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Review

Sleep, dreams, and sudden death: the case for sleep as an autonomic stress test for the heart

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"To sleep, perchance to dream. Ay, there's the rub" — Hamlet I,3

1. Introduction

The tranquility of slow wave sleep is abruptly disrupted several times a night by major changes in brain physiology that cause rapid eye movement (REM) sleep and dreaming. This is Hamlet's "rub," when the dreaded psychologic tumult is played out. In patients with cardiovascular disease, dire consequences may be precipitated by the intense alterations in autonomic activity which accompany dreaming.

Sudden cardiac death, defined as unexpected death within 1 h of onset of symptoms, occurs during the nocturnal period at an annual rate of 36000 in the United States. This amounts to nearly 80% of the number of fatalities due to automobile accidents or 40% more than deaths due to HIV infection. Since only 12% of all cardiovascular deaths occur at night [1], and middle-aged adults spend approximately 25% of time asleep, it would appear at first glance that sleep is a time of relative protection against cardiovascular death. However, if one assumes that heightened susceptibility to sudden death coincides with periods of increased ischemia and arrhythmias, then cardiac mortality is likely to be concentrated during the 90 min of REM. Thus, the relative risk for sudden death during REM sleep may be as high as 1.2 times that of wakefulness. Finally, the impact of sleep may be underestimated by these statistics, since the final early morning bout of intensely phasic REM sleep could initiate coronary plaque disruption, with death delayed until wakefulness.

Clinical reports have provided evidence that REM sleep and dreams play an even greater role in precipitating myocardial infarction and sudden death in patients already afflicted with coronary disease, myocardial infarction, or heart failure, in patients with respiratory disorders ranging from snoring to central and obstructive sleep apnea, in patients with the pause-dependent long QT syndrome or at risk for sudden infant death, and in Southeast Asians who experience "sudden unexpected death." While nocturnal death can be viewed as a benign mode of exit, it is often premature, as it can occur in infants, adolescents, and adults with ischemic heart disease, for whom the median age is 59 years.

This review has two main goals. The first is to discuss the physiologic and pathophysiologic mechanisms responsible for sleep-related sudden cardiac death. The second is to introduce the concept that the profound surges in autonomic activity during sleep may constitute a diagnostic stress test capable of disclosing undocumented cardiac electrical instability. This concept is not new, as it was explicitly proposed in the early 1920s by MacWilliam [2] that dreams constitute a period of increased risk for cardiovascular mortality and morbidity because of heightened sympathetic activity. The renowned clinicians Samuel Levine [3] and Paul Dudley White [4] also stressed the importance of sleep in the genesis of angina and infarction. In the 1960s and 1970s, Zanchetti, Mancia, and their colleagues [5], pioneers in the field of cardiovascular regulation during sleep, amassed considerable experimental and

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clinical data underscoring the significant impact of REM and slow wave sleep on the cardiovascular system. However, practical exploitation of the concept is only now being made possible by the development of noninvasive, portable technology for home-based monitoring of sleep state [6,7], autonomic function [8], and vulnerability to arrhythmias [9].

2. Central nervous system sites influencing cardiac electrical stability

Because sleep ultimately exerts its influence on cardiac vulnerability through alterations in activity of the central (CNS) and peripheral autonomic nervous systems, it is worthwhile to summarize the state of our knowledge with respect to neural control of cardiac electrophysiologic and coronary hemodynamic function. Two major concepts have surfaced from extensive investigation of CNS-induced cardiac arrhythmias. The first is that triggering of arrhythmias by the central nervous system is not only the consequence of intense activation of the autonomic nervous system but is also a function of the specific neural pattern elicited. Thus, the balance in cardiac input from either limb of the autonomic nervous system and their interaction must be considered [10–14].

The second pivotal concept is that triggering of arrhythmias by central nervous system activity may also depend on several intermediary mechanisms. These include direct effects of neurotransmitters on the myocardium and its specialized conducting system and changes in myocardial perfusion due to alterations in coronary vasomotor tone and/or enhanced platelet aggregability. The net influence on the heart thus depends upon a complex interplay between the specific neural pattern elicited and the underlying cardiac pathology (Fig. 1).

