artery disease(CAD) in India. Its prevalence has been reported to increase from 1.05% in 1962 to 12% in urban areas.[2] Also there has been a steady increase in the prevalence of diabetes in India.[3] Sleep disorders also affect metabolic pathways. Obstructive sleep apnea is a risk factor for development of diabetes. Diabetes is a cardiovascular disease.

There are several risk factors for CAD viz heredity, age, sex, obesity, sedentary life style, hypertension, hyperlipidemia , diabetes and these have received ample attention. Sleep disorders as a risk factor for the development of CAD has not been highlighted. Sleep has a close relation to cardiovascular system both scientifically and emotionally.

Normal Sleep and Cardiovascular Disorders

NREM Sleep and Cardiac Functions

Following are cardiac effects of NREM Sleep

- Generalized decrement of mean heart rate and blood pressure.
- Marked autonomic stability with parasympathetic dominance.
- Prominent respiratory sinus arrhythmia.
- Bradycardia
- Stable blood pressure
- Overall cardiac homeostasis giving an opportunity for metabolic restoration, but minor elevations in muscle sympathetic nerve activity, heart rate, arterial blood pressure accompany

high amplitude K complexes which is a feature of stage 2 sleep.

- Reduced neuronal activity in brain stem and other regions of brain with reduction in cerebral blood flow.

These changes are important clinically in patients suffering from severe coronary disease or acute coronary syndromes who run the risk of further ischemia due to hypotension and bradycardia.[4]

During transition from NREM to REM sleep following cardiac effects are observed:

- Heart rate acceleration
- Pauses in heart rhythm or even frank asystole due to bursts of vagal activity.
- Shifts in posture resulting in autonomic activation. With aging these shifts are more frequent.

Autonomic Control of the Heart in REM Sleep

At the initiation of REM sleep there is dramatic alteration in activity of autonomic nervous system. The brain has increased excitability resulting in profound bursts in sympathetic activity. These bursts trigger intermittent increase in heart rate and blood pressure. These cardiac changes are comparable to changes during wakefulness. Breathing patterns become irregular and can result in oxygen desaturations. REM sleep therefore has the capacity to disturb cardiorespiratory homeostasis. However cardiovascular homeostasis must be maintained in sleep and this is achieved by close co-ordination of respiratory and cardiovascular systems. Respiratory mechanisms help by assisting venous return and by reflexively altering heart rate. During inspiration heart rate increases to accommodate increased venous return and increased cardiac output while during expiration there is progressive slowing of heart rate. The normal sinus heart rate variability particularly during NREM sleep is generally indicative of cardiac health and absence of this intrinsic variability has been associated with cardiac pathology and advancing age.There is hypotonia in REM sleep with resultant near paralysis of accessory respiratory muscles with breathing patterns highly irregular. There are chances of desaturation particularly in patients with cardiac and respiratory disease.[4] The existence of sleep apnea puts tremendous burden on the cardiovascular and respiratory system (intermittent respiratory failure). The nocturnal events are more in REM sleep.

Abnormal Sleep and Cardiovascular Disorders

Sleep is generally beneficial and protective but not in subjects suffering from respiratory and cardiac disease as it can precipitate cardiac arrhythmias, myocardial ischemia, breathing disorders and even death. The population group who are at risk of these complications are as follows (Table 1):

Basically there are two main factors responsible for nocturnal events in cardiac patients

- Sleep state dependent surges in autonomic activity.
- Depression of respiratory control mechanisms.

Other factors are:

- Tobacco chewing / smoking
- Underlying sleep disorder e.g. sleep disordered breathing
- Medications e.g. Betablockers, calcium channel blockers.
- Underlying respiratory disease
- Underlying metabolic disorder e.g. Diabetes causing nocturia and arousals.

