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# Sleep and Cardiovascular Disease

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**Abstract:** Sleep is an important modulator of cardiovascular function, both in physiological conditions and in disease states. In individuals without a primary sleep disorder, sleep may exert significant effects on the autonomic nervous system, systemic hemodynamics, cardiac function, endothelial function, and coagulation. Some of these influences can be directly linked to specific modulatory effects of sleep stages per se; others result from the natural circadian rhythm of various physiological processes. There is a temporal association between physiological sleep and occurrence of vascular events, cardiac arrhythmias, and sudden death. Epidemiological and pathophysiological studies also indicate that there may be a causal link between primary sleep abnormalities (sleep curtailment, shift work, and sleep-disordered breathing) and cardiovascular and metabolic disease, such as hypertension, atherosclerosis, stroke, heart failure, cardiac arrhythmias, sudden death, obesity, and the metabolic syndrome. Finally, sleep disturbances may occur as a result of several medical conditions (including obesity, chronic heart failure, and menopause) and may therefore contribute to cardiovascular morbidity associated with these conditions. Further understanding of specific pathophysi-

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**ological pathways linking sleep disorders to cardiovascular disease is important for developing therapeutic strategies and may have important implications for cardiovascular chronotherapeutics. (Curr Probl Cardiol 2005;30:625-662.)**

**C**ardiovascular disease is the leading cause of mortality and morbidity in the US and other Western societies. Multiple preventive and therapeutic measures have been implemented in the last few decades. However, at the population level these measures remain insufficient. One possible reason for the failure of current strategies to effectively tackle the epidemic of cardiovascular disease may be the lack of recognition of some important risk factors. In this review we will argue the case for sleep as an important modulator of cardiovascular function, both in physiological conditions and in disease states.

The potential importance of sleep in the pathogenesis and progression of cardiac and vascular disease has been recognized relatively recently. Hence, there is only limited evidence from which definitive conclusions can be drawn. Epidemiologic data are also relatively sparse in that sleep studies have not been incorporated as a routine measurement in prior epidemiologic work. Furthermore, the information presented in this review needs to be considered in the context of publication bias in that studies showing a positive link between sleep and cardiovascular pathophysiology are more likely to be published than those showing the absence of any relationship. In addition, many studies suggesting involvement of sleep apnea in cardiovascular disease have not been well-controlled in that the sleep apnea patient population often has cardiovascular comorbidities, which makes it difficult to confirm pathophysiologic effects of sleep apnea per se. Available data are often observational, uncontrolled, and confounded by common comorbidities of hypertension, diabetes, heart failure, hyperlipidemia, and, most often, obesity.

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**J. S. Alpert:** Recent studies in patients with heart failure have shown a surprisingly large percentage with sleep abnormalities. Whether the sleep disturbances are the result of heart failure or an independent occurrence in this often elderly population with concomitant lung disease is not known at this time.

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## Normal Sleep in Health and Disease

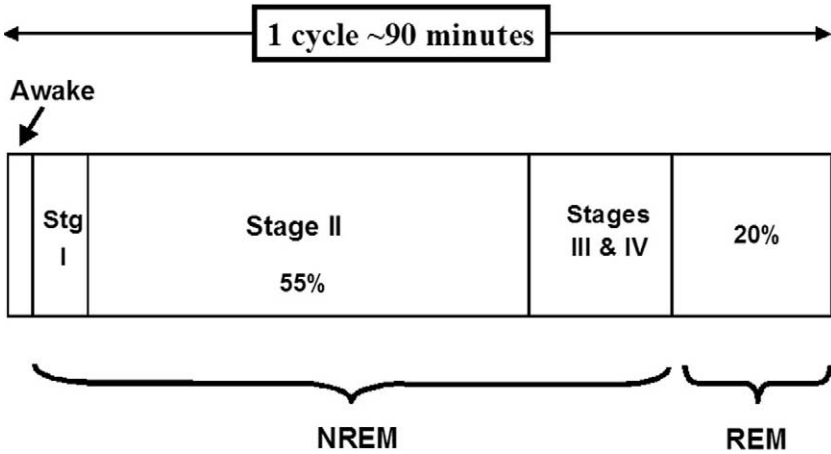
Considering that sleep occupies more than 30% of our lives, the contribution of sleep to cardiovascular regulation has been studied inadequately. This is in part due to a long-held perception that sleep is a passive state of relative functional quiescence at the systemic level, and its only function is rest and restoration. While it may well be true that the primary role of sleep is physiological rest, it is becoming clear that even normal sleep is a complex and dynamic process with profound effects on cardiovascular homeostasis. Some of these effects of sleep are related to circadian variations/rhythms in the activity of regulatory pathways, and others correspond to specific sleep stages.

### *Autonomic and Hemodynamic Effects of Normal Sleep*

Cardiovascular function is affected by rhythmic patterns in homeostatic regulatory mechanisms, including of the autonomic nervous system. In general, the highest sympathetic activity is seen during the day and parasympathetic activity is more pronounced at night.<sup>1,2</sup> As a result, there is also cyclical variation in hemodynamic measurements over a 24-hour cycle, with the lowest heart rate and blood pressure observed during the night, followed by an early-morning increase in heart rate and blood pressure, as well as increased vasomotor tone in coronary arteries in the morning.<sup>3</sup> However, in addition to this diurnal profile, significant fluctuations in the autonomic tone and systemic hemodynamics are also seen in association with specific sleep phases.

Physiological sleep can be divided into nonrapid eye movement (NREM) and rapid eye movement (REM) stages (Fig 1), which ensue in a cyclical manner, with ~4 to 5 NREM/REM cycles occurring every night. As sleep progresses, each recurring REM episode gets gradually longer. Non-REM sleep is characterized by a progressive decrease in neural sympathetic activity with an accompanying parasympathetic predominance, downward resetting of the arterial baroreceptor reflex, and decreases in heart rate, cardiac output, peripheral vascular resistance, and blood pressure. REM sleep is accompanied by neural sympathetic and electroencephalographic activity similar to that when awake, with distinct cardiovascular effects. A single REM cycle comprises a tonic state, which is interspersed by periods of phasic activity (characterized by rapid eye movements).<sup>4</sup> Tonic and phasic REM differ in their effects on the autonomic nervous system and systemic hemodynamics, and there may be rapid changes in the autonomic profile even within each of these two states.

REM sleep is a predominantly vagotonic state. However, superimposed



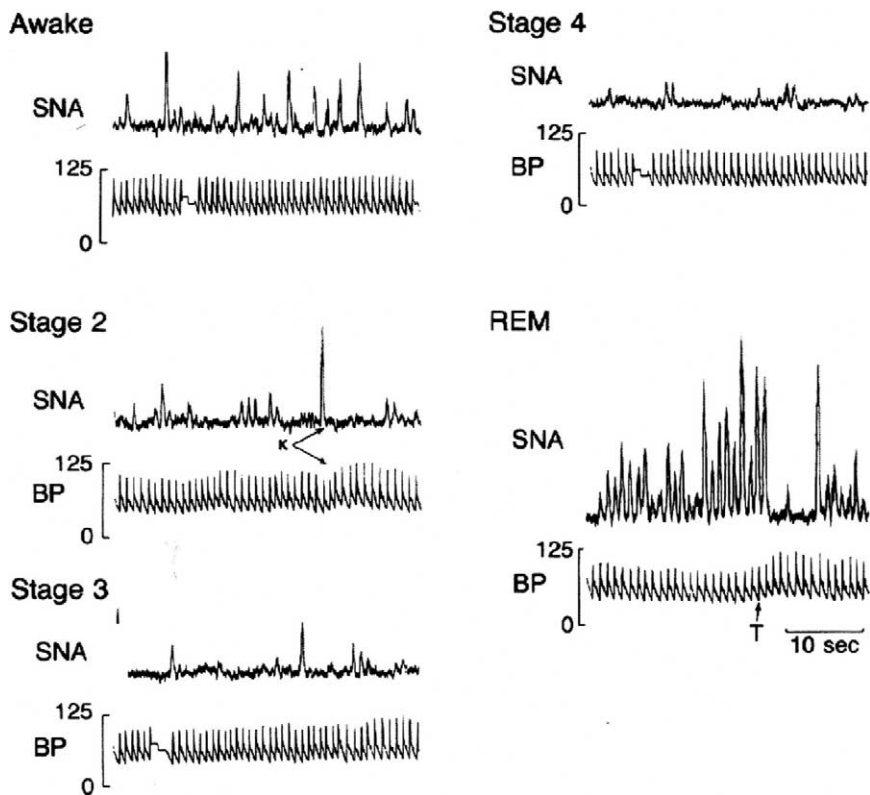
**FIG 1.** Sleep architecture. Normal sleep is composed of nonrapid eye movement (NREM) and rapid eye movement (REM) stages. The figure shows a single NREM/REM cycle. On average, a healthy person undergoes four to five such cycles every night. Overall, NREM and REM stages occupy 70 to 80% (6 hours) and 20 to 25% (1.5 hours) of total sleep time, respectively.

on the backdrop of increased cardiac parasympathetic tone are sudden bursts of sympathetic nerve activity that occur in phasic REM, which are in part linked to changes in muscle tone.<sup>4,5</sup> As a result, surges in sympathetic nerve activity during REM lead to increases in blood pressure and heart rate, similar to levels during wakefulness (Fig 2). Momentary bursts of sympathetic activity to peripheral blood vessels (with accompanying increases in heart rate and blood pressure) can be also elicited by arousal stimuli (such as a knock on the door) during NREM sleep (Fig 2).