Over 80 years ago Levy demonstrated that ventricular tachyarrhythmias can be elicited in normal animals by stimulating specific areas in the brain [15]. This finding was subsequently confirmed in several species. Hockman and colleagues, using stereotaxic techniques, demonstrated that cerebral stimulation and hypothalamic activation evoked a spectrum of ventricular arrhythmias [16]. The posterior hypothalamus is an important locus of centrally induced arrhythmias. Stimulation of this structure increased ten-fold the incidence of ventricular fibrillation elicited experimentally by occlusion of the coronary artery [17]. This enhanced vulnerability was linked to increased sympathetic activity, because beta-adrenergic receptor blockade but not vagotomy prevented it [18]. These findings are consistent with clinical reports that cerebral vascular disease, and particularly intracranial hemorrhage, can elicit significant cardiac repolarization abnormalities and life-threatening arrhythmias [19,20].

Arrhythmias also ensued immediately upon cessation of diencephalic or hypothalamic stimulation, but these required intact vagi and stellate ganglia [21,22]. The likely electrophysiologic basis for such post-CNS stimulation arrhythmias is the loss of rate-overdrive suppression of ectopic activity. This occurs when the vagus regains its activity following cessation of centrally induced adrenergic stimulation. Accordingly, the enhanced automaticity induced by adrenergic stimulation of ventricular pacemakers is exposed when vagal tone is restored and slows the sinus rate, as Manning and Cotten proposed in their original article [21]. Whereas these arrhythmias may be dramatic in appearance, as they include ventricular tachycardias, they rarely degenerate into ventricular fibrillation [23]. Their occurrence, however, is the basis for the widely held view that dual autonomic activation is highly conducive to arrhythmias, but this proarrhythmic effect has been erroneously interpreted as profibrillatory [24].

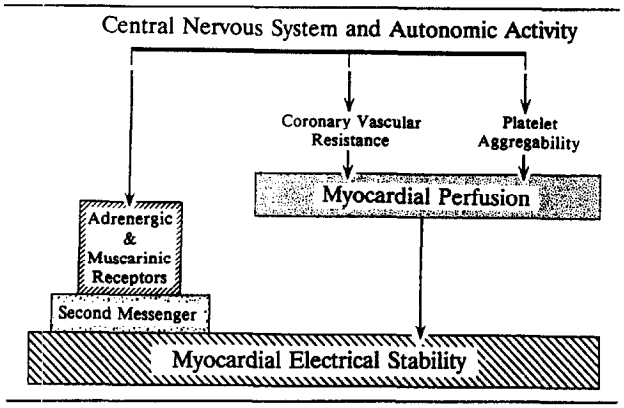

Fig. 1. The interaction between neural triggers and cardiovascular substrate during CNS-induced autonomic activation. As will be discussed in detail, stimulation of $beta_1$-adrenergic receptors can decrease electrical stability directly as a result of changes in second messenger formation and alterations in ion fluxes. This deleterious influence is opposed by muscarinic receptor stimulation, which inhibits presynaptically the release of norepinephrine and opposes its action at the receptor level. Catecholamines may also alter myocardial perfusion by complex means, including alpha-receptor stimulation of coronary vessels and platelets and by impairing diastolic perfusion time due to adrenergically mediated sinus tachycardia. (Reprinted with permission from the Kluwer Academic Publishers from [262].)

Skinner and Reed have provided insights into the central nervous system pathways involved in behaviorally induced arrhythmias [25]. Cryogenic blockade of the thalamic gating mechanism or its output from the frontal cortex to the brainstem delayed or prevented the occurrence of ventricular fibrillation during stress in pigs. Carpeggiani, Skinner and colleagues more recently showed that cryogenic blockade of the amygdala is also capable of preventing stress-induced ventricular fibrillation [26]. Thus, these distinct pathways within the central nervous system appear to play a critical role in mediating arrhythmogenesis due to intense behavioral arousal. Central nervous system regulation of cardiovascular function has been reviewed in depth by Smith and DeVito [27], Gutterman and colleagues [28], Jordan [29], Cechetto and Saper [30], LeDoux [31], and Skinner [24,32].

