CARDIOVASCULAR PHYSIOLOGY AND SLEEP

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1. ABSTRACT

Sleep is a natural periodic suspension of consciousness during which processes of rest and restoration occur. The cognitive, reparative and regenerative accompaniments of sleep appear to be essential for maintenance of health and homeostasis. This brief overview will examine the cardiovascular responses to normal and disordered sleep, and their physiologic and pathologic implications. In the past, sleep was believed to be a passive state. The tableau of sleep as it unfolds is anything but a passive process. The brain's activity is as complex as wakefulness, never "resting" during sleep. Following the demise of the 'passive theory of sleep' (the reticular activating system is fatigued during the waking day and hence becomes inactive), there arose the 'active theory of sleep' (sleep is due to an active general inhibition of the brain) (1). Hess demonstrated the active nature of sleep in cats, inducing "physiological sleep" with electrical stimulation of the diencephalon (2). Classical experiments of transection of the cat brainstem (3) at midpontine level inhibited sleep completely, implying that centers below this level were involved in the induction of sleep (1, 4). For the first time, measurement of sleep depth without awakening the sleeper using the electroencephalogram (EEG) was demonstrated in animals by Caton and in humans, by Berger (1). This was soon followed by discovery of the rapid eye movement sleep periods (REM) by Aserinski and Kleitman (5), demonstration of periodical sleep cycles and their association with REM sleep (6, 7). Multiple studies and steady discoveries (4) made polysomnography, with its ability to perform simultaneous whole night recordings of EEG, electromyogram (EMG), and electrooculogram (EOC), a major diagnostic tool in study of sleep disorders. This facility has been of further critical importance in allowing evaluation of the interaction between sleep and changes in hemodynamics and autonomic cardiovascular control. Consequently the effects of sleep could be objectively differentiated from the effects of rest and recumbency. Furthermore, the specific effects of sleep onset and termination, and the effects of different sleep stages, could be assessed. Technological advances, with consequently enhanced and relatively non-invasive approaches to cardiovascular regulation, have greatly broadened our understanding of the effects of sleep stage on cardiovascular function. Continuous monitoring of simultaneous measures of polysomnographic and cardiovascular variables enables characterization of the effects of dynamic changes and rapid transitions in sleep stage, such as arousals. The capacity for measuring acute and immediate changes in autonomic, EEG and hemodynamic responses to sleep and arousal on a continuous basis has played an important role in enabling us to understand the interplay between changes in EEG and changes in the more peripheral measurements of neural and circulatory variables, such as sympathetic nerve traffic, heart rate (HR) and blood pressure (BP). Measurements of heart rate variability (HRV) (8-10), baroreflex sensitivity (BRS) (11-16), and intraneural measurement of sympathetic nerve traffic to muscle (MSNA) (17-22) and skin (SSNA) (23-24) have further advanced our understanding of mechanisms linking sleep and cardiovascular physiology.

2. CARDIOVASCULAR RESPONSES TO NORMAL SLEEP

Cardiovascular regulatory mechanisms in sleep and wakefulness have traditionally been studied by measurements of HR, BP, and baroreflex gain. Sleep has two distinct states (25, 26) – Quiet and Active Sleep. They occupy approximately 70 – 80% (6 hours) and 20 - 25% (1.5 hours) of normal sleep time respectively (27).
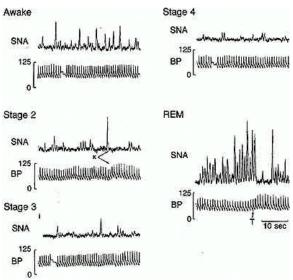
Figure 1. Recordings of Sympathetic-Nerve Activity (SNA) and Mean Blood Pressure (BP) in a Single Subject while Awake and while in Stages 2, 3, 4, and REM Sleep. As non-REM sleep deepens (stages 2 through 4), SNA gradually decreases and BP (measured in millimeters of mercury) and variability in BP are gradually reduced. Arousal stimuli elicited K complexes on the electroencephalogram (not shown), which were accompanied by increases in sympathetic-nerve activity and blood pressure (indicated by the arrows, stage 2 sleep) In contrast to the changes during non-REM sleep, heart rate, BP, and BP variability increased during REM sleep, together with a profound increase in both the frequency and the amplitude of SNA. There was a frequent association between REM twitches (momentary periods of restoration of muscle tone, denoted by T on the tracing) and abrupt inhibition of sympathetic-nerve discharge and increases in BP. Used with permission from 17.

2.1. Non-REM or quiet sleep

Quiet Sleep (QS) is also known as non-REM, Slow Wave Sleep (SWS) or Synchronized Sleep. It has four discrete stages. They are reflected by progressive slowing in frequency and increase in amplitude of EEG activity. In all of these stages HR, BP, peripheral MSNA and arterial pressure variability is lower than when awake. The sympathetic nerve activity (SNA) in particular is reduced by more than half that of wakefulness (17) (figure 1). SSNA also decreases during QS (24).

During stage 2 there are two distinct features on the EEG – high amplitude K-complexes and sleep spindles, synchronized waves of 7-14 Hz. K-complexes are either spontaneous or elicited by arousal stimuli. MSNA and SSNA seem to be related to "spontaneous" K-complexes (23). K-complexes elicited by arousal are accompanied by increase in MSNA, HR albeit transiently, BP (17, 21) (figure 1), skin resistance and skin blood flow (28). No clear association has been observed between sleep spindles and SNA during stage II and III of QS.