### *Electrophysiological Effects of Normal Sleep*

Consequent on these fluctuations in autonomic tone are changes in cardiac electrophysiology. As a result of increased parasympathetic activity, marked sinus arrhythmia, conduction disturbances (eg, first-degree and Wenckebach atrioventricular block), and sinus pauses have all been described in healthy people during sleep, particularly REM.<sup>6,7</sup>

There is also evidence of changes in electrocardiographic QT interval during sleep, indicative of sleep-induced alterations in cardiac repolarization.<sup>8,9</sup> It is interesting that these electrophysiological effects may be sleep stage- and gender-dependent. Specifically, in a recent study of healthy individuals free of any occult sleep disorder, heart rate-corrected

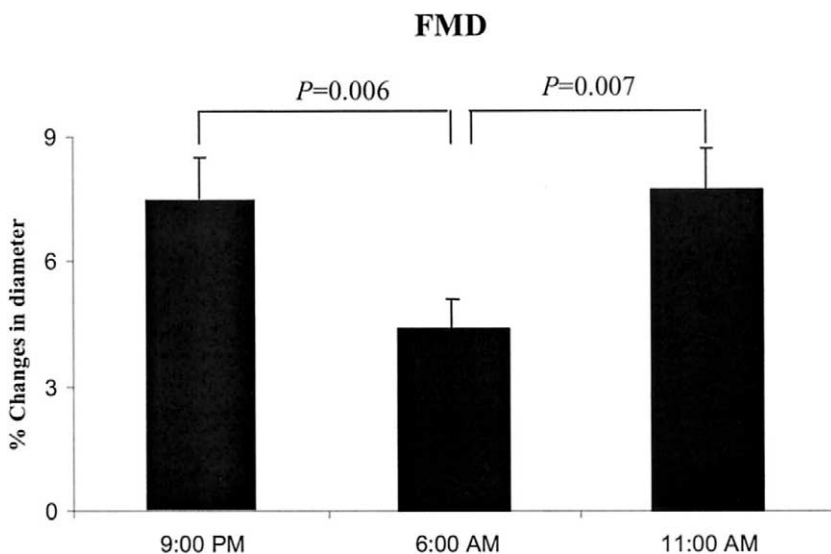


**FIG 2.** Recordings of sympathetic nerve activity (SNA) and blood pressure in a single subject while awake, while in stages 2, 3, and 4 of NREM sleep, and while in REM sleep. As NREM sleep deepens (stages 2 through 4), SNA gradually decreases and BP (measured in mmHg) and variability in BP are gradually reduced. Arousal stimuli elicited K complexes on the electroencephalogram (not shown), which were accompanied by increases in SNA and BP (indicated by the arrows, stage 2 sleep). In contrast to the changes during NREM 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. (Reproduced with permission from Somers et al, 1993.<sup>5</sup>)

QT interval remained stable from wakefulness through all sleep stages in men, but in women it significantly increased during REM sleep compared with wakefulness.<sup>10</sup>

### *Endothelial Function and Vascular Tone*

There are several reasons to expect that sleep could affect vascular tone and endothelial function in healthy subjects, including changes in



**FIG 3.** Percent changes of brachial artery flow-mediated vasodilation (FMD) in 30 healthy subjects. (Reproduced with permission from Otto et al, 2004.<sup>16</sup>)

sympathetic activity,<sup>11</sup> plasma catecholamines,<sup>12</sup> and shear stress. However, several studies on endothelial function before and after sleep provided conflicting results, reporting a decrease, no change, or an increase in endothelial function in the morning as compared with the evening.<sup>13-15</sup> Although the reasons for these discrepancies are not entirely clear, they may conceivably be related to differences in the methodology of blood flow measurements, different vascular beds studied, as well as the presence of occult sleep disorders in study subjects (chronic or occurring just on the night of the study). Recent results obtained in healthy individuals, proven by polysomnography to be free of any acute or chronic sleep abnormalities, suggest that brachial artery flow-mediated endothelium-dependent vasodilation (measured using high-resolution ultrasound) is markedly decreased in the early morning (after waking and before arising) compared with before sleep, and subsequently recovers by late morning (Fig 3).<sup>16</sup> The magnitude of morning attenuation in endothelial function observed in that study was very similar to the attenuation of brachial artery reactivity noted in smokers<sup>17</sup> and in diabetics,<sup>18</sup> speaking to the functional and clinical significance of the overnight variation in endothelial function in healthy individuals.

It is interesting that a similar circadian variation likely occurs also with respect to coronary vascular tone in patients with coronary artery disease

(in parallel with changes in postischemic forearm blood flow),<sup>19</sup> suggesting that systemic neurohumoral rather than local factors are responsible for the circadian changes in vascular function. One such possible systemic factor is sympathetic activation. Also, in patients with variant angina, flow-mediated vasodilation deteriorates in the early morning and improves by the afternoon, and the frequency of spontaneous ischemic episodes is highest from midnight to morning.<sup>14</sup> Decreased endothelial function in the early morning may have implications for our understanding of the morning peak in cardiac and vascular events, as discussed below.

Whether endothelial function is acutely and significantly affected by autonomic fluctuations during various sleep stages in humans remains to be established. Nevertheless, preliminary data in animals indicate that sleep stages (in particular phasic REM) are associated with changes in regional vascular flow (including the coronary circulation), which are mediated by the sympathetic nervous system.<sup>20,21</sup>

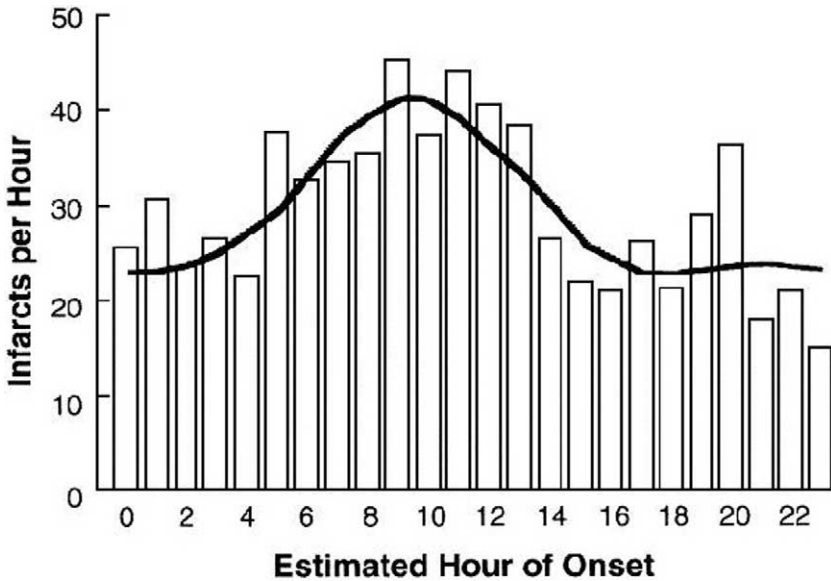
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**J. S. Alpert:** The potentially complex interactions between the autonomic central nervous system, the heart, the lungs, and the peripheral vascular tree stagger the imagination. Considerably more work in basic physiology and observations in the clinical arena are needed. Given that sleep disturbances are so common, it is likely that they play an important role in the pathophysiology of a variety of cardiac conditions.

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## Coagulation

Circadian patterns have been reported for platelet aggregation, blood viscosity, tissue plasminogen activator, and fibrinolytic activity in the direction favoring increased coagulability in the early morning.<sup>22-24</sup> An association between increased platelet activation and cardiac events in the morning has also been suggested.<sup>23</sup> However, whether enhanced platelet aggregability in the morning is directly related to any effects of sleep is uncertain, because it does not occur in subjects who remain supine, but rather only after arising and assuming the upright posture.<sup>23,25-27</sup> Furthermore, the morning increase in platelet aggregation is not accompanied by platelet activation (assessed by changes in expression of activation-dependent platelet surface markers), but is likely related to increased catecholamine levels, platelet count, and hemoconcentration.<sup>25,28</sup> Nevertheless, the causal association between catecholamines and platelet activation<sup>28,29</sup> raises an intriguing possibility, namely that sympathetic surges during normal sleep (especially REM stage) may also be condu-



**FIG 4.** Circadian variation in the frequency of onset of myocardial infarction. (Reproduced from Muller et al, 1985.<sup>31</sup>)

cive to platelet aggregation, especially in susceptible individuals, and thus may explain any association between sleep and cardiovascular events (see below).