3. Role of the peripheral autonomic nervous system

3.1. Sympathetic influences

The sympathetic nervous system has been extensively implicated in the genesis of life-threatening arrhythmias both in animals and humans. It has been demonstrated in the experimental laboratory that activation of the sympathetic nervous system by stimulation of central [15–18,21,22] and peripheral adrenergic structures [33,34], infusion of catecholamines [35], or imposition of behavioral stress [10,36–41] can increase cardiac vulnerability in the normal and ischemic heart. These profibrillatory influences are substantially blunted by beta-adrenergic receptor blockade [42]. A wide variety of supraventricular arrhythmias can also be induced by autonomic activation [23,43].

Experimentally, we have found that a striking surge in sympathetic activity occurs within minutes of left anterior descending coronary artery occlusion. This phenomenon has been documented by both direct nerve recording measurements [44] and more recently by complex demodulation of heart rate variability [45]. The enhancement in sympathetic activity is associated with a marked increase in susceptibility to ventricular fibrillation as evidenced by the spontaneous occurrence of the arrhythmia [46], a reduction in ventricular fibrillation threshold [44], and increased T-wave alternans magnitude [46–49]. Upon reperfusion, a second peak in vulnerability occurs, probably due to liberation of ischemic byproducts from the myocardium [44,50,51]. Stellectomy blunts the surge in vulnerability to ventricular fibrillation during occlusion but enhances its magnitude during reperfusion. These observations are in agreement with the findings that adrenergic factors are pivotal during ischemia [52], and that stellectomy enhances reactive hyperemia during reperfusion [44]. The net effect is a greater release of profibrillatory ischemic byproducts.

Enhanced sympathetic activity increases cardiac vulnerability in the normal and ischemic heart by complex mechanisms. The major indirect effects include impaired oxygen supply–demand ratio due to increased cardiac metabolic activity and coronary vasoconstriction, particularly in vessels with injured endothelium and in the context of altered preload and afterload [53]. The direct profibrillatory effects on cardiac electrophysiologic function are attributable to derangements in impulse formation, conduction, or both [13,23]. Increased levels of catecholamines activate beta-adrenergic receptors which in turn alter adenylate cyclase activity and intracellular calcium flux. These actions are probably mediated by the cyclic nucleotide and protein kinase regulatory cascade, which can alter spatial heterogeneity of calcium transients and consequently increase dispersion of repolarization. The net influence is an increase in susceptibility to ventricular fibrillation [54–56]. Conversely, reduction of cardiac sympathetic drive by stellectomy has proved to be antifibrillatory. The extensive influences of the sympathetic nervous system on cardiac electrophysiologic properties are summarized in Tables 1 and 2.

Table 1
Direct cardiac electrophysiologic effects of sympathetic nervous system stimulation

- Shifts pacemaker from sinus node to junctional region
- Alters P-wave morphology
- Abbreviates P-R interval
- Increases Purkinje fiber automaticity
- Increases early afterdepolarizations
- Prolongs QT interval on body surface
- Increases TQ depression and enhances reentry during acute myocardial ischemia
- Decreases ventricular fibrillation threshold
- Induces T-wave alternans in the long QT syndrome and during acute myocardial ischemia

Reprinted with permission from reference [42].

The protective influence of beta-adrenergic receptor blockade may result in part from blockade of central beta-adrenergic receptors [57–59]. Parker and coworkers [59] have shown that intracerebroventricular administration of subsystemic doses of l-propranolol but not d-propranolol significantly reduced the incidence of ventricular fibrillation during combined left anterior descending coronary artery occlusion and behavioral stress in the pig. Surprisingly, intravenous administration of even a relatively high dose of l-propranolol was ineffectual. The latter result may relate in part to a species dependence, since, unlike canines, pigs do not show a suppression of ischemia-induced arrhythmias in response to beta-blockade [60]. Parker and coworkers proposed that the centrally mediated protective effect of beta-blockade is due to a decrease in sympathetic nervous system activity and in plasma norepinephrine concentration [59,61,62]. Importantly, whereas central actions of beta-adrenergic receptor blockers may play an important role in reducing susceptibility to ventricular fibrillation during acute myocardial ischemia, they are unlikely to constitute the sole mechanism. This conclusion derives from the fact that beta-blockers prevent the profibrillatory

Table 2
Protective effect of stellectomy against sudden cardiac death

Animal studies:
- Prevents malignant ventricular arrhythmias and decreases T-wave alternans and ventricular fibrillation threshold changes associated with acute coronary artery occlusion
- Reduces TQ depression and heterogeneity of repolarization during myocardial ischemia
- Prevents stress-induced cardiac vulnerability in response to aversive conditioning
- Abolishes REM sleep-related heart rate surges and reduction in coronary flow in the stenosed coronary circulation