Ischemic Heart Disease and Nocturnal Events

The decreased metabolic demands of myocardium in sleep is reflected in less incidence of nocturnal cardiac events. However 20% of myocardial infarctions and 15% of sudden deaths occur between midnight and 6.00 am. This non uniform distribution[6] implicates pathophysiologic triggers

Table 1 : Patient Groups at Potentially Increased Risk for Nocturnal Cardiac Events.[5]

Indication	U.S. Frequency	Potential Mechanism and Observations
Angina, myocardial infarction (MI), arrhythmias, myocardial ischemia, or cardiac arrest at night	20% of MI (250,000 cases/yr) and 15% of sudden deaths (38,000 cases/yr.)	The nouniform nocturnal distribution suggests a sleep-state-dependent autonomic trigger or respiratory distress.
		Non-demand myocardial ischemia and angina peak between midnight and 6.00 AM. and are temporally linked with nocturnal MI. These episodes may disclose a critical underlying coronary lesion, coronary vasospasm, or transient coronary artery stenosis.
		The number of female death attributed to hypertensive disease is elevated between midnight and 6 AM
		In elderly subjects, nighttime multifocal ventricular ectopic activity predicts increased cardiac mortality independently of clinically evident cardiac diseases.
Acute myocardial infarction	1.5 million patients/ yr.	Disturbances in sleep, nocturnal respiration, blood pressure and autonomic balance may be factors in MI.
Spousal or family report of highly irregular breathing, excessive snoring, or apnea in patients with coronary disease.	5 to 10 million U.S. patients with apnea	Patients with CAD should be screened for the presence of sleep apnea, which conduces to hypertension, myocardial ischemia, arrhythmia, and atrial fibrillation and is a risk factor for lethal daytime cardiac events, including MI
Heart failure	4.6 million	20% of sudden deaths in heart failure patients occur between midnight and 6.00 AM. Cheyne-Stokes respiration accelerates deterioration in cardiac function in heart failure patients. Apnea-hypopnea index predicts poor prognosis.
Near-miss or siblings of SIDS victims	-	Crib-death occurs during sleep with characteristic cardiorespiratory symptoms
Atrial Fibrillation	2.5 million patient/ yr	29% to 40% of episodes occur between midnight and 6.00 AM. Respiratory and autonomic mechanism are suspected.
Patients on cardiac medications	13.5 million patients with cardio-vascular disease	Beta-blockers and calcium channel blockers that cross the blood-brain barrier may increase nighttime risk, as poor sleep and violent dreams may be triggered.
		Medications that lengthen repolarization in the cardiac cycle may trigger pause-dependent torsades de points during heart rate surges and pauses.
		Because arterial blood is decreased during NREM sleep, additional lowering by antihypertensive agents may induce a risk of myocardial ischemia and infarction due to lowered coronary perfusion.
Hypertension	-	Hypertensive patients with $<$ 10% nocturnal decline in blood pressure are at increased risk of cerebrovascular insult, frequent or complex ventricular arrhythmias, organ damage, and cardiac hypertrophy. Nocturnal hypertension is a marker of left-ventricular filling impairment.

particularly the autonomic surges of REM sleep. These surges can also result in nocturnal cardiac events due to disruption of plaques and generation of arrhythmias. Patients of hypothyrodism who have co existing obstructive sleep apnea (OSA) which has not been treated may experience arrhythmias in sleep after administration of thyroid medication. [Cardiac stimulation against background of cyclical hypoxemia]. It is important to appreciate that OSA and hypothyroidism often co-exist.

Arrhythmias, cardiac ischemia may be precipitated in NREM sleep due to bradycardia and hypotension. Non demand related myocardial ischemia may be provoked by low heart rates and arterial blood pressure and increased coronary vasomotor tone which decrease coronary perfusion pressure.