Other approaches to studying autonomic control during sleep have included measurements of cardiovascular

variability, primarily the variability of the RR interval (29). These measurements have suggested that during QS there is an increase in the high frequency (HF) power of RR variability with an associated reduction in the low frequency (LF) power (30, 31) (figure 2). This change in the distribution of HF power increases progressively from stage I to stage IV sleep,(32) suggesting increased vagal and decreased sympathetic cardiac drive during QS (8, 31, 33).

Normally, a drop in BP during wakefulness is appropriately countered by the baroreflex with increases in HR and MSNA(17). However, in QS, a synchronous reductions in HR, MSNA and BP occur (17) (figure 3). It appears that arterial baroreflex, serves an accommodating role in permitting synchronous reduction of HR, MSNA and BP in QS. However, interpretation of these studies could be difficult given the varying absolute reductions of HR, BP and SNA during the different stages of sleep. Several investigators have demonstrated a gain in arterial baroreceptor reflex during sleep (11, 34). Thus it is evident that during non-REM sleep the level of BP that the baroreflex attempts to defend is lowered.

From the cardiovascular perspective, non-REM is a period of relative autonomic stability, incorporating sympathetic inhibition, increased vagal tone with bradycardia (17, 35), enhanced respiratory sinus arrhythmia (36), and heightened baroreceptor gain. The lowest levels of arterial BP are reached in stages III and IV. This decrease in arterial pressure is primarily related to reduction in HR and sympathetic vasomotor tone (37). Stages III-IV of QS are probably the most "restful", with 10 to 30 % decrease in BP, respiratory rate, and basal metabolic rate.

2.2. REM or active sleep

Active Sleep (AS) is also called REM, Fast Wave, Desynchronized or Paradoxical Sleep. As one falls asleep, sleep transits stages I – IV of QS and then is interrupted episodically by REM sleep till it lightens. REM sleep is due to increased brain stem reticular activity. REM latency occurs 90 to 120 minutes into sleep and is the first REM intrusion of QS. The duration and intensity of these intrusions progressively increase (27) from 5 minutes up to 20 minutes as one becomes more rested.

REM sleep can be thought to consist of two somewhat different states – tonic and phasic epochs (figure 4). Phasic bursts or phasic REM epoch is recognized by occurrence of rapid eye movements, twitching muscles and pontine cholinergic discharge (27, 38-40) interspersed between periods of tonic REM sleep. A majority of individuals awakened from REM sleep report dreaming as opposed to only 10-15% of those in SWS (27). There is active inhibition of spinal outflow at the level of anterior horn cells in REM sleep despite intense cerebral metabolic activity and central nervous system excitation. Cortical desynchronization, a suppressed postural tone, rapid eye movements, and instability of cardiovascular as well as respiratory variables characterize REM sleep. Also anger and fear appear to form a majority of the emotions
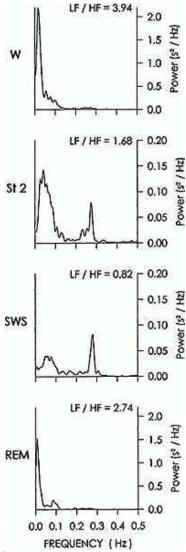
Figure 2 Power spectra of R-R intervals, according to sleep states: intrasleep awaking (W), stage 2 (St2), slow-wave sleep (SWS), and rapid eye movement sleep (REM) Used with permission from 30.

expressed in dreams(41). It is not surprising that measurement of cardiovascular indices reflect this state of heightened emotional arousal.
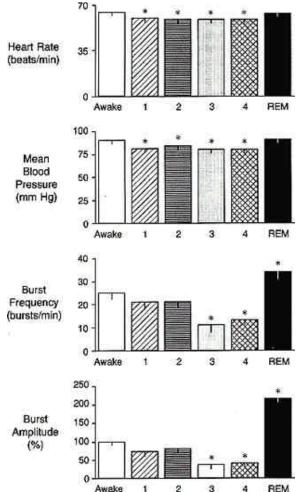
In relation to its influences on the neural circulatory profile, REM sleep is a predominantly parasympathetic (vagal) state (42). However, phasic REM sleep, is punctuated by sudden bursts of sympathetic nervous system (SNS) activity(17, 20, 21, 38, 39, 43) with intense eye movements. Marked sinus arrhythmia with respiration bradycardia with first degree and Wenckebach AV block and sinus pauses are consistent with an enhanced vagal tone. Also, they may have intermittent tachycardia. In healthy young people, sinus node pauses, short central apneas, hypopneas are not uncommon during phasic bursts of REM (44). These respiratory irregularities during REM may in and of themselves contribute to HR, BP and

autonomic changes independent of the effects of REM sleep per se.

There is an increase in MSNA during REM, predominantly in phasic REM. This increase in MSNA is about twice the level seen during wakefulness, with BP and HR on average similar to levels during wakefulness (17, 45). MSNA firing occurs in groups of bursts and its activity has been associated with sudden increases in arterial BP, and changes in HR and respiratory rate (17, 21). The BP increase from non-REM to REM sleep is due in part to sympathetic mediated vasoconstriction in skeletal muscles, which is opposed by vasodilation in the mesenteric and renal vascular beds. Provided afferent impulses are intact, increased MSNA activity during REM appears to be linked to a loss of postural muscle tone that seems to excite (disinhibit) sympathetic nerve activity of the muscle, but not of the renal or mesenteric vascular beds (46). Also, when muscle tone is momentarily restored during "REM twitches" there is abrupt surge in BP (17, 47). It is conceivable that REM sleep, and phasic REM sleep in particular, may be a potential trigger for cardiovascular events that are reported to occur more frequently in the early morning hours (17).