Human studies:
- Reduces mortality associated the long QT syndrome
- Decreases reinfarction and sudden death in post-myocardial infarction patients

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effect of direct stimulation of peripheral sympathetic structures such as the stellate ganglia [34]. It is noteworthy that the three beta-blockers which have longterm effects on mortality, namely, propranolol, timolol, and metoprolol, are all lipophilic [63], whereas the longterm effects of beta-blockers which are less lipophilic have not been as extensively studied. Thus, it remains to be established whether the protective effect reflects a fundamental pharmacologic difference or is related to study design. Finally, it is quite possible that in the longterm, the differences in efficacy among agents based on lipophilicity are offset by diffusion of the agent across the blood–brain barrier.

3.2. Parasympathetic influences

Whereas there is substantial evidence indicating that enhanced sympathetic nervous system activity is generally profibrillatory, vagal activation can result in either beneficial or adverse effects. As will be discussed, the net effect depends on a complex interaction between neural influences and intrinsic cardiovascular factors, including heart rate, arterial blood pressure, coronary blood flow, and the electrophysiologic state of the myocardium, e.g., whether there is ongoing ischemia or infarction. Furthermore, changes in vagal tone are often accompanied by simultaneous activation of the sympathetic limb of the autonomic nervous system. These patterns are under both central and reflex control.

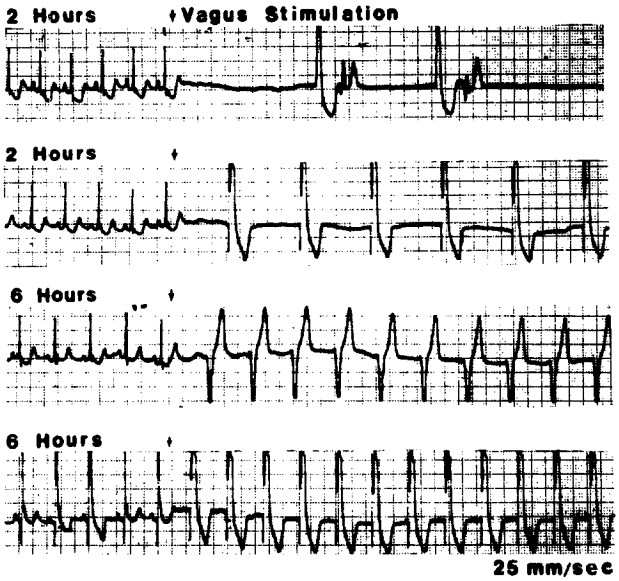

Fig. 2. Vagal stimulation and ventricular pacing. Top: 2 h after coronary artery occlusion, vagal stimulation induces asystole which, after 2 seconds, is followed by couplets of ventricular ectopic beats. Second band: 2 h after occlusion, when the ventricles are paced at a rate of 58 beats/min during vagal stimulation, couplets do not appear. Third band: 6 h after coronary occlusion, within 0.5 seconds of vagal stimulation, VT appears at a rate of 100 beats/min, the concurrent sinus rate being 115 beats/min. Bottom: 6 h after occlusion, when the ventricles are paced before and during vagal stimulation at the sinus rate of 120 beats/min, VT does not appear during vagal stimulation. (Reprinted with permission from the American Heart Association from [64].)

3.2.1. Proarrhythmic effects of vagus nerve activation

There are several conditions under which intense vagus nerve excitation can increase ventricular arrhythmogenesis. The first is when the vagus nerve is stimulated on a background of heightened adrenergic activity. For example, it has been shown that when the stellate ganglia are stimulated, activation of the vagus can lead to ventricular ectopic beats and even tachycardias. For many years, medical student laboratory demonstrations have shown that infusion of catecholamines followed by vagus nerve stimulation results in a plethora of ventricular premature beats and tachycardias. This classic demonstration has left an indelible impression in the minds of generations of clinicians that vagal activation is deleterious. It has also been shown that the ventricular arrhythmias which ensue immediately following cessation of diencephalic or hypothalamic stimulation require that both sympathetic and parasympathetic limbs be intact [21]. The highly arrhythmogenic effect resulting from sympathetic and parasympathetic interactions has been designated the "dual autonomic tone" theory of arrhythmogenesis by Skinner [24]. In a recent review article, he has attempted to explain neurally induced arrhythmias in terms of chaos theory involving rotating waves.