Non-demand related ischemic events usually cluster between midnight and 6.00 a.m. in patients with critical coronary lesions. Patel et al[4] documented a nocturnal peak in ischemic events in patients with unstable angina and non Q wave myocardial infarction who were receiving optimum medical therapy aimed to contain demand related myocardial ischemia. Non-demand nocturnal myocardial ischemia is most prevalent in patients with severe coronary disease and the acute coronary syndrome of unstable angina or non-Q wave myocardial infarction. Andrews et al[7] observed that non demand related ischemic episodes cluster between midnight and 6.00 am in patients with more advanced stable coronary disease. Non-demand nocturnal ischemic episodes may be reflection of critical underlying lesion, coronary vasospasm or transient coronary artery stenosis.[4]

Sleep is disturbed in post myocardial infarction patients. Myocardial infarction with impaired left ventricular function often results in nocturnal desaturations, which in turn provoke arrhythmias and myocardial ischemia.[8] Residual myocardial ischemia results in increased sympathetic activity and diminished parasympathetic activity. Nighttime heart rate of > 90 / min increases the risk for fatal events.

Nocturnal myocardial infarction occurs due to

1. NREM sleep induced hypotension (incidence of subendocardial myocardial infarction clusters around 2.00 am and 4.00 am when arterial blood pressures are the lowest).
2. Antihypertensive medication consumed late night may induce more hypotension early morning (antihypertensives are best taken in the daytime).
3. Increased ventricular diastolic pressures and volumes due to fluid shifts resulting from supine position.
4. Unfavorable fibrinolytic and thrombotic factors environment.
5. Desaturations (chronic and episodic)
6. Elevated nocturnal diastolic arterial blood pressure.
7. Non dippers (< 10 % decrease in blood pressure from day to night) Faulty baroreceptor mechanisms may be responsible. Polysomnography in these subjects may reveal reduced length and depth of NREM sleep, microarousals and shortened REM latency. Non dippers have a high prevalence of strokes and cardiovascular events like complex ventricular arrhythmias, organ damage and cardiac hypertrophy. It is important to note that nocturnal hypertension is a marker of left ventricular filling impairment.[5]
8. The autonomic background in elderly subjects (impaired baroreceptor sensitivity and increased sympathetic activity) is conducive to development of myocardial infarction, arrhythmias and sudden death. There is also increased prevalence of sleep apnea in the elderly.[9]

Sleep Disorders

Obstructive sleep apnea (OSA), central sleep apnea (CSA), sleep deprivation, nightmares, certain medications have adverse effects on the cardiovascular system.

OSA is a common disorder but is usually not recognized in clinical practice. The disorder is characterized by repeated pharyngeal collapse pharynx in sleep resulting in cyclical hypoxemia. Sympathetic stimulation coupled with release of stress hormones and endothelin impose a significant burden on the cardiovascular and metabolic systems. OSA is a risk factor for the development of hypertension, ischemic heart disease, strokes, type 2 diabetes mellitus, and others. Habitual snoring (often loud) and excessive daytime sleepiness are the two prominent symptoms of the disorder. The other nocturnal symptoms witnessed apneas, choking, dyspnea (can be mistaken for dyspnea of cardiac origin) restlessness manifested by frequent change of posture, nocturia due to release of atrial natriureticpeptide, gastroesophageal reflux, diaphoresis and drooling. Some subjects may just complain of insomnia (patient unable to continue sleep due to repeated arousals) and may compel a physician to prescribe an hypnotic. Sedatives, hypnotics and antianxiety medicines are often prescribed in cardiology practice. Such drugs increase the hypotonia of pharyngeal muscles and therefore should be avoided. Alcohol is used as sleeping aid by some patients and it also carries similar risk. It is not uncommon to observe patients have choked themselves in sleep after consuming such medications/ alcohol before retiring to bed. It is also important to note that OSA patients are often REM sleep deprived. Chronic REM sleep deprivation results in anxiety, excessive eating and hypersexuality.[10] Excessive eating promotes obesity which in turn aggravates sleep apnea. It is therefore necessary to treat sleep apnea in obese individuals to achieve optimal body weight.

Daytime symptoms of OSA includes sleepiness, fatigue, morning headaches, poor concentration, decreased attention, depression, decreased dexterity and personality changes. Subjects of OSA often exhibit angry behavior and may seek psychiatrist's opinion. Although obesity is risk factor for development of OSA it is not uncommon to observe OSA in low and normal body weight subjects due to anatomical factors (narrow upper airway). Polysomnography is the gold standard to diagnose OSA.