### *Sleep, Circadian Rhythm, and Cardiovascular Events*

**Vascular events.** A diurnal rhythm has been consistently reported in the occurrence of cardiovascular and cerebrovascular events (such as myocardial ischemia, myocardial infarction [Fig 4], and stroke), with a peak between 6 and 11 AM.<sup>30-35</sup> The temporal association between these events and the circadian variations in sympathetic activity, endothelial function, and coagulation (as discussed earlier) suggest that these pathophysiological processes may be causally related to the morning peak of vascular events.

In addition to the morning rise in ischemic events, autonomic and hemodynamic effects of normal sleep may decrease the ischemic threshold and increase susceptibility to myocardial ischemia during the actual sleep hours. It is possible that nocturnal myocardial ischemia may be related to different pathophysiological mechanisms depending on sleep stage, with decreased coronary perfusion pressure conceivably being important in NREM sleep and increased myocardial oxygen demand playing an important role in REM sleep.<sup>36,37</sup>



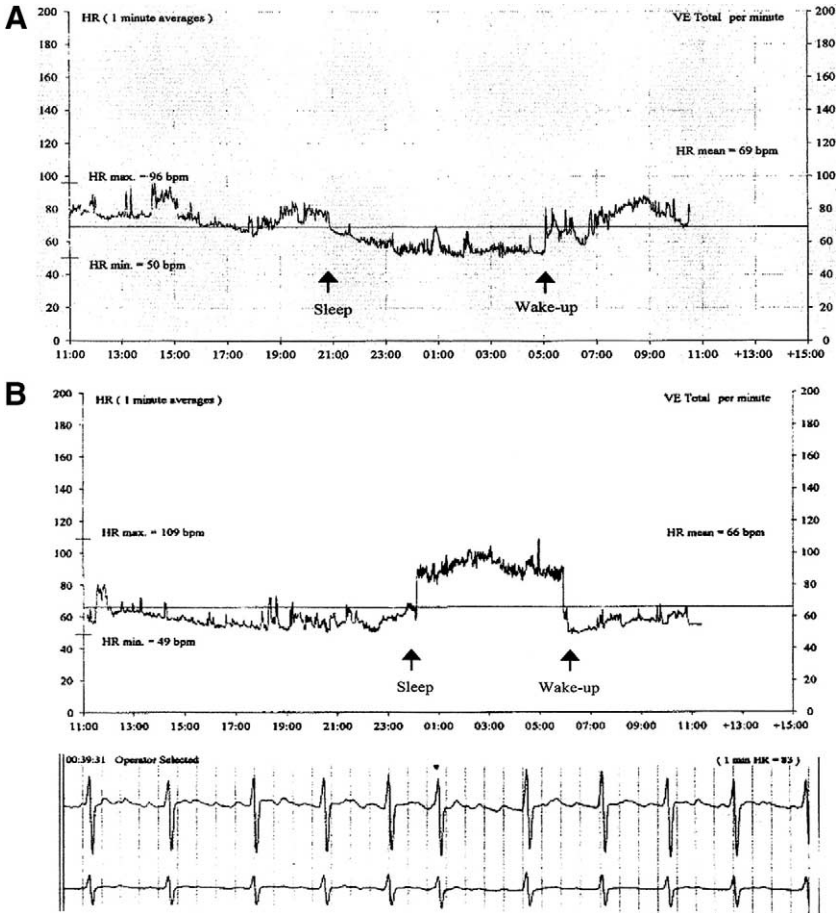
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**J. S. Alpert:** Another area of cardiovascular disease with a connection to sleep disorders relates to the diurnal pattern of onset of acute myocardial infarction. Muller at Harvard pointed out 20 years ago that acute myocardial infarction occurred more commonly in the early morning hours than at other time periods during the day. Although no firm explanation for this phenomenon has been proven, to me it seems that changes in sleep dynamics might be an important etiologic factor in these patients.

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***Cardiac arrhythmias and sudden death.*** Similar to vascular events, there is also diurnal variation in the occurrence of ventricular arrhythmias and sudden death, with a peak in the early morning hours after awakening.<sup>38-42</sup> Because ischemia is a potent stimulus for cardiac arrhythmias, these arrhythmic events may in fact be related to early morning ischemic episodes as discussed above. On the other hand, it is possible that surges in sympathetic activity may be pro-arrhythmic in their own right independent of ischemia, especially in the presence of an arrhythmogenic substrate.

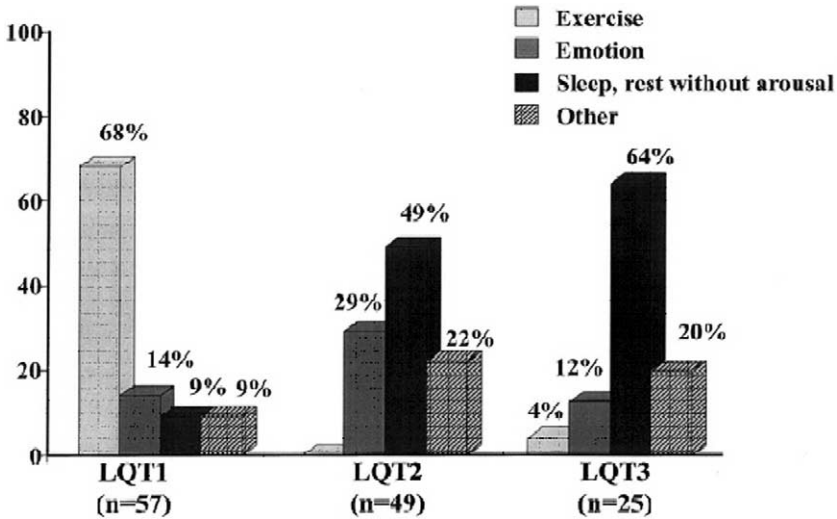
The importance of the autonomic nervous system in triggering cardiac arrhythmias is particularly evident with regard to arrhythmic events taking place during sleep. A classic example is the so-called vagal-induced atrial fibrillation, which resolves spontaneously after awakening (Fig 5).<sup>43</sup> Sleep may also be arrhythmogenic in some patients with mutations in the genes regulating cardiac ion channel function. The long QT syndrome is a familial arrhythmogenic disorder, characterized by prolonged ventricular repolarization on the 12-lead electrocardiogram. LQT1, LQT2, and LQT3 are the most common forms of the long QT syndrome caused by mutations in cardiac ion channel genes. These mutations are responsible for a reduced outward potassium current (LQT1 and LQT2) or for an increased inward sodium current (LQT3), resulting in a lengthened action potential duration and a consequent prolonged QT interval.<sup>44</sup> The long QT syndrome has been associated with nocturnal sudden cardiac death, although the incidence of events depends on the genotype. In LQT1 patients only 3% of events occur during rest/sleep, whereas in LQT2 and LQT3, the occurrence of nocturnal events has been found to be 29 and 39%, respectively.<sup>45</sup> Furthermore, 49 and 64% of lethal events occur during rest/sleep without arousal in LQT2 and LQT3, respectively (Fig 6). Thus, there appears to be a pathophysiological link between sleep and arrhythmic triggers in the long QT syndrome.



**FIG 5.** (A) Holter recording showing a normal circadian rhythm with a sleep-induced decrease in heart rate. (B) Sleep-induced atrial fibrillation (see the electrocardiogram (EKG) strip), followed by a decrease in heart rate upon awakening (due to conversion to sinus rhythm). (Reproduced with permission from Singh et al, 2004.<sup>43</sup>)

## Cardiovascular Consequences of Primary Sleep Disorders

As discussed in the previous section, normal (physiological) sleep exerts important influences on the cardiovascular system both in healthy individuals and in subjects with medical conditions that are not primarily related to sleep disorders. Here we will present evidence that primary disturbances of sleep physiology may be causally related to the development of cardiovascular disease in otherwise healthy persons. However, it



**FIG 6.** Lethal cardiac events according to classified triggers in three genotypes of the long QT syndrome. (Reproduced from Schwartz et al, 2001.<sup>45</sup>)

has to be emphasized that, in many studies of the effects of sleep and diurnal rhythm discussed earlier, the absence of any occult sleep disorder has not been confirmed by polysomnography or any other formal sleep evaluation, so that some contribution of occult sleep abnormalities to diurnal variation in cardiovascular characteristics cannot be excluded. Occult sleep disorders may also be confounding factors in the evaluation of the epidemiologic impact of sleep duration discussed below.