However, there is a simpler explanation for all of these observations, which is based on fundamental principles of cardiac electrophysiology. Specifically, adrenergic stimulation markedly increases automaticity of Purkinje fibers [23], and when the vagus nerve is activated on a background of enhanced automaticity, the sinus node rate is markedly reduced, thereby permitting expression of latent pacemakers within the ventricles. This, in turn, results in diverse ventricular rhythms including ventricular ectopic beats, bigeminy, and tachycardias. However, it is critical to recognize that these rhythm disturbances are benign inasmuch as they rarely culminate in ventricular fibrillation. Thus, dual activation of sympathetic and parasympathetic limbs in the normal heart is arrhythmogenic but not profibrillatory.

A second condition in which vagal activation has been shown to be arrhythmogenic is in the context of myocardial infarction. Within a few hours or days after total coronary artery occlusion in the experimental laboratory, stimulation of the vagus nerve can elicit premature beats and ventricular tachycardias. This effect, again, appears to be due to the fact that vagus nerve stimulation slows the sinus rate and exposes latent automaticity and triggered activity within the Purkinje fibers. When rate is fixed by ventricular pacing, activation of the nerve in the infarcted ventricle no longer elicits arrhythmias [64] (Fig. 2). Thus, the arrhythmias caused by vagus nerve stimulation are due to inhibition of the normal overdrive suppression of ventricular rhythms by sinoatrial node pacemaker activity. Similarly, by slowing heart rate, slow wave sleep may

result in firing of latent ventricular pacemakers and triggered activity. This mechanism may be relevant to the occurrence of ventricular ectopic activity in slow wave sleep in animals subjected to acute myocardial infarction [65]. It is important to emphasize that ventricular fibrillation rarely occurs under these conditions [23] and did not occur in this sleep study of pigs undergoing infarction. Thus, vagal activation in the context of myocardial infarction is proarrhythmic but not profibrillatory.

3.2.2. *Profibrillatory effects of vagus nerve activation*

Vagus nerve activity can predispose to ventricular fibrillation during acute myocardial ischemia, when the hypotensive effect of vagally induced bradycardia is sufficient to depress coronary perfusion pressure. This phenomenon has been observed by Billman, Schwartz, and Stone [66] in dogs in which exercise has been superimposed on a background of ischemia and prior infarction. In some animals, following cessation of exercise, a major slowing of heart rate occurred, presumably of vagal origin, and ventricular fibrillation ensued. Reflex activation of the sympathetic nerves in response to hypotension may have contributed to the onset of fibrillation. Clinically, severe hypotension, as occurs during hemorrhage, has been shown to increase coronary insufficiency and exacerbate myocardial ischemia [67].

The potential deleterious effects of vagus nerve stimulation on heart rhythm are summarized in Table 3.

3.2.3. *Antifibrillatory influences of vagus nerve activation*

In a milestone article published over 20 years ago, Kent and coworkers [68] provided evidence of a potent antifibrillatory effect of vagus nerve stimulation in dogs. They found that electrical excitation of the cardiac end of the cervical vagi significantly increased the ventricular fibrillation threshold, indicating reduced vulnerability to that arrhythmia. They also demonstrated that the enhanced rate associated with vagotomy in the acutely ischemic myocardium results in increased heterogeneity of repolarization and vulnerability to fibrillation. A component of the antifibrillatory influence of the vagus was independent of heart rate. This basic observation of a protective effect of vagal activation against fibrillation was subsequently documented and extended by numerous investigators using a variety of experimental animal models in both conscious and anesthetized animals (Table 3).

An antifibrillatory effect of vagus nerve stimulation has been demonstrated in anesthetized animals and administration of a variety of vagomimetic agents has been shown to increase the vulnerable period threshold and to reduce the incidence of spontaneous ventricular fibrillation during acute myocardial ischemia. The extensive series of interventions has recently been reviewed [69,70] and the main results can be summarized as follows. Vagotomy has been shown to be profibrillatory during acute myocardial ischemia and reperfusion. In conscious animals, stress-induced decreases in the threshold for inducing repetitive extrasystoles are exacerbated by blockade of vagal activity with atropine [69], and electrical stimulation of the vagus nerves can reduce the incidence of fibrillation associated with exercise superimposed on acute ischemia in animals with a prior infarction [71] (Fig. 3).