Young et al[11] reported that 4% of men and 2% of women in a middle-aged North American population had symptoms of OSA and an apnea hypopnea index of greater than 5 events per hour of sleep. This signifies that approximately 5 -10 million Americans are affected. In India Udwadia et al[12] reported that the estimated prevalence of sleep disordered breathing was 19.5% and that of obstructive sleep apnea hypopnea syndrome (SDB and daytime hypersomnolence) was 7.5%. Further, snoring can be observed when a group of subjects are sleep together as for example in railway sleeper coaches . It is not uncommon to observe atleast 6-7 loud snorers in each coach. (the usual number of berths in each railway sleeper coach is 72). There are also several mild snorers. The prevalence of SDB in elderly increases with age ranging from 5% - 15% in middle aged adults to 24% in community dwelling older adults.[9] Also the prevalence of SDB is greater in persons with hypertension, obesity and patients with cardiac arrhythmias.

The apneic hypoapneic episodes of OSA have the capability of disrupting myocardial perfusion even in individuals without cardiac disease. The resultant effects are manifested by nocturnal myocardial ischemia, arrhythmias and hypertension. A greater prevalence of cardiovascular complications is seen through out the spectrum of sleep disordered breathing which consists of snoring, upper airway resistance syndrome and obstructive sleep apnea.

Sleep apnea and hypertension

OSA is an established risk factor for hypertension. In fact it is one of the common and important causes for reversible hypertension. The underlying mechanisms for development of hypertension include :

- Sympathetic nerve activation as a result of nocturnal hypoxia (cyclical hypoxia).

- Impaired baroreceptor sensitivity. It is important to note that baroreceptor sensitivity is usually impaired in elderly and prevalence of sleep apnea increases with age.

  Carotid chemoreceptors also contribute by way of maintaining increased peripheral sympathetic activity and blood pressure after cessation of asphyxia or exposure to hypoxia. Nicotine is known to increase sleep apnea and to affect chemoreceptor activation of respiration adversely, dulling the response to hypoxia.
- An enhanced chemoreceptor reflex in borderline hypertensive subjects
- Repeated arousals
- Increased catecholamine release.
- Enhanced endothelin release

More than half of patients with obstructive sleep have systemic hypertension compared with an expected prevalence of 20% in middle aged obese men.[13] Approximately 25% of patients with hypertension have obstructive sleep apnea.[14,15,16]

Lindberg et al [17] in his study observed that habitual snoring was an independent predictor for the development of hypertension. The chronic usage of continuous positive airway pressure (CPAP) in patients with hypertension and obstructive sleep apnea results in reduction of hypertension both while awake and during sleep[18]. Partinen et al[19] observed that patients of sleep apnea who were successfully treated had a substantial reduction in cardiovascular events compared with an equally affected patient who refused treatment.

Sleep disordered breathing in pregnancy may have adverse effects both on the mother and fetus (pregnancy induced hypertension and small for gestational age birth).[20] It is interesting to note that approximately 28% of children born in India are of low birth weight and low birth weight is associated with elevated levels of glucocorticoid in later life.[21] A story from womb to the tomb.

Cardiac medications and Sleep

Lipophilic beta-blockers pindolol, propranolol and metoprolol increases the number of awakenings and period of wakefulness as compared to placebo and non-lipophilic betablockers like atenolol. Drugs possessing intrinsic sympathomimetic activity e.g. Pindolol increase REM latency and increase REM sleep time.

Betablockers in general do cause daytime lethargy possibly due to sleep disruption. Melatonin is also depleted by beta-blockers. Melatonin is a key sleep regulating hormone that modulates sympathetic nerve activity. In general lipophilic betablockers like propranolol cause more sleep disturbance than hydrophilic ones e.g. atenolol. However atenolol has been shown to increase total wake time at least acutely in normal subjects. Propranolol and timolol are highly lipid soluble, Pindolol, bisoprolol, metoprolol and acebutolol are moderately lipid soluble while nadolol, sotalol and atenolol is least lipid soluble. Beta-blockers and calcium channel blockers may provoke nightmares.