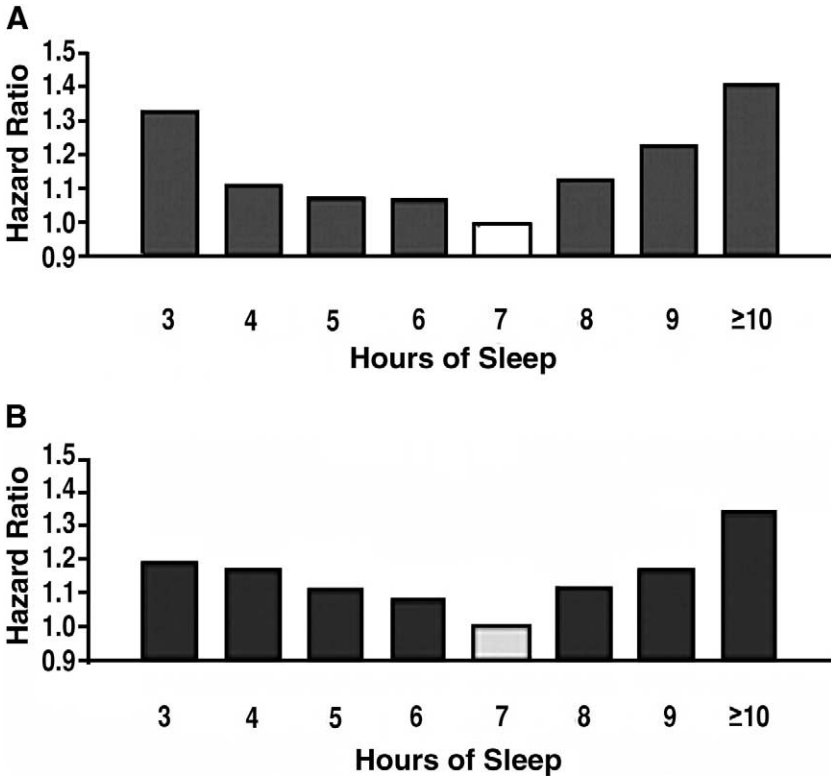
### *Sleep Duration and Cardiovascular Disease*

While a century ago people slept an average of 10 hours a night, the National Sleep Foundation's 2002 Sleep in America poll suggests that today Americans average only 6.9 hours of sleep on weeknights and 7.5 hours per night on weekends.<sup>46</sup> Only one-third of all adults get at least the recommended 8 hours of sleep or more and one-third of adults get fewer than 6.5 hours of sleep per night. Recent data indicate that this decrease in sleep duration (due to either cultural factors or voluntary sleep curtailment) is not a benign phenomenon. Instead, acute sleep deprivation and/or accumulated sleep debt has been linked to health problems, including metabolic and cardiovascular disease. For example, in the Nurses' Health Study of 71,617 female subjects without coronary heart disease at baseline and followed up for 10 years for the occurrence of

coronary events, short self-reported sleep duration was independently associated with an increased risk of events.<sup>47</sup> Sleep deprivation has also been shown to be an independent risk factor for diabetes<sup>48</sup> and has been associated with increased risk for hypertension.<sup>49-51</sup> In addition, short sleep duration is associated with increased mortality.<sup>52-55</sup>

Although the exact pathophysiological mechanisms underlying the association between sleep deprivation and cardiovascular disease have not been defined, several potential explanations can be proposed. First, sleep deprivation in rats causes a decrease in the activity of anti-oxidative enzymes accompanied by markers of cell injury.<sup>56</sup> Second, endothelin levels are elevated in sleep-deprived rats.<sup>57</sup> Third, sleep restriction to 4 hours for six consecutive nights in humans increases activity of the sympathetic nervous system in the heart (assessed using heart rate variability).<sup>58</sup> By contrast, one night of complete sleep deprivation raised blood pressure, decreased muscle sympathetic nerve activity, and did not change heart rate or plasma catecholamine levels.<sup>51,59</sup> This may suggest differential autonomic effects of acute versus chronic sleep deprivation, or a differential effect of sleep deprivation on cardiac versus vascular autonomic regulation. Fourth, it is possible that chronic sleep deprivation may contribute to impaired endothelium-dependent vasodilation.<sup>60</sup> Fifth, there is evidence that both acute and sustained sleep deprivation may activate inflammatory processes, leading to elevated C-reactive protein (CRP) concentrations, increased peripheral circulation of leukocytes, as well as elevated levels of interleukin-6 and TNF-alpha.<sup>61-65</sup> Finally, evidence has recently emerged that sleep deprivation may be independently associated with metabolic derangements and glucose intolerance.

Reduced amount of sleep is associated with overweight and obesity, and obese subjects show a near inverse linear relationship between weight and sleep time.<sup>66</sup> Several other reports on non-American populations also support the association between sleep duration and adiposity.<sup>67,68</sup> Although the exact mechanisms linking sleep deprivation to obesity remain to be established, preliminary data point to several neurohumoral consequences of sleep restriction, such as changes in sympathovagal balance, cortisol levels, thyrotropin concentration, growth hormone secretion patterns, or diurnal rhythms and plasma levels of leptin (which regulates appetite and energy expenditure).<sup>58,69,70</sup> Thus, it can be argued that sleep deprivation may be indirectly (through obesity) implicated as a risk factor for metabolic dysregulation. However, studies of acute sleep deprivation suggest a direct link between sleep curtailment and insulin resistance, which is independent of obesity per se. For example, healthy subjects limited to 4 hours of sleep for six consecutive nights demonstrated



**FIG 7.** Adjusted hazard ratios for death in 636,095 women (A) and 480,841 men (B) according to hours of sleep. The reference sleep duration with HAZARD = 1 is 7 hours. (Adapted from Kripke et al, 2002.<sup>54</sup>)

reduced glucose tolerance and a blunted insulin response to glucose.<sup>58</sup> Decreased insulin sensitivity is observed with different durations of sleep deprivation,<sup>71,72</sup> and also as a result of sustained sleep debt due to habitual sleeping less than 6 hours per day.<sup>67</sup> Thus, restricted sleep and glucose intolerance may be causally related and explain the epidemiologic association between sleep deprivation and cardiovascular disease.

An intriguing and consistently reported finding from several epidemiologic studies is the U-shaped relationship between sleep duration and mortality, such that both sleep deprivation and excessive sleep are associated with impaired survival (Fig 7).<sup>54,55,73</sup> This relationship suggests that there may be an optimum sleep duration of 7 to 8 hours per night. Whether greater mortality in association with increased sleep duration is primarily related to sleep extension or reflects some other abnormalities manifested as excessive sleepiness is not clear. Also,

further studies investigating the mechanisms of this association will have to make a distinction between extended sleep and prolonged stay in bed while not sleeping.

## *Shift Work*

Insufficient sleep is a common feature of shift work. On average, shift workers get less sleep during the week (6 hours and 30 minutes) compared to regular day workers (6 hours and 54 minutes).<sup>46</sup> Forty-nine percent of shift workers state that they sleep 6.5 hours or less, with many sleeping less than 5 hours per work day. Shift workers have excess risk of cardiovascular disease that is estimated at 40%.<sup>74</sup> For example, shift work increases risk of coronary artery disease<sup>75-77</sup> and hypertension.<sup>78,79</sup> Although many health consequences of shift work may be merely a result of sleep deprivation (as discussed in the previous section), it should be noted that, compared with habitual nightly sleep curtailment, shift work is also characterized by other features, such as changes in biological rhythms, cumulative circadian phase delay, variable photoperiod, napping, “paying back” sleep debt at daytime, etc. While the exact pathophysiology of shift work needs to be elucidated, several important cardiovascular consequences and associations of shift work should be noted.

Shift work may have unfavorable effects on autonomic balance, increasing cardiac sympathetic and decreasing parasympathetic activity.<sup>80,81</sup> However, others reported that night-time work was associated with reduced cardiac sympathetic modulation.<sup>82</sup> In addition, nightshift work may exert potentially detrimental effects on circadian blood pressure control, such that it is changed from a dipper to a nondipper pattern.<sup>78,79</sup> Decreased brachial artery endothelial function was found in shift workers and was independently related to the length of shift work history.<sup>83</sup> Cardiovascular effects of shift work may also be related to obesity, dyslipidemia, changes in lipid and glucose tolerance (all suggestive of the metabolic syndrome), as well as elevated homocysteine levels.<sup>84-88</sup> Finally, shift workers show increased frequency of ventricular extrasystoles, which correlate with the number of nights worked,<sup>89,90</sup> as well as QT<sub>c</sub> interval prolongation,<sup>91</sup> conceivably indicating a possible pro-arrhythmic potential of shift work.