Increased sympathetic traffic to peripheral blood vessels, increased BP and sinus tachycardia precede heart pauses (48, 49). These suggest a baroreflex-mediated change. Guillemenault and co-workers have described "periods of sinus arrests" in normal young adults during phasic REM sleep (44). In cats, during tonic REM, a vagally mediated primary deceleration in HR has been observed (50). This deceleration is neither preceded nor followed by any increase in HR or BP. It is eliminated immediately by glycopyrrolate and unaltered with atenolol, suggesting that these decelerations are cholinergically mediated, and are secondary to bursts in cardiac vagal efferent activity due to changes in the central regulation of cardiac autonomic control (50). Akin to abrupt bursts of sympathetic vasoconstrictor activity, vagal activation in REM also appears to occur intermittently and abruptly. This mechanism has been proposed as the probable explanation for the sinus pauses or arrests observed in tonic REM (50). Change in rhythm may be due to cardiac and respiratory interactions which maintain homeostasis in sleep (36). However, the authors noted no temporal association with respiration in their experiments (50), therefore believe sinus arrhythmia has no role in this phenomenon.

REM therefore appears to induce rapid and complex fluctuations in autonomic function, with evidence for abrupt vagal discharge to the sinoatrial node as well as abrupt sympathetic traffic to peripheral blood vessels. These sudden changes in RR interval, together with the irregular respiratory patterns in REM, have made it difficult to employ tools such as HRV (which depend very much on stable respiratory patterns) to help define changes in HF and LF oscillatory powers during REM. Any overall characterization of REM is in any event likely to be flawed because of the increasing evidence that REM sleep itself can have very divergent effects at different times even on

Figure 3. Heart rate and blood pressure were significantly lower during all stages of non-REM sleep than during wakefulness, and sympathetic activity was significantly lower during stages 3 and 4 (the asterisk denotes P<0.001) During REM sleep, sympathetic activity increased significantly (P<0.001), but the values for blood pressure and heart rate were similar to those recorded during wakefulness. Values are means ±SE. Used with permission from 17.

the same component of the autonomic nervous system. Tonic and phasic REM for example appear to be different in their autonomic and hemodynamic characteristics, and even within tonic REM, it appears that the autonomic profile can change very quickly. The mechanisms underlying these differential effects and rapid fluctuations during REM remain to be clarified.

Despite the difficulties associated with studies of spectral analysis of RR variability during the instability that characterizes REM, several studies have suggested that there is an increase in the LF component of HRV and an increase in the LF/HF ratio, compared to non-REM (51). Interestingly, this increase is more pronounced in the last phase of the night when REM is most likely to occur. Any interpretation of the increase LF power and increased LF/HF ratio of RR interval variability during REM as an

index of cardiac sympathetic activation during REM, needs to also consider the evidence supporting abrupt surges in cardiac parasympathetic drive with consequent bradycardia and bradyarrhythmias that are also noted to occur during REM. Whether surges in parasympathetic drive against a backdrop of pre-existing cardiac sympathetic activation have any implications for the development of clinically significant arrhythmias during REM, in patients a vulnerable substrate, is of considerable interest.

2.3. Arousal

It is important that arousal from sleep be accompanied by increases in HR and BP. These hemodynamic adjustments would help facilitate any fight or flight response that would threaten the organism that is awoken from sleep. Thus, the autonomic responses to arousal are consistent with those that would facilitate increases in HR and BP so that appropriate action can be taken on waking from sleep.

As discussed earlier, brief arousal stimuli during sleep, such as those would elicit K-complexes are often accompanied by brief bursts of sympathetic vasoconstrictor activity to muscle blood vessels, transient increases in HR and BP. Skin resistance and skin blood flow also can change significantly (28). When K-complexes occur spontaneously during sleep, these occurrences also relate to changes in MSNA and SSNA (23). HR increases have also been demonstrated to occur 10 beats prior to EEG arousal (23, 31) suggesting that sympathetic activation may have a role to play in arousal (figure 5).

It is interesting that there appears to be a change in neural processing of arousal stimuli during sleep as compared to wakefulness. During wakefulness, an arousal stimulus such as a sudden noise does not increase MSNA but has a very potent influence on activating SSNA (52). However, during sleep, the similar arousal stimulus is able to generate an increase in MSNA, suggesting that during sleep there is "rewiring" of reflex responses to arousal (17), and perhaps to other provocative interventions.