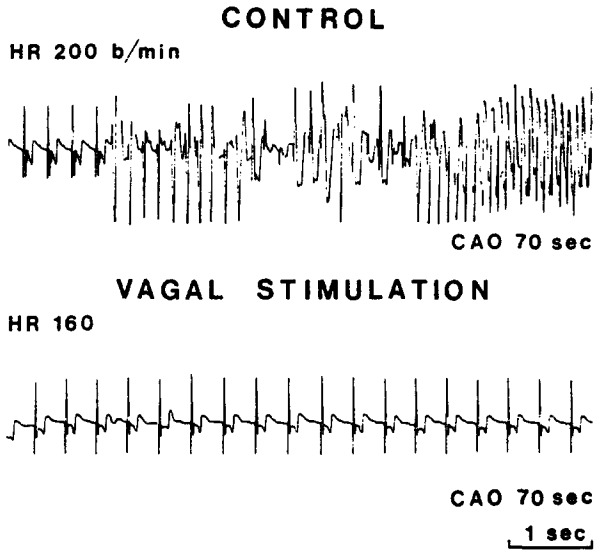

Fig. 3. ECG recording in a representative canine during a test involving submaximal exercise followed by occlusion of the circumflex coronary artery. The intact right cervical vagus nerve was electrically stimulated a few seconds after the beginning of the occlusion. Upper tracing: control test. Ten seconds after cessation of exercise, ventricular tachycardia occurred and degenerated into fibrillation. Lower tracing: test with vagal stimulation. The animal had no ventricular arrhythmia. (Reprinted with permission from the American Heart Association from [71].)

Table 3
Effects of vagal stimulation on ventricular electrical stability

Beneficial influences

Vagal tone exerts a rate-independent increase in myocardial electrical stability which reduces vulnerability to ventricular fibrillation during myocardial ischemia

The basis for the antifibrillatory influence is antagonism of adrenergic effects due to

- Inhibition of norepinephrine release from nerve endings
- Attenuation of response to catecholamines at receptor sites

Vagal tone exerts additional protection due to its rate-slowing effect during myocardial ischemia and reperfusion by increasing diastolic perfusion time and reducing cardiac metabolic demand.

Potentially deleterious effects

The rate-slowing effect of vagal activation may expose latent pacemakers and lead to ventricular tachyarrhythmias during either enhanced sympathetic activity or during the early phase of recovery from myocardial infarction. These arrhythmias rarely degenerate into fibrillation and thus this constitutes a proarrhythmic but not profibrillatory action.

Beneficial effects of vagal activity may be vitiated if profound bradycardia leads to hypotension, exacerbation of myocardial ischemia, and reflex sympathetic activation. This potentially deleterious action may operate during the acute phase of a myocardial infarction, especially when mechanical function of the heart is compromised.

Adapted from reference [42].

The major component of the antifibrillatory action of the vagus nerve appears to result from an antagonism of the deleterious effects of sympathetic nervous system activity. The molecular and cellular basis for this accentuated antagonism appears to be presynaptic inhibition of norepinephrine release and stimulation of muscarinic receptors, which inhibits second messenger formation by catecholamines [72]. Vagus nerve activity is not effective in preventing reperfusion-induced ventricular fibrillation during fixed rate pacing. However, during spontaneous rhythm, the rate-reducing effect of vagus nerve excitation decreases susceptibility to fibrillation by increasing diastolic perfusion time and reducing myocardial oxygen deficit, thereby lessening the release of ischemic byproducts.

At present there is no direct evidence for an antiarrhythmic effect of vagal activation at the ventricular level in human subjects. However, inferential data suggest that some of the mechanisms described in experimental animals may operate in the clinical setting. In particular, it has been shown that impairment of or a decrease in either vagal tone, as assessed by heart rate variability, or in reflex activation of the nerve, as assessed by baroreceptor sensitivity to phenylephrine infusion, are both associated with increased mortality and incidence of sudden death among post-myocardial infarction patients [73,74]. The potential hazard of blocking tonic vagal activity during the acute phase of myocardial ischemia is underscored in a case reported by Pantridge in which atropine administration precipitated ventricular fibrillation [75].