## *Obstructive Sleep Apnea*

Obstructive sleep apnea (OSA) is another primary sleep disorder associated with cardiovascular disease.<sup>92,93</sup> Sleep deprivation is one of the cardinal features of OSA, but in contrast to sleep loss related merely to shift work or voluntary sleep curtailment, the pathophysiology of OSA

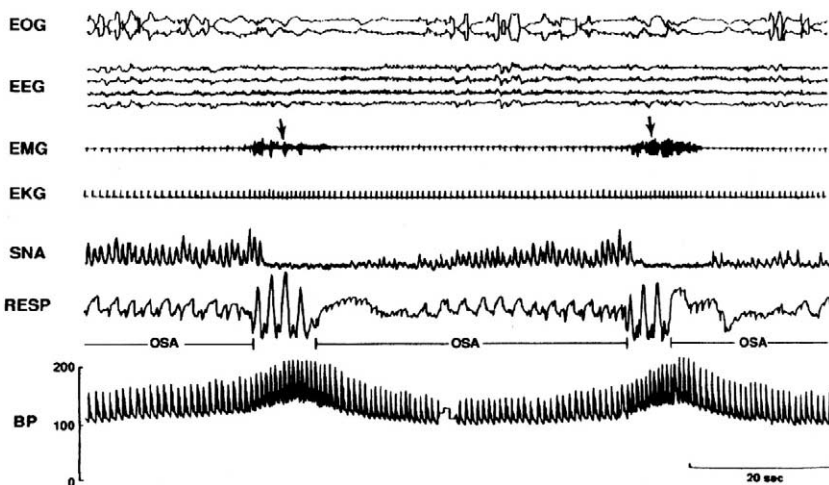
is more complex. Namely, OSA is characterized by recurrent episodes of cessation of respiratory airflow during sleep secondary to upper airway collapse on inspiration. As a result, frequent arousals and sleep fragmentation lead to sleep loss, but each OSA episode also causes significant hemodynamic and neuroendocrine effects, as well as profound decreases in oxygen saturation with consequent systemic hypoxemia (which may be as low as 40 to 50%). OSA is very common and affects 24 and 9% of middle-aged men and women, respectively.<sup>94</sup> In some populations at risk, the prevalence of OSA may even reach 50%. Because of its high prevalence, the potential clinical impact of OSA is of great importance.

**Acute effects of OSA.** The acute effects of OSA occur in association with each individual OSA episode during sleep. The main underlying mechanism of these effects is neurogenic. Cessation of airflow results in hypoxemia and hypercapnia, and consequently, leads to activation of the chemoreflex.<sup>95</sup> This in turn causes an increase in vascular sympathetic nerve activity as well as in circulating catecholamines, with an accompanying increase in peripheral vascular resistance. Vasoconstriction in the peripheral vasculature and increased cardiac output (due to changes in intrathoracic pressures upon termination of apnea) lead to dramatic surges in arterial blood pressure (Fig 8).<sup>95</sup> The acute hemodynamic effects of OSA are also evident in the cerebral circulation. Doppler measurements of cerebral blood flow suggest that individual obstructive apnea episodes are associated with blood flow reduction,<sup>96-98</sup> likely related to impairment of cerebral vascular autoregulation, as well as to the presence of negative intrathoracic pressure and increased intracranial pressure.

These autonomic and hemodynamic effects of OSA may explain the clinical observations that acute episodes of OSA may trigger cardiac nocturnal ischemia with ST-segment depression in subjects with or without a history of coronary artery disease.<sup>99-101</sup> They may also explain the relationship between OSA and stroke.<sup>102-105</sup> However, other factors may also contribute to these cardiovascular events, such as oxygen desaturation and a prothrombotic state.<sup>106</sup> OSA has been linked to platelet activation,<sup>107-109</sup> elevated fibrinogen levels,<sup>110,111</sup> increased whole blood viscosity, and decreased fibrinolytic activity.<sup>112</sup> Regardless of the exact mechanism involved, it has been suggested that untreated OSA may be associated with an increased risk of cardiovascular mortality,<sup>113,114</sup> thus arguing that it should be actively treated. OSA in stroke survivors has been proposed to be associated with increased mortality and a worse long-term functional outcome.<sup>103,104</sup>

Another acute autonomic effect of breathing cessation and hypoxemia is activation of the diving reflex, which leads simultaneously to peripheral





**FIG 8.** Recordings of the electrooculogram (EOG), electroencephalogram (EEG), electromyogram (EMG), electrocardiogram (EKG), muscle sympathetic nerve activity (SNA), respiration (RESP), and systemic blood pressure (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. Arrows indicate arousals from REM sleep. (Reproduced from Somers, et al, *J Clin Invest*, with permission via Copyright Clearance Center, copyright 1995 by Am Soc Clin Invest.<sup>95</sup>)

sympathetic vasoconstriction (except in the heart and the brain) and vagal activation to the heart. Therefore, in some patients with OSA, nocturnal apneas may be associated with severe bradyarrhythmias, including AV block and sinus arrest. The number of bradyarrhythmias seems to be greater in REM sleep.<sup>115,116</sup> Treatment of OSA may be curative in some patients primarily referred for pacemaker therapy with asymptomatic bradyarrhythmias during sleep,<sup>117</sup> so that persons with asymptomatic bradyarrhythmias at night should be investigated for the presence of OSA.

In addition, OSA may be a trigger for supraventricular and ventricular tachyarrhythmias. For instance, OSA is highly prevalent in patients undergoing electrical cardioversion of atrial fibrillation,<sup>118</sup> in patients with heart failure,<sup>119</sup> and after coronary artery bypass surgery.<sup>120</sup> Recurrence of atrial fibrillation after cardioversion is also greater in patients with untreated OSA.<sup>121</sup> Although the most likely mechanisms of this association are acute pro-arrhythmic effects of OSA (such as sympathetic activation, atrial stretch, acute hemodynamic stress, and hypoxia), it cannot be excluded that recurrent OSA episodes may exert more sustained, long-term effects on atrial electrical and structural remodeling,



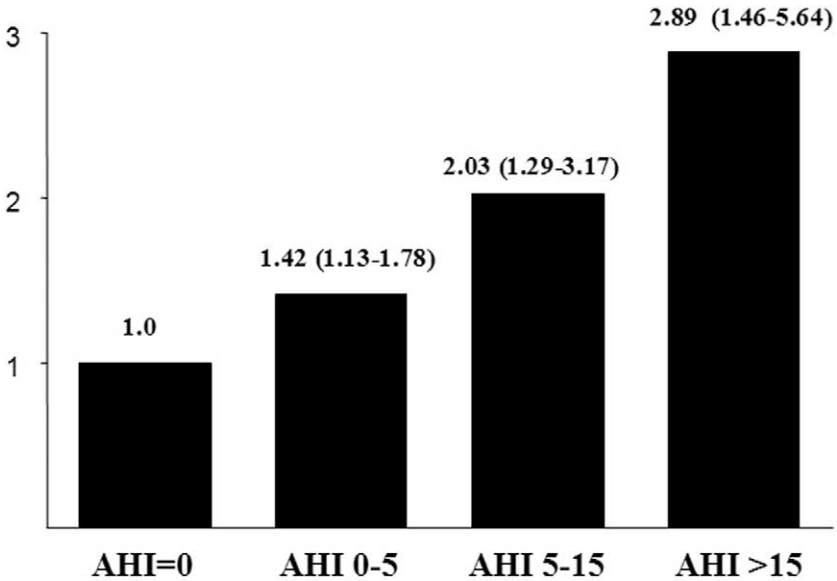
creating a favorable milieu for atrial fibrillation. Regarding ventricular tachyarrhythmias, there is also evidence to support the etiologic role of OSA.<sup>119,122,123</sup> The nighttime occurrence of these arrhythmias and their resolution after treating sleep apnea suggests a causal association.

Finally, recent studies suggest that persons with OSA have a significant alteration in an established day/night pattern of sudden cardiac death. Specifically, OSA increases risk of sudden cardiac death during the sleeping hours (with a relative risk of 2.57), which is in marked contrast to the low occurrence of sudden cardiac death during this time in persons without OSA and in the general population.<sup>124</sup> Furthermore, the severity of OSA correlated directly with the risk of nocturnal sudden cardiac death.<sup>124</sup> While these observations suggest that OSA changes the timing of sudden cardiac death, and that the acute effects of OSA on cardiac ischemia and arrhythmias may in fact have significant clinical consequences, whether OSA actually increases the overall risk of sudden cardiac death is not yet known.