Arousals with acoustic signals cause significant changes in HR, pulse transit time, and skin blood flow consistent with rapid parasympathetic withdrawal and SNS activation (53, 54). Elegant canine studies have shown that the cardiovascular effect of apnea-induced arousal is predominantly due to withdrawal of the parasympathetic tone to the heart (55). The increases in HR and systemic pressure with arousal are blocked after atropine administration. These studies indicating the dominant role of parasympathetic withdrawal in dogs on arousal need to be interpreted in the light of the general high parasympathetic tone in the canine model. While the available evidence suggests that withdrawal of parasympathetic cardiac tone is important in regulation of heart rate, activation of sympathetic vasoconstrictor activity may contribute importantly to changes in BP on arousal from sleep. In response to auditory stimuli during non-REM sleep, cortical evidence of arousal is accompanied by substantial increases in systolic and diastolic BP (approximately 21 and 15 mmHg, respectively), with a HR
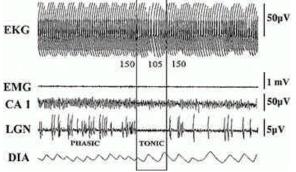
Figure 4. Representative polygraphic recording of a primary heart rate (HR) deceleration during tonic rapid eye movement sleep (T-REM) During this deceleration, HR decreased by 30%. Deceleration occurred during a period devoid of pontogeniculooccipital (PGO) spikes in lateral geniculate nucleus (LGN) or theta rhythm in hippocampal (CA1) leads. Deceleration is not a respiratory arrhythmia, because it is independent of diaphragmatic movement. Abrupt decreases in amplitude of CA1, PGO waves (LGN), and respiratory amplitude and rate (DIA) are typical of transitions from phasic to tonic REM. EKG, electrocardiogram; EMG, electromyogram; DIA, diaphragm. Used with permission from 27.

change of 11 beats per minute. Associated with the increases in BP and HR are increases in MSNA (56). The simultaneous increases in sympathetic traffic, HR and BPs suggest that the baroreflexes are very rapidly reset or overwhelmed by the arousal stimuli. Accompanying the increased sympathetic traffic is a decrease in sympathetic burst latency (56). The physiologic basis and implications of changes in burst latency are not clear. These changes may be related to either changes in baroreflex function or due to breathing related changes in the dynamics of sympathetic nerve traffic. Along with the hemodynamic and autonomic changes described above, cortical arousal is also accompanied by transient hyperpnea.

*In situ*ations where arousal stimuli do not elicit cortical evidence for arousal, there is a smaller but significant pressor response in the absence of any evidence of sympathetic activation (56). Arousal stimuli without corresponding evidence for cortical arousal do not appear to elicit changes in ventilation (57).

These responses to arousal likely represent an important physiologic preparation in anticipation of rapid assumption of the upright posture and a fight or flight reaction. However, it is also conceivable that the neural, circulatory and other responses elicited by arousal from sleep in the morning may contribute in part to initiation of pathophysiologic processes that present with cardiac and vascular events in the early hours of the morning after waking.

3. FACTORS INFLUENCING CARDIOVASCULAR RESPONSES TO SLEEP

While the general pattern of neural circulatory responses to sleep, sleep stage and arousal from sleep have been described based on studies in normal subjects, it is important to recognize that a number of demographic and other factors may have important influences on modulating the specific responses to sleep within an individual. For example, we know that the structure and often quality of sleep have direct effects on sleep hemodynamics. It is likely that age may have important differential effects on BP, HR and autonomic responses to sleep.

Similarly, issues such as gender may also importantly influence sleep. This is particularly true for changes in RR interval, RR variability and the QT during REM sleep.

Recent studies examining the effects of sleep stage on RR and QT intervals in healthy women compared to men, showed that both these variables differed significantly between the genders. In men, RR interval and RR variability increased through all sleep stages. The QTc remains stable from wakefulness, throughout sleep. In women, however, RR interval increased only during non-REM, and was virtually identical in wakefulness and in REM. RR variability remained very stable from wakefulness through all stages of sleep in women. Furthermore, in women during REM, both absolute QT interval and QTc increased significantly compared with wakefulness (58) (figure 6). Thus, the influence of sleep on RR, RR variability and QTc is gender dependent, and findings in men cannot be easily extrapolated to understanding the physiology in women. Further studies are needed to determine whether menopausal status affects the control of these variables in women and how they relate to changes in men

Even within the same subject, the possibility of changes in the patterns and magnitude of autonomic and hemodynamic responses to sleep and arousal during the different periods of sleep, i.e. early during sleep compared to late during sleep, and compared to just before waking, must also be considered. The potential influence of late sleep, i.e. just before waking, on the early morning peak of cardiovascular and other events remains to be determined. REM for example is more evident in the later stages of sleep.