In summary, vagus nerve activation is capable of exerting both deleterious and beneficial effects on heart rhythm. The former may result from exposing latent ventricular pacemakers and cycle-length-dependent triggered activity, particularly under conditions of heightened sympathetic tone or acute myocardial infarction. This influence is proarrhythmic but not profibrillatory. Vagus nerve stimulation can exert a potent antifibrillatory influence by presynaptic inhibition of norepinephrine release from adrenergic nerve endings and by direct muscarinic opposition of second messenger formation (Fig. 4). Cardiac vagal tone also reduces ischemia-induced susceptibility to ventricular fibrillation by reducing heart rate and the consequent cardiac metabolic demands. However, if the reduction in rate is excessive, the beneficial effects of vagal activity may be vitiated because of the development of hypotension and impaired coronary perfusion.

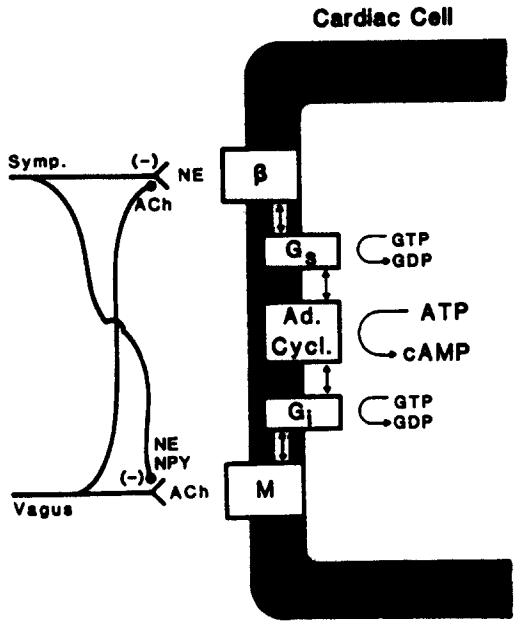

Fig. 4. Mechanisms responsible for cardiac sympathetic–parasympathetic interactions. Prejunctionally, vagal activity inhibits (−) the release of norepinephrine (NE) from sympathetic nerve endings, whereas NE and neuropeptide Y (NPY) inhibit the release of acetylcholine (ACh) from vagal nerve endings. Postjunctionally, the norepinephrine (NE) released from sympathetic nerve endings occupies beta-adrenergic receptors (β) on the cardiac cell surface. This process stimulates adenyl cyclase (Ad.Cycl.) to catalyze the formation of cyclic-AMP (cAMP) from adenosine triphosphate (ATP). The beta-adrenergic receptor (β) is coupled to adenyl cyclase through a stimulatory protein, G_S. Acetylcholine (ACh) released from vagus nerve endings occupies muscarinic receptors (M) on the cell surface. These receptors are coupled to adenyl cyclase through an inhibitory protein, G_i. (Reprinted with permission from Futura Publishing Company from [263].)

4. Physiology of sleep and dreaming

4.1. Neurophysiology and affective components

The physiology of sleep is a complex subject and has been reviewed [76–83]. This section is intended to provide a synopsis of sleep-state dependent changes which play a major role in cardiovascular regulation.

The brain's dynamic changes in state during sleep are coordinated by the pons and other subcortical structures. The main neurotransmitters involved are norepinephrine, serotonin, and acetylcholine [82–88]. The electroencephalographic (EEG) patterns and changes in autonomic and somatic activity elicited by this brain state are complex and subserve many functions. Recent evidence indicates that sleep is essential to thermal and immunologic homeostasis. The death of rats during sleep deprivation is caused by overwhelming sepsis after the animals have lost their capacity to regulate both dietary calories and body temperature [89]. A prime example of the adaptive response to stress is the release of cytokines into the cerebrospinal fluid to increase sleep [90] and to optimize effectiveness of the immune defense system [76]. Other specific physiologic and behavioral functions include somatic rest, tissue repair, immunity, consolidation of learning and memory, and adaptation to the behavioral challenges of the awake state. The neurobiology of rapid eye movement sleep has recently been reviewed in detail in an excellent article by Lydic and Baghdoyan [91].