***Chronic effects of OSA.*** OSA exerts chronic neurohumoral and metabolic effects that may directly or indirectly affect cardiovascular disease. However, while the possibility of OSA as a causal mechanism in chronic cardiovascular disease is very attractive, this relationship remains largely unproven.

There is emerging evidence that OSA may be conducive to obesity and, in particular, to deposition of visceral fat (ie, android obesity). Patients with newly diagnosed OSA have difficulty losing weight and are predisposed to excessive weight gain.<sup>125,126</sup> One possible mechanism of this effect of OSA is leptin resistance.<sup>125,127</sup> In addition, treatment of OSA may decrease visceral fat accumulation,<sup>127</sup> suggesting that OSA has an independent effect on body fat distribution. Thus, OSA may conceivably increase cardiovascular risk indirectly by leading to obesity-induced metabolic abnormalities, such as the metabolic syndrome and insulin resistance. However, recent studies favor a direct association between OSA and insulin resistance, which is independent of obesity and other anthropometric measures, and is seen in both obese and nonobese subjects.<sup>79,128-131</sup> Therefore, one of the chronic effects of OSA may be glucose intolerance, which may conceivably lead to overt diabetes.<sup>132</sup>

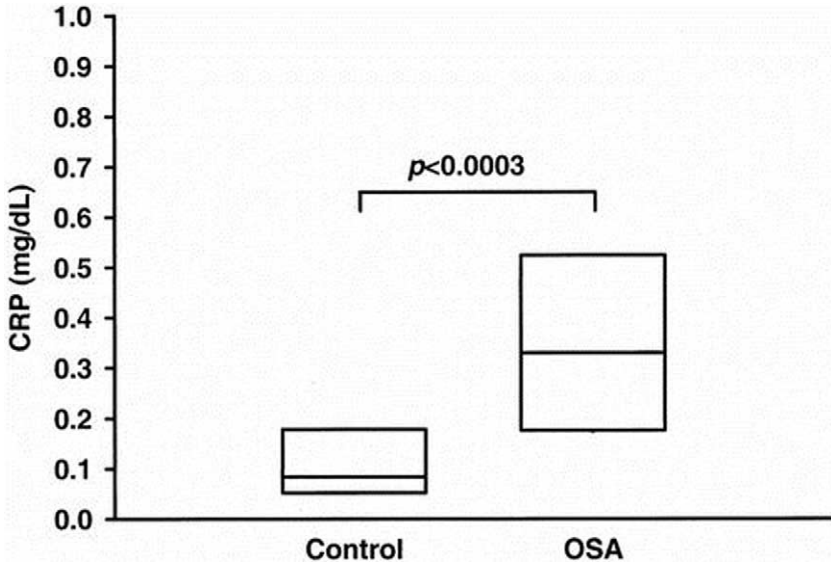
There is also compelling evidence linking OSA to chronic arterial hypertension. This evidence is based not only on cross-sectional observations of a high prevalence of hypertension in patients with OSA and a high incidence of OSA in hypertensive patients (especially the “nondippers”), but also on large epidemiological and prospective studies.<sup>133-136</sup> For instance, the Wisconsin Sleep Cohort Study showed a dose–response



**FIG 9.** Odds ratios (vertical axis) for the presence of incident hypertension at 4-year follow-up according to the apnea-hypopnea index (AHI) at baseline. The odds ratios are adjusted for baseline hypertension status, age, gender, body habitus (body mass index, waist and neck circumference), alcohol consumption, and cigarette use. Data are shown as odds ratio (lower and upper 95% confidence interval). *P* for trend = 0.002. (Data from Peppard et al, 2000<sup>133</sup> and figure reproduced from Wolk et al, 2003.<sup>92</sup>)

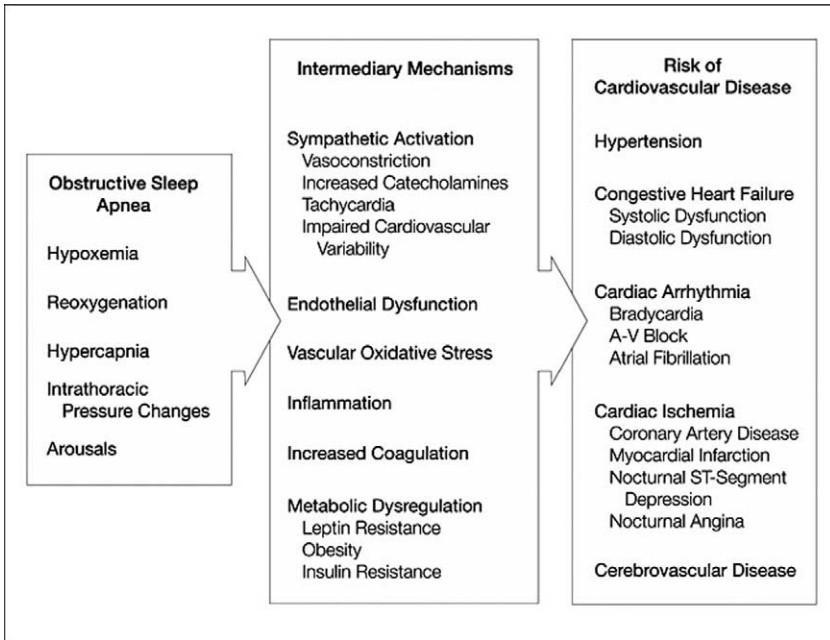
association between sleep-disordered breathing at baseline and the presence of hypertension 4 years later that was independent of other known risk factors (Fig 9).<sup>133</sup> The pathophysiological mechanisms leading to chronic hypertension as a result of OSA are likely complex. A prominent role is undoubtedly played by enhanced sympathetic activity, as evidenced by elevated circulating catecholamine levels and increased sympathetic nerve activity.<sup>95,137-140</sup> This daytime increase in sympathetic activity may be a carryover effect from the nocturnal events, but it may also be related to chemoreceptor resetting and tonic “normoxic” chemoreceptor activation.<sup>141-143</sup> Other potential contributing mechanisms include impaired baroreflex,<sup>140</sup> endothelial dysfunction,<sup>144</sup> increased endothelin,<sup>145,146</sup> and decreased nitric oxide,<sup>147,148</sup> all of which have been described in OSA. OSA should therefore always be considered in the differential diagnosis of secondary hypertension,<sup>149</sup> especially hypertension that is refractory to treatment.

In addition to obesity and hypertension, OSA may be conducive to atherosclerosis. Not only is the prevalence of OSA elevated in patients



**FIG 10.** Plasma C-reactive protein (CRP) levels in OSA patients and in control subjects without OSA. Middle horizontal line inside box indicates median. Bottom and top of the box are 25th and 75th percentiles, respectively. (Reproduced from Shamsuzzaman et al, 2002.<sup>157</sup>)

with coronary artery disease, but patients with OSA may also have an increased prevalence of markers of systemic atherosclerosis, such as calcified carotid artery, atheroma and increased carotid wall thickness.<sup>150,151</sup> Furthermore, OSA may be a predictor of coronary artery disease both in cross-sectional and in prospective studies.<sup>120,136,152-155</sup> This association is independent of age, gender, race, body mass index, hypertension, smoking habits, lipid levels, and diabetes, indicating that OSA may be causally and directly related to atherogenesis in humans. There are probably multiple mechanisms increasing the risk of atherosclerosis in OSA, including oxidative stress,<sup>156</sup> sympathetic activation, and endothelial dysfunction, which were mentioned earlier. Of particular interest is the association between OSA and inflammation. Inflammatory processes play a pivotal role in the initiation and progression of atherogenic processes. Some inflammatory mediators, such as C-reactive protein, are in fact directly involved in endothelial damage and atherogenesis. Recent data suggest that OSA induces an inflammatory state and is accompanied by elevation of C-reactive protein (Fig 10),<sup>157,158</sup> serum amyloid A,<sup>159</sup> and various adhesion molecules, as well as increased expression of adhesion molecules on leukocytes and their enhanced



**FIG 11.** Intermediary mechanisms associated with OSA that potentially contribute to increased risk of cardiovascular disease. (Reproduced from Shamsuzzaman et al, 2003.<sup>93</sup>)

adherence to endothelial cells.<sup>160-162</sup> Thus, systemic inflammation may in part explain the epidemiologic association between OSA and the development of atherosclerosis.