Last, the effects of disease states may also be important in alterations of neural circulatory mechanisms during sleep. These alterations may be secondary to other powerful reflexes being activated during sleep, as is seen in patients with obstructive sleep apnea(59-62). Alternatively, the disease condition itself may conceivably alter the intrinsic central processing of sleep or posture related autonomic responses. For example, assumption of the supine posture during sleep in itself has distinct and important effects on cardiovascular function. The increased cardiac filling pressures accompanying the horizontal posture is easily accommodated by the healthy normal heart. However, in conditions of pre-existing cardiovascular disease, particularly cardiac failure, increased cardiac filling pressures may potentiate disease pathophysiology, by causing paradoxical vasoconstriction and further worsening heart failure.
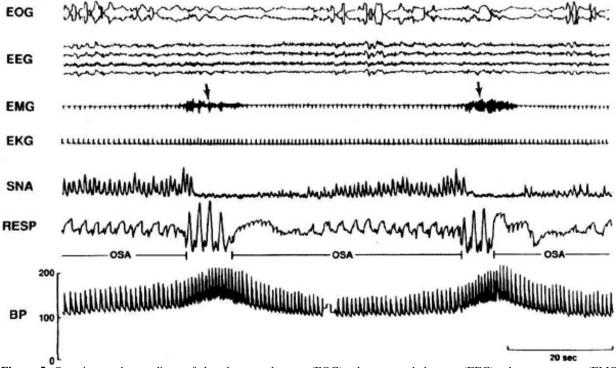
Figure 5. Superimposed recordings of the electrooculogram (EOG), electroencephalogram (EEG), electromyogram (EMG), electrocardiogram (EKG), SNA, RESP, and BP during REM sleep in a patient with OSA. BP during REM, even during the lowest phases (approximate 160/105 mmHg), was higher than in the awake state (130/75 mmHg) BP surges at the end of the apneic periods reached levels as high as 220/130 mmHg. EOG shows the sharp eye movements characteristic of REM sleep. Increase in muscle tone (EMG) and cessation of rapid eye movements toward the end of the apneic period indicates arousal from REM sleep (arrows) Used with permission from 76.
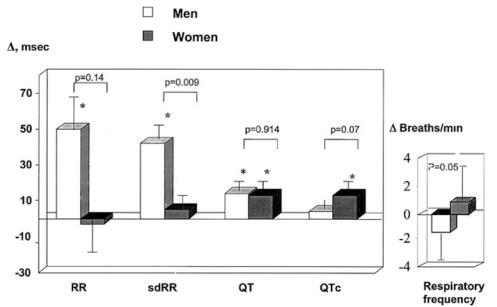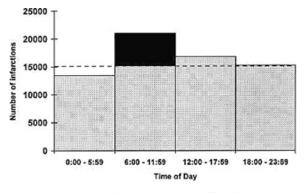

Figure 6. Comparison of changes of electrocardiographic measurements and breathing frequency from wakefulness to REM (=REM-wakefulness) in men and women (unpaired t test) The presence of a significant difference between REM and wakefulness within subjects is indicated by an asterisk (see also Tables 2 and 3) RR interval and RR variability (sdRR) significantly increase in men while remaining stable in women from wakefulness to REM. In both men and women, the QT interval increases. However, the QTc remains stable through sleep in men while increasing significantly during REM sleep in women. Breathing frequency decreases in men whereas it increases in women, leading a statistically significant difference between the 2 groups. Used with permission from 58.
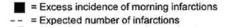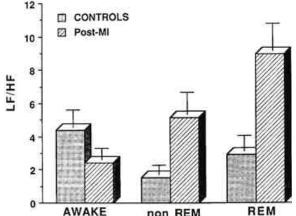
Figure 7. Circadian pattern of nonfatal myocardial infarction (n = 66,635) Used with permission from 66.

Figure 8. Bar graphs indicating mean±SEM of the low- to high-frequency ratio (LF/HF) from spectral analysis of heart rate during the awake state (left), during non–rapid eye movement (REM) sleep (middle), and during REM sleep (right) in normal subjects and in post–myocardial infarction (MI) patients. *P<.01 when comparing control subjects versus post-MI patients.Used with permission from 73.

4. CLINICAL IMPLICATIONS OF CARDIOVASCULAR RESPONSES TO SLEEP AND AROUSAL

The neural, circulatory and hemodynamic adjustments to the different phases of normal sleep and arousal, have important implications for understanding cardiovascular disease mechanisms and presentations. For example, abrupt changes in cardiac autonomic activation and balance may have implications for arrhythmogenesis in individuals with predisposition to cardiac electrical instability. Patients with certain variants of the long QT genotype for example, are particularly susceptible to sudden death events during sleep or during arousal from sleep (63)**.**

Sudden cardiac death, myocardial infarction, unstable angina, ventricular tachyarrhythmias, fatal pulmonary thromboembolism, rupture of the thoracic aorta,

and ischemic and hemorrhagic cerebrovascular accidents exhibit a prominent circadian pattern, with more frequent events during the morning after awakening (64-66) (figure 7).

A review of morbidity and mortality data may lead one to believe that sleep per se is a safe haven, since only 8 to12% of all cardiovascular deaths occur at night and a normal adult spends a third of the day in sleep (67) However, given the state of somatic rest that characterizes sleep, it is surprising that any events at all should occur, speaking again to the importance of autonomic and hemodynamic mechanisms in initiating acute cardiovascular processes, even during supine rest.

The sympathetic surges, arrhythmias and ischemic changes that have been noted, have been associated mainly with REM sleep (17, 68-70). REM sleep occupies between 90 to 120 minutes of a typical 8-hour sleep time. If this is indeed the hour of peril, this period then would translate into a far higher relative risk of sudden death, rising to as high as 1.2 times that of wakefulness (27). Furthermore, the morning surges in cardiac, vascular and arrhythmic events have been related to an increased sympathetic drive in the morning after waking. It is hypothesized that this could again be related to REM sleep. REM is most manifest toward the end of sleep, before arousal (27). It is possible that REM may initiate changes in processes involving platelet aggregability, plaque rupture or coronary vasospasm (68, 70) which act as triggering mechanisms for thrombotic events, and may present clinically only after arousal (17, 27)

Below we will review several aspects of sleep related changes in cardiac and vascular function both in health and disease states, that may have direct consequences for understanding interactions between sleep and cardiovascular disease.

4.1. Coronary circulation and sleep

In canine studies, coronary blood flow decreases significantly from wakefulness to non-REM sleep and is dramatically increased in REM sleep. The blood flow surges and decreased coronary vascular resistance are coupled with episodes of sinus tachycardia. Demonstrable surges, of up to 90%, in HR and coronary flow are concentrated during periods of phasic REM sleep and only 10% are seen in tonic REM sleep (38). Both tachycardia and blood flow surges are eliminated by bilateral stellectomy suggesting that the SNS is responsible for initiating these changes by increasing frequency, metabolic activity, and rate pressure product (HR x Systolic BP), thereby increasing flow.