Sleep Deprivation and Cardiovascular Events

Chronic sleep deprivation is associated with cardiovascular events by more than one mechanism. Irwin et al[22] has recently concluded that sleep loss induces a functional alteration of the monocyte proinflammatory cytokine response. A modest amount of sleep loss also alters molecular processes that drive cellular immune activation and induce inflammatory cytokines; mapping the dynamics of sleep loss on molecular signaling pathways has implications for understanding the role of sleep in altering immune cell physiologic characteristics. Intervention that target sleep might constitute new strategies to constrain inflammation with effects on inflammatory disease risk. Sleep deprivation induces or aggravates snoring by increasing muscular hypotonia and delaying contraction of the dilator muscles of pharynx.[23]

Chronic sleep deprivation causes an autonomic imbalance and decreases intracellular magnesium which could be associated with chronic sleep deprivation induced cardiovascular events.[24]

Chronic sleep deprivation in young healthy volunteers has been reported to increase levels of proinflammatory cytokines decrease parasympathetic and increase sympathetic tone, increase blood pressure, increases cortisol levels as well as elevate insulin and blood glucose levels.[25]

Coronary Artery Disease (CAD) and sleep apnea

Several studies have suggested that there is a greater risk of CAD in sleep related breathing disorders.[19,26,27] There is 20 fold risk of developing myocardial infarction in untreated OSA. The prevalence of sleep related breathing disorders was 37% among men and 30% among women with angiographically verified coronary artery disease.[28] The Stockholm female coronary angiographic study concluded that snoring contributes to the atherosclerotic process and history of habitual snoring should be taken into consideration when treating patients with cardiac disease.[29] Andreas et al observed clinically important sleep apnea in 50% of patients with coronary artery disease.[30] It is also interesting to note that nearly 30% of patients with coronary artery disease and concomitant sleep apnea experienced myocardial ischemia during apnea primarily during REM sleep.[31]

It is therefore important to screen all patients of coronary artery disease for sleep apnea. Its treatment is rewarding in multiple ways viz. good quality of sleep, daytime alertness, normal physical activity which helps in reducing body weight, good cardiovascular function and better glycemic control. Continuous positive airway pressure(CPAP) is the widely accepted mode of treatment of OSA.

Diabetes is a cardiovascular disease. There is a close association between OSA and insulin resistance. The nocturnal events in OSA ultimately culminate in cyclical hypoxia, cylclical hypertension release of catecholamines & stress hormones, insulin resistance and diabetes.[32] Recently the authors[33] has reported favorable results in glycemic control in 4 patients of type 2 diabetes who had associated obstructive sleep apnea with regular usage of CPAP. The beneficial metabolic effects of CPAP has been discussed recently.[34] There is a close association between diabetes, hypertension, ischemic heart disease, sleep disorders particularly sleep apnea.

Sleep Apnea and atrial fibrillation

Sleep apnea and atrial fibrillation frequently coexist.[35] OSA has been implicated in the recurrence of atrial fibrillation.[36]

Idiopathic Cardiomyopathy

Thomas[37] has reported the presence of cardiomyopathy in patients of OSA. Also left ventricular hypertrophy was more common in 30 normotensive patients with OSA than in controls.[38] Malone et al[39] reported that all patients with congestive cardiomyopathy of unknown origin had OSA. Treatment with CPAP in these patients for 4 weeks increased the mean ($\pm$ SD) left ventricular ejection fraction significantly from 37% $\pm$ 4% to 49% $\pm$ 5%.