Several other chronic effects and associations of OSA have been proposed. Some epidemiologic data suggest that OSA is independently associated with increased odds for heart failure,<sup>155</sup> and a negative relationship between OSA severity and left ventricular ejection fraction has been reported.<sup>163</sup> Associations between OSA and daytime pulmonary hypertension,<sup>164-166</sup> as well as venous thromboembolism,<sup>167</sup> have also been suggested. Many of these findings are still controversial, such that their etiology, pathophysiology, and clinical significance will have to be confirmed in future studies. OSA-related abnormalities that may serve as intermediary mechanisms contributing to cardiovascular disease are shown in Fig 11.

## Secondary Sleep Disorders in the Course of Other Medical Conditions—Cardiovascular Implications

In addition to disordered sleep being a possible factor in the development of cardiovascular disease in otherwise healthy individuals, sleep

disorders may also appear in association with or as a result of other medical conditions and may therefore have cardiovascular consequences which are part of the clinical phenotype of those conditions. Some of such examples will be discussed below. Considering the huge cardiovascular impact of sleep, other common medical conditions associated with cardiovascular morbidity should also be investigated for the presence of any sleep disorders.

## *Obesity*

As discussed earlier, both sleep deprivation and OSA may lead to increased adiposity and obesity. However, obesity may also affect sleep in its own right and is in fact the primary risk factor for OSA. A 10% weight gain is associated with a sixfold increase in the odds of developing OSA<sup>168</sup> and every 6 kg/m<sup>2</sup> increment in body mass index increases OSA risk more than fourfold.<sup>169</sup> Conversely, weight loss leads to a decrease in OSA severity.<sup>168,170</sup> The frequent coexistence of obesity and OSA (such that significant OSA is present in ~40% of obese individuals) suggests that sleep-disordered breathing should be considered as part of the pathophysiology and clinical presentation of obesity. As such, OSA may lead to several cardiovascular abnormalities of obesity and may perhaps even explain some cardiovascular pathologies traditionally ascribed to obesity alone.

## *Chronic Heart Failure and Central Sleep Apnea*

Although OSA may also occur in the course of chronic heart failure (CHF), the primary sleep disorder that accompanies CHF is central sleep apnea (CSA). CSA is due to diminution or cessation of respiratory movements as a result of decreased central respiratory drive. The consequences of CSA include sleep fragmentation and sleep loss, repetitive decreases in oxygen saturation, and systemic neuroendocrine effects.

In some populations the prevalence of CSA in CHF may be as high as 70%.<sup>119,171-173</sup> CSA is also prevalent in patients with asymptomatic LV dysfunction<sup>174</sup> and it is also seen in diastolic CHF.<sup>175</sup> Characteristic of CHF-induced CSA is periodic breathing (alternating periods of hyper- and hypoventilation or hyperventilation and apnea, known as Cheyne–Stokes respiration). Although the exact mechanisms whereby CHF causes CSA are complex and still not fully understood, the principal abnormality seems to be instability of the closed-loop chemical ventilatory control system, triggered by hypocapnia, enhanced chemoreceptor sensitivity, increased lung-to-chemoreceptor circulatory delay, and probably also

increased pulmonary pressures. These abnormalities increase as CHF worsens, so that CSA can be sometimes considered as an index of CHF severity. Indeed, those CHF patients with CSA constitute a clinically distinct CHF population, characterized by lower exercise capacity and ejection fraction, increased left ventricular volumes and filling pressures, as well as a higher prevalence of cardiac arrhythmias.

However, it also appears that, once present, CSA likely contributes to CHF severity and progression. Cheyne–Stokes respiration in CHF patients has been shown to be associated with higher urinary and plasma norepinephrine levels as well as an increase in sympathetic nerve activity.<sup>176,177</sup> Plasma endothelin levels are also higher in CHF patients with CSA.<sup>162</sup> These neuroendocrine effects, together with repetitive hypoxia and oscillations in blood pressure and heart rate, may conceivably lead to further progression of cardiovascular damage. In fact several cardiovascular consequences of sleep deprivation and OSA described earlier should also be expected in CSA. Consistent with the notion that CSA contributes to CHF pathophysiology is the observation that the presence of CSA increases mortality risk in CHF.<sup>171,178,179</sup> Several studies have also suggested that treatment of CSA with continuous positive airway pressure may improve neuroendocrine profiles, may increase ejection fraction, and may be associated with a relative risk reduction in the mortality-cardiac transplantation rate.<sup>177,180</sup> However, more recent preliminary data from the CANPAP trial have revealed no survival benefit of treating CSA in CHF patients,<sup>197</sup> contradicting the positive results of the smaller earlier studies.

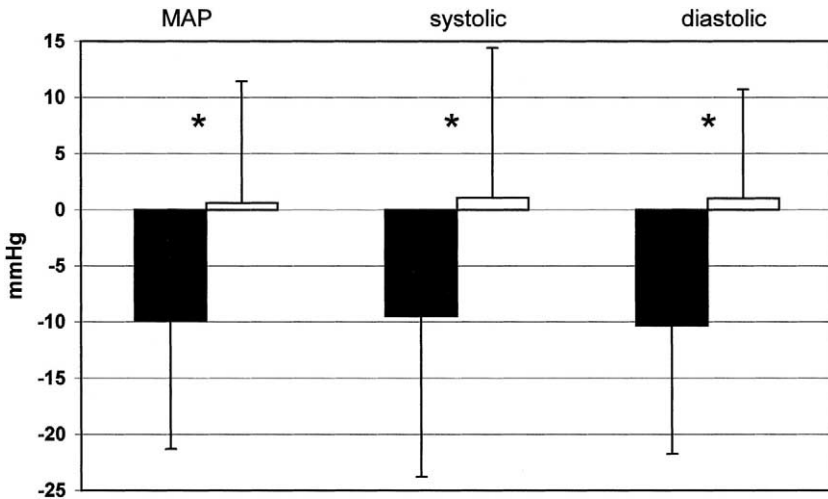
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**J. S. Alpert:** One could imagine a vicious cycle in patients with left ventricular dysfunction. This cycle would involve the interaction of left ventricular functional abnormalities, intermittent obstructive sleep apnea with hypertensive episodes and hypoxemia, as well as a propensity for arrhythmogenesis. Combating this unpleasant combination would present a significant challenge for the clinician.

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## *Menopause*

Menopause may also be a risk factor for sleep disorders. Marked differences in the prevalence of OSA are seen between pre- and postmenopausal women, with much greater apnea prevalence and severity in the latter.<sup>181,182</sup> This association is independent of other coexisting risk factors, including body mass. The inverse relationship between hormone replacement therapy and sleep-disordered breathing also supports a causal



**FIG 12.** Changes in mean (MAP), systolic, and diastolic arterial pressures with effective (closed bars) and subtherapeutic (open bars) CPAP in patients with OSA (\* indicates  $P < 0.05$ ). (Reproduced from Becker et al, 2003.<sup>187</sup>)

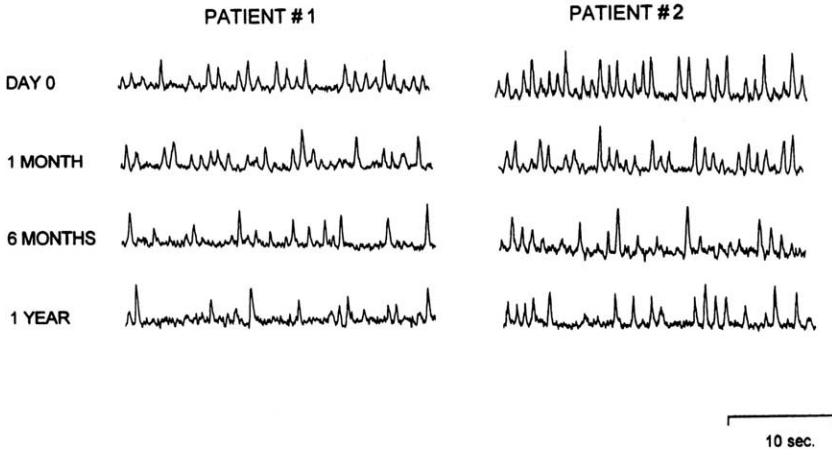
association.<sup>183</sup> Since the incidence of central obesity, metabolic syndrome, and cardiovascular disease also increases dramatically after the onset of menopause, part of this increased cardiovascular risk may conceivably be ascribed to sleep disordered breathing.

## Effects of Treatment of Sleep Disorders on Cardiovascular Disease

In the previous sections we discussed the evidence that sleep disorders may possibly have important cardiovascular consequences and lead to cardiovascular disease. An important question, therefore, is whether treatment of sleep disorders can prevent, cure, or at least halt the progression of sleep-related cardiovascular disease. The answer is probably a qualified and conditional yes, although the available data are still preliminary, sometimes contradictory, and limited primarily to sleep-disordered breathing.