Regional blood flow distribution during REM sleep in piglets is associated with left ventricular blood flow even as early as the age of 6 days (71). Changes in the magnitude of HR and blood flow increments are closely matched, suggesting that metabolic vasoactive substances are responsible for reduced coronary resistance. On the other hand, when marked stenosis (43) is induced by cuff inflation in the left circumflex coronary artery, the surges in
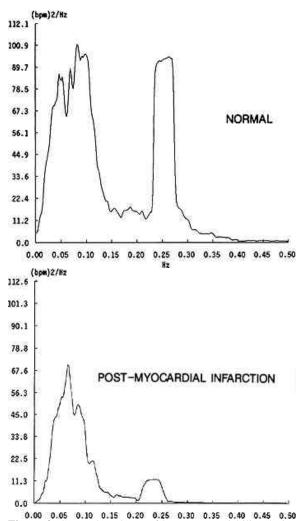
Figure 9. Spectral analyses of heart rate variability during non–rapid eye movement sleep from one normal individual (top) and in a patient with a recent myocardial infarction (bottom) A marked difference in the high-frequency band power is evident. The low-frequency to high-frequency ratio is 0.91 in the control subject and 5.52 in the post–myocardial infarction patient. bpm indicates beats per minute. Used with permission from 73.

heart rate during REM sleep are accompanied by a decrease in coronary blood flow.

Thus, physiologic changes during REM may be severely disturbed in the setting of pre-existing coronary artery stenosis, suggesting a mechanism to explain the association between REM and nocturnal cardiac ischemia (72)

4.2. Heart rate control during sleep after myocardial infarction

In normal sleep, acceleration of HR occurs with inspiration and deceleration during expiration. This is to accommodate the increased venous return with lung expansion. This variability is indicative of good cardiac

health, and causes a decrease in the LF/HF ratio of the RR interval in NREM sleep.

Pathophysiological conditions and advancing age may significantly alter measures of HRV during sleep. HRV patterns are severely disrupted after myocardial infarction (73). In a study of 8 patients following myocardial infarction, the expected non-REM related decrease in the LF/HF ratio was absent, and the ratio actually increased during non-REM sleep (73) (figure 8, 9). During REM sleep, the LF/HF ratio increased further in these patients to levels even greater than those recorded during wakefulness. This suggests inappropriate sympathetic dominance in sleep and loss of sleep related vagal activation. Whether these findings are true for the post-myocardial infarction population in general, and their pathophysiological implications, remain to be determined.

4.3. Blood pressure and sleep

As described earlier, BP decreases during sleep, compared to wakefulness, by about 10-20 % (74). This nocturnal decline has come to be known as "dipping". There is emerging evidence that the absence of the expected nocturnal BP decline as seen in "non-dippers", as well as an excessive BP decline during sleep ("extreme dipping"), may both have important cardiovascular implications (75).

Patients with OSA (76, 77), and those who are obese (78) tend not to have the expected BP decline during sleep. In addition, elderly individuals, perhaps because they spend more time in bed, experience less SWS, and have more arousals and more sleep fragmentation, are also less likely to show the expected nocturnal BP decline. Verdechia and colleagues noted that those individuals in whom BP did not decline as expected during sleep, were at increased risk for left ventricular hypertrophy and possibly also for other cardiovascular events (79, 80).

Excessive dipping may also have clinical implications. Nocturnal hypotension has been linked to central ischemia, presenting as anterior ischemic optic neuropathy (AION) (81, 82). Kario and colleagues (83) in studies of elderly individuals with hypertension, noted that a large proportion of an elderly asymptomatic hypertensive patient sample, had evidence for cerebral ischemia, including lacunar infarction and periventricular hyperlucencies on magnetic resonance brain imaging (figure 10). In differentiating these individuals with asymptomatic strokes from those with normal brain scans, these investigators noted that patients with lacunar infarction were those in whom the nocturnal BP fall was especially marked.

While the BP decline during sleep is physiologic, it is important that this BP reduction should not be potentiated excessively by iatrogenic interventions such as antihypertensive medication, perhaps administered just before sleep. Any pharmacologic BP fall may be especially problematic in patients with impaired regulatory mechanisms such as diabetics with autonomic neuropathy, and the very elderly.
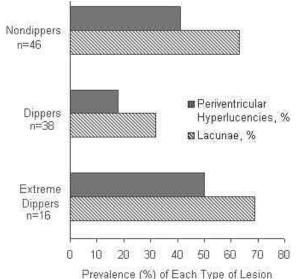
Figure 10. Target-organ damage of elderly patients with sustained hypertension with different nocturnal blood pressure fall. Periventricular hyperlucencies (PVH) indicate PVH grades III and IV on T_2-weighted images by MRI. Values are means. Adapted from 83.

5. SLEEP DISORDERED BREATHING

The heart and lungs share an adjacent anatomy, blood flow and autonomic innervation in the chest. They are intimately related in structure and function - changes in the one significantly affect the other. Breathing results in closely tracking changes in HR and cardiac output due to mechanisms involving increases in venous return, right ventricular filling and changes in left ventricular filling and afterload. This coupling between breathing and cardiac function is evident as sinus arrhythmia and inspiratory related decreases in systolic BP (SBP).