OSA and Congestive Heart Failure (CHF)

Central sleep apnea(CSA) which can occur in healthy subjects during sleep onset also occurs in patients of CHF and OSA. Central Sleep apnea is frequently observed (33 to 40%)in patients with congestive heart failure (CHF).[40] The condition affects cardiovascular function adversely by causing tissue hypoxia, arousals from sleep and activation of the sympathetic nervous system. It also independently increases the risk of death. It is also observed that CSA might get converted to OSA as the effort is restored. In fact there is a significant overlap between CSA and OSA. The presence of Cheyne-Stokes respiration in CHF indicates a bad prognosis. Pulmonary congestion triggers hyperventilation, which results in lowering of $PaCO_2$ below the apneic threshold. The resulting apnea or hypopnea causes a rise in $PaCO_2$. which

in turn causes hyperventilation only to wash out $PaCO_2$. This propagates a vicious cycle of apnea and hyperpnea.[41]

Canadian Positive Airway Pressure Trial (CANPAP)

The CANPAP trial[40] concluded that CPAP attenuated central sleep apnea, improved nocturnal oxygenation, increased ejection fraction, lowered epinephrine levels and increased the distance walked in six minutes. It did not affect survival. There were several limitations and the trial ultimately lacked the power to conclude with certainty that CPAP is ineffective in this patient population. Also the data do not support its routine use to extend life in patients with CSA and heart failure. However this recommendation is not applicable to patients with heart failure who have OSA. Therefore polysomnography is mandatory in all subjects of CHF.

Cerebrovascular Disease

About one third of strokes occur apparently during sleep and only snoring was significantly associated with stroke in sleep.[42] Sleep related breathing disorders affect cerebral hemodynamics adversely. There is greater than 50% reduction in central blood flow during apneic and hypopneic events. There appears to be a bi-directional relationship between CVA and sleep disordered breathing. OSA is a risk factor for strokes. The factors which contribute to the development of stroke or TIA in a patient of OSA are nocturnal desaturations, autonomic instability and increase in intracranial pressure which reduces the cerebral perfusion pressure. Elevated catecholamine levels in OSA also promote thrombosis. These events are prominent in REM sleep. OSA syndromes significantly increases the risk of stroke or death from any cause and the increase is independent of other risk factors including hypertension.[43] Untreated OSA patients have more strokes, stroke morbidity and mortality than those who are treated. It is to be noted that strokes themselves may generate sleep disordered breathing. There is high prevalence of OSA syndrome in patients with acute stroke.[44] Studies have shown that usage of CPAP in stroke patients who have OSA is highly rewarding. Broadley et al[45] studied in the prevalence & association of OSA and the safety and tolerability of early treatment with nasal CPAP in a cohort of stroke patients. They observed that portable diagnostic system for detecting OSA in acute stroke was well accepted and early treatment with nCPAP was effective and well tolerated. The strong association of OSA and stroke justifies the use of polysomnogram in the diagnostic evaluation of stroke and transient ischemic attacks.[46]

Conclusions

Sleep disorders are common in clinical practice. It is time that we took cognizance of this in various cardiovascular disorders since patients usually do not attach much importance to sleep while narrating the history. Society in general has held the view that snoring is a sign of sound sleep. In literal terms sound sleep needs to be differentiated from healthy sleep. A close association exists between anatomical factors in the face, life style, sleep deprivation, sleep disorders, eating, obesity, hypertension, coronary artery disease, metabolic syndrome, cardiovascular morbidity and mortality. It is important to record sleep history in all patients suffering from hypertension, metabolic syndrome and coronary artery disease. Adequate sleep history is the key to the suspicion of an underlying sleep disorder. Also while recording sleep history it is important to interview the subject also who is sharing the bedroom. Identifying patients with narrow airway by looking at the face and tongue (face reading) is valuable. Premature death in OSA patients is most often due to cardiovascular disorders. It is now accepted that treatment of OSA by CPAP is rewarding since it can prevent or improve hypertension, reduce abnormal elevations of inflammatory cytokines and adhesion molecules, reduce excessive sympathetic tone, avoid increased vascular oxidative stress, reverse coagulation abnormalities and reduce leptin levels.[46] This should

give enough basis to include polysomnogram in the clinicians armamentarium. It is often argued that sleep studies may not be economically feasible but given the benefits and properly placed before the patient in question would definitely improve compliance for the test.

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