Effective treatment of OSA with continuous positive airway pressure (CPAP) reduces arterial blood pressure in patients with hypertension (Fig 12).<sup>184-187</sup> This therapy likely targets specific pathophysiological mechanisms involved in OSA-induced hypertension, as evidenced by the observation that CPAP therapy also decreases elevated nighttime and daytime sympathetic drive, which is a hallmark of OSA (Fig 13).<sup>95,141</sup> In

## TREATED OSA



**FIG 13.** Sympathetic neurograms in two OSA patients treated with CPAP, obtained at baseline (day 0) and after 1 month, 6 months, and 1 year of treatment. (Reproduced from Narkiewicz et al, 1999.<sup>141</sup>)

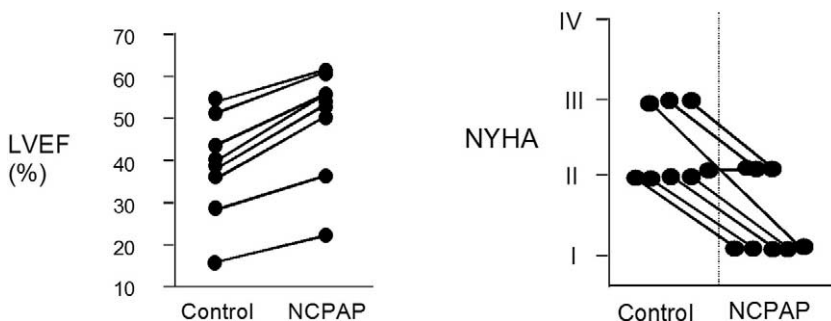
addition to systemic hemodynamics, CPAP also reverses hemodynamic changes in the cerebral circulation<sup>151</sup> and may reduce pulmonary pressures, both in pulmonary hypertensive and normotensive OSA patients.<sup>166,188</sup>

Regarding coronary artery disease, CPAP treatment has been shown to reduce ST-segment depression.<sup>99</sup> Whether this therapy exerts any chronic effects on progression of atherosclerosis and incidence of coronary events is not known, although such beneficial effects could be expected based on the observations that CPAP decreases C-reactive protein levels,<sup>158</sup> decreases plasma levels and expression of adhesion molecules and production of reactive oxygen species,<sup>160,161</sup> decreases platelet aggregability,<sup>108,109</sup> and prevents the early morning increase in fibrinogen levels.<sup>110</sup>

Chronic therapy of OSA with CPAP may also bring about beneficial metabolic effects. Specifically, CPAP may decrease visceral fat accumulation,<sup>127</sup> improve insulin sensitivity,<sup>189,190</sup> and lower serum leptin levels.<sup>127</sup>

Finally, CPAP may improve cardiac electrical and mechanical function. With regard to electrical function, CPAP prevents OSA-associated bradyarrhythmias,<sup>115,117</sup> decreases recurrence of atrial fibrillation after cardioversion,<sup>121</sup> and abolishes ventricular arrhythmias.<sup>122,191</sup> In addi-





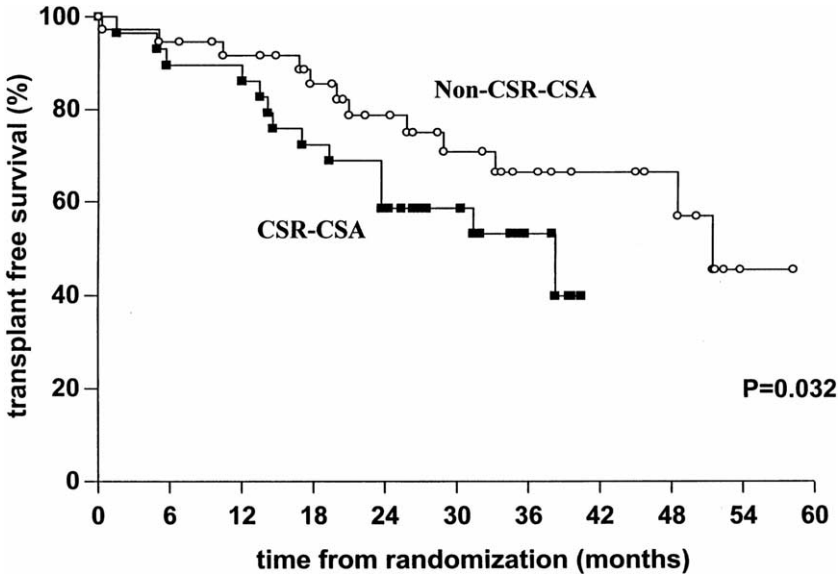
**FIG 14.** Effects of CPAP on left ventricular ejection fraction (LVEF) and functional class (New York Heart Association) in patients with CHF and OSA. (Reproduced from Malone et al, 1991.<sup>163</sup>)

tion, a marked improvement in left ventricular ejection fraction and functional class in patients with CHF has been noted after treatment of OSA with CPAP (Fig 14).<sup>163,192</sup>

All of these data suggest that treating OSA may have the potential to exert favorable acute and chronic effects on cardiovascular disease, although unequivocal data showing long-term benefits with regard to cardiovascular endpoints remain to be obtained. The treatment of choice in OSA is CPAP. Occasionally, surgical intervention (such as tracheostomy) may be indicated in life-threatening OSA.

CPAP is also efficacious in treating CSA in CHF patients, which may be due to some direct hemodynamic effects of CPAP or may be related to a decrease in the obstructive component accompanying CSA. However, although CPAP may reduce the severity of CSA and although earlier studies suggested that long-term transplant-free survival would be improved significantly in CSA heart failure patients treated with CPAP (Fig 15),<sup>180</sup> these initial data from smaller studies have not been borne out by the more recent larger multicenter CANPAP study, which showed no evidence of improved cardiac morbidity or mortality in CPAP-treated heart failure patients with CSA.<sup>8</sup> Theophylline and nocturnal oxygen supplementation also decrease CSA severity. The presence of CSA often indicates decompensated CHF, which requires optimization of specific pharmacological therapy of CHF. Novel, currently emerging therapeutic approaches include cardiac resynchronization therapy<sup>193</sup> and overdrive atrial pacing,<sup>194</sup> which may decrease CSA in selected patients with symptomatic sinus bradycardia. However, the initial excitement over atrial overdrive pacing in treating OSA and CSA has diminished as subsequent studies have been unable to show similar results.<sup>195,196</sup>

The need for behavioral and lifestyle modifications should be empha-



**FIG 15.** Transplant-free survival in CHF patients with CSA treated and not treated with CPAP. (Reproduced from Sin et al, 2000.<sup>180</sup>) However, the recent large multicenter CANPAP study has shown no evidence of survival benefit from CPAP treatment of CSA in OSA.<sup>197</sup>

sized. For example, measures leading to weight loss should be implemented in all overweight subjects with sleep-disordered breathing. In the absence of any specific pharmacologic treatments, changes in lifestyle may be particularly important in shift workers and those with sleep debt related to voluntary sleep curtailment (as a result of work or social pressures). Whether improvements in the amount and quality of sleep may have any impact on cardiovascular morbidity at a population scale remains to be established.

The associations between sleep and cardiovascular disease may also have important implications for cardiovascular chronotherapeutics. Understanding the influences of circadian rhythms, physiological sleep, and sleep disorders on cardiovascular physiology and pathophysiology may influence the clinical management of hypertension, coronary artery disease, heart failure, cardiac arrhythmias, and other cardiovascular conditions.

## Conclusions

There are many important pathophysiological interactions between sleep and the cardiovascular system. The development of cardiovascular

disease and cardiac events may be influenced both by physiological sleep as well as by sleep disorders, including sleep deprivation. Treating sleep disorders may conceivably have a major impact on improvement of cardiovascular morbidity in the population. This, however, remains unproven. Nevertheless, given current knowledge, an inquiry about sleep habits should be part of every clinical evaluation of patients with cardiovascular disease. This is particularly true for subjects with risk factors for sleep disorders (such as obesity, male gender, daytime somnolence, a history of witnessed apneas during sleep, shift work) and those in whom cardiac events have a distinct diurnal pattern or in whom clinical management is unsatisfactory despite optimal therapy. The diagnosis and treatment of sleep disorders is important even in the absence of any clinically overt cardiovascular diseases, since sleep abnormalities might be conducive to the future development of cardiovascular dysfunction.

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**J. S. Alpert:** Wolk and colleagues have presented an outstanding monograph reviewing an area that is traditionally assigned to the pulmonary specialist. However, recent work that is extensively cited in this monograph demonstrates that sleep disorders produce extensive autonomic dysfunction with major effects on the heart and the peripheral vasculature. As our understanding of these disorders increases, interventions aimed at stabilization of the autonomic nervous system and relief of sleep disorders may become common in various clinical cardiology settings.

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