Therefore, abnormalities in breathing for example may have direct hemodynamic and reflex influences on cardiovascular functional and structural characteristics. Chemoreflex excitation by hypoxemia and/or hypercapnia, also contributes importantly to cardiovascular responses to disturbed breathing. These interaction are most evident in patients with sleep related breathing disorders such as obstructive sleep apnea (OSA) and central sleep apnea (CSA).

Sleep facilitates the appearance of breathing disorders due to instability in ventilatory control, decrease in the neuromuscular tone of the upper airways, alteration in respiratory reflexes, altered carbon dioxide (CO_2) homeostasis, decreased Functional Residual Capacity in the supine position and decreased VCO_2. We will limit our focus to OSA and CSA.

5.1. Obstructive sleep apnea

Patients with OSA characteristically have repetitive episodes of upper airway occlusion causing hypoxemia and CO_2 retention despite strenuous efforts to breathe. The apneic events last more than 10 seconds and

can persist for up to 60 seconds or longer, accompanied by oxygen desaturation to levels as low as 40%. A myriad of hemodynamic, metabolic and reflex adjustments occurs acutely in response to each apneic event. Some of these include chemoreflex activation by hypoxemia and hypercapnia (84-86) with consequent sympathetic vasoconstriction to peripheral blood vessels, resulting in marked surges in BP (59, 87). Because of decreased venous return during the apnea itself, on resumption of breathing there is an abrupt increase in venous return and hence cardiac output. This increased cardiac output enters a very vasoconstricted periphery so that the surges in BP are most evident on termination of the apnea (76) (figure 11).

The obstructive apneic events are also occasionally accompanied by significant bradyarrhythmias. This is because of excitation of the diving reflex by the combined stimuli of hypoxia, apnea and distortion of the upper airway. This reflex classically induces simultaneous sympathetic activation to peripheral blood vessels and vagal activation to the heart (88)**.** In patients with OSA, bradyarrhythmias will be evident even in the absence of any primary disorder of the cardiac conduction system. The bradyarrhythmias are very sensitive to atropine and resolve when the OSA is treated appropriately with continuous positive airway pressure (CPAP) (89-91) (figures 12, 13).

The cardiovascular consequences of acute obstructive apneic events include abrupt surges in BP as described above. Cardiac ischemia (92-95) may occur due to the increased afterload in the setting of severe hypoxemia, and increased cardiac wall stress because of the marked negative pressure generated during the obstructive apnea, causing increased transmural pressure gradients across the myocardium (60). Tachyarrhythmias may also occur acutely during the night particularly in patients with pre-existing significant ischemic or other cardiac disease.

OSA may also have significant implications for the development of chronic cardiovascular diseases. The most compelling causal evidence implicating OSA in a cardiovascular disease condition are the data from the Wisconsin Sleep Cohort Study(96) (figure 14). These investigators noted that in patients with significant sleep apnea, followed over 4 years, there was a three-fold increased risk of developing new hypertension(96). Other diseases that have been associated with OSA include stroke (97), cardiac ischemia (95, 98) and heart failure (99). There is a high prevalence of OSA in patients with stroke. However, whether the sleep apnea occurs as a consequence of the stroke and whether sleep apnea is directly implicated in stroke development, remains to be determined.

5.2. Central sleep apnea

CSA also loosely referred to as Cheyne Stokes Respiration (CSR), affects 40-60% of patients with chronic systolic heart failure (100-104). CSR is a type of CSA which is characterised by recurrent episodes of central apnea or hypopneas and hyperventilation which show a typical crescendo-decrescendo pattern in tidal volume.
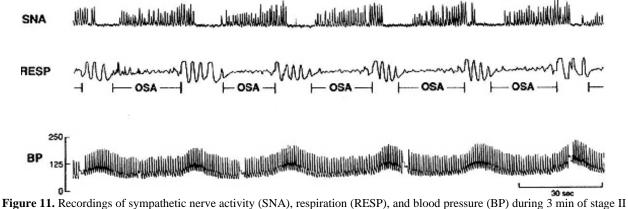
Figure 11. Recordings of sympathetic nerve activity (SNA), respiration (RESP), and blood pressure (BP) during 3 min of stage II sleep, showing incessant oscillations in BP and SNA in response to the repetitive OSAs. These oscillations occurred continuously during sleep, throughout all sleep stages. Used with permission from 76.
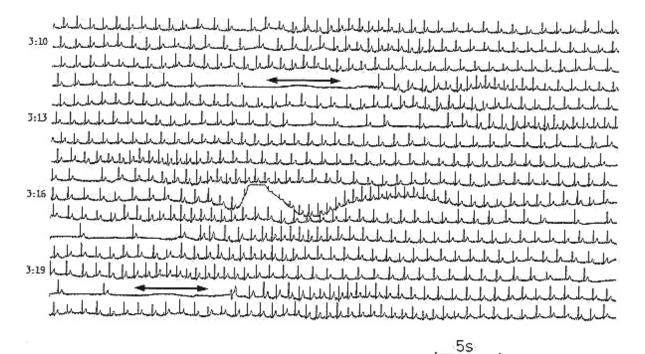

Figure 12. Holter recording (12.5 mm/s) of a patient with obstructive sleep apnea showing 2 episodes with sinus arrest or third-degree sinoatrial block, with ventricular asystole of 11.2 and 10.2 seconds duration, respectively (arrows) Used with permission from 89.

Hemodynamic and non-hemodynamic factors are implicated in the genesis of this breathing disorder in the context of heart failure (CHF) (105). However, CSA-CSR appears to perhaps be part of a cycle whereby congestive heart failure (CHF) leads to CSA, which, in turn, may aggravate cardiac failure, perhaps predisposing to ventricular arrhythmias and even impaired prognosis.

The immediate consequence of CSA is sleepiness and fatigue linked to the sleep fragmentation perhaps explaining some of the fatigue that characterizes CHF patients. The long term implications of CSA in CHF include poorer quality of life and diminished life expectancy (92, 106, 107).

Severe CSA is associated with an impaired cardiac autonomic control and electrical instability, with a higher incidence of premature ventricular contractions and ventricular tachycardia (102). The high levels of sympathetic drive evident in patients with heart failure increase even further during episodes of central apnea (108). The plasma and urine norepinephrine levels are also significantly higher (109). In patients with heart failure generally, increased adrenergic drive, as measured by catecholamine levels, is associated with increased mortality
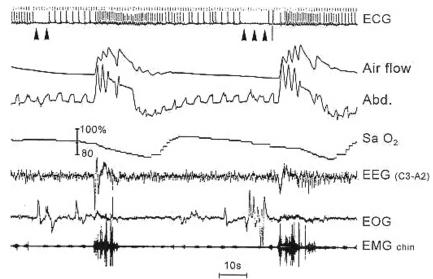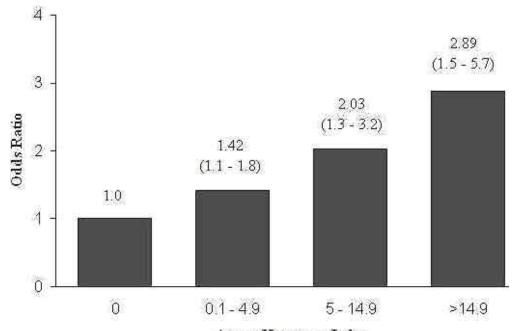
Figure 13. Two-minute segment of diagnostic polygraphic recording showing 2 episodes of obstructive sleep apnea during rapid eye movement sleep characterized by cessation of nasal airflow despite continuous thoracic and abdominal respiratory efforts. Note that third-degree atrioventricular block with ventricular asystole of 6 and 11 seconds duration occurs toward the end of the first and second apnea episodes, respectively (arrows) After 40 seconds of apnea, ventilation is resumed briefly during an arousal, and sinus speeding occurs with resumption of 1:1 atrioventricular conduction. Abd. = ——; ECG= electrocardiogram; EEG = electroencephalogram; EMG = electromyogram; EOG = electro-oculogram; Sa O2 = oxygen saturation. Used with permission from 89.

Figure 14. Association of hypertension with apnea hypopnea index (AHI) adjusted for baseline hypertension, body mass index (BMI), waist and neck circumference (Wisconsin Sleep Cohort Study) Adapted from 96.

6. SLEEP DEPRIVATION

The National Commission on Sleep Disorders Research estimates that 30 million adults and teenagers in the United States are chronically sleep deprived (112, 113). Habitual sleep deprivation and premature cardiovascular morbidity (114) and mortality (115,116) have been reported in longitudinal or cross-sectional studies (117, 118). Sleep problems and exhaustion upon waking may be markers of subclinical heart disease. In Japan, sleep deprivation and "karoshi" (sudden death caused by overwork) has developed into serious socioeconomic problems (119-121). In the USA, there also appears to be a modest increase in health care utilization in patients with chronically disrupted sleep (122).

Cardiovascular consequences of sleep deprivation remain unclear (123, 124). A recent prospective study suggested that sleep curtailment to 5 or less hours was associated with a 39% increase in risk of CHD (125). There is some evidence that acute episodes of sleep deprivation cause increases in daytime BP (126-129). Longer-term sleep deprivation disrupts glucose regulation so that the metabolic profile tends toward a diabetic-like state (130). Other mechanisms that are activated in sleep deprivation that may have adverse longer-term cardiovascular consequences include inflammation (131). Increases in levels of interleukins may enhance production of inflammatory mediators that have adverse cardiovascular effects including C-reactive protein (132-134). It is also likely that sleep deprivation and its consequences may contribute to some of the cardiac and vascular dysfunction and disease that have been associated with sleep apnea.

7. SUMMARY

Despite a precipitous increase in our understanding of cardiovascular physiology and pathology during sleep over the last two decades, there remain significant and important gaps in our knowledge. What is clear is that sleep, sleep stage and arousal are intermittently linked to distinct and important changes in neural circulatory control and hemodynamics. These physiologic changes may potentially have pathologic implications in patients with pre-existing significant cardiovascular disease, or with tissue substrates that are vulnerable to sleep associated autonomic fluctuations. The consequences of sleep related cardiovascular processes may be evident in cardiac events occurring either during sleep, or in a circadian pattern with a peak incidence in the early hours of the morning after waking.

Disturbed sleep, whether as a consequence of sleep deprivation or because of sleep disordered breathing, may also be linked to both acute and chronic cardiovascular disease conditions. A comprehensive understanding of the physiologic responses to normal sleep at every level - neural, vascular, myocardial, inflammatory, and hemorheologic - is important to better understand the mechanisms and implications of changes in these systems occurring during disordered sleep.

8. ACKNOWLEDGEMENTS

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