A typical night's sleep in a normal adult begins with slow wave sleep, which is characterized by progressive

increases in high voltage, low frequency EEG activity (Fig. 5A). This pattern is due to the absence of desynchronizing activity emanating from the brain stem reticular formation and the cholinergic neurones of the dorsolateral pons [92,93]. The noradrenergic locus coeruleus and serotoninergic raphe neurones, which fire regularly throughout

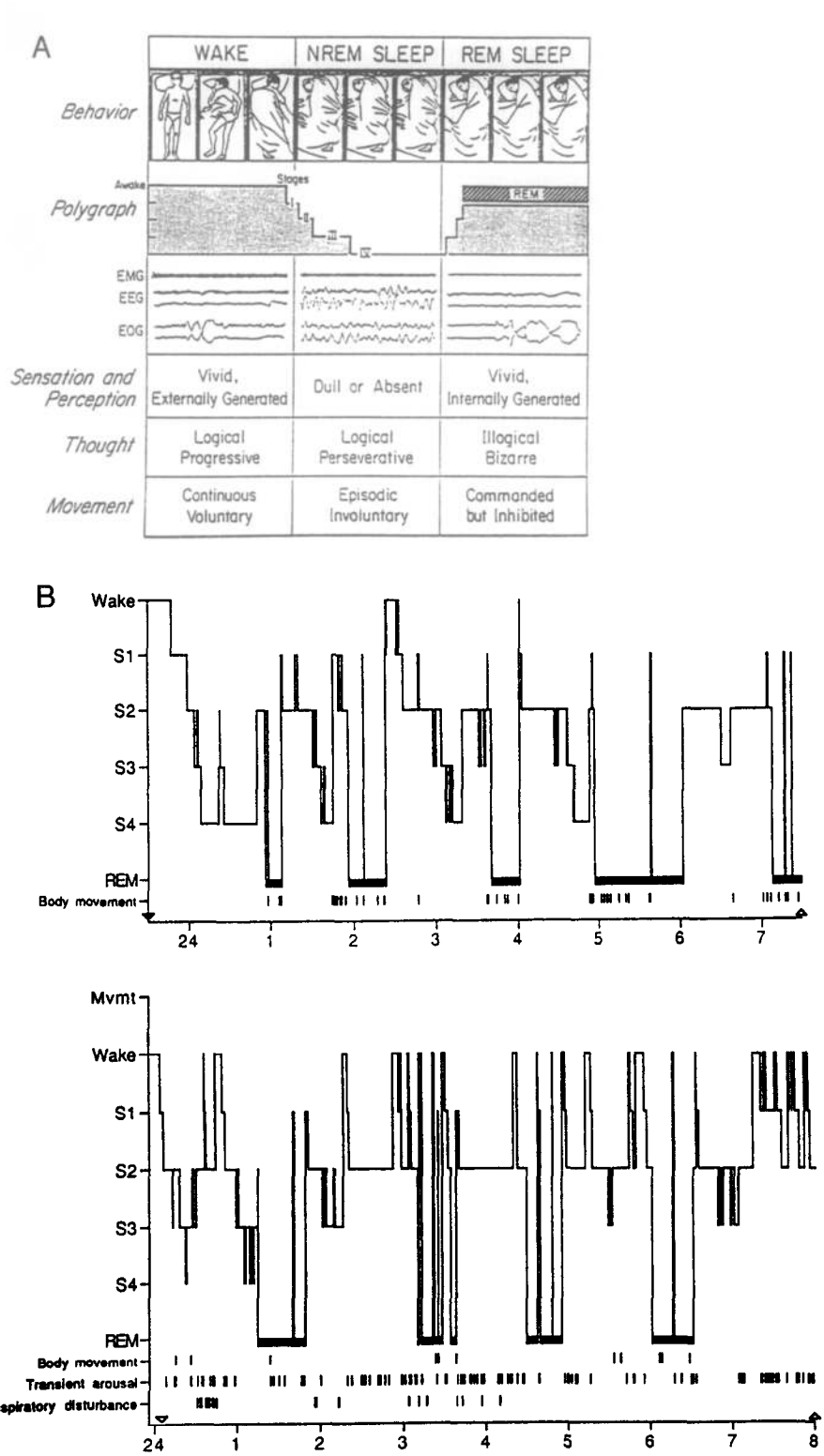

Fig. 5. (A) Behavioral states in humans. States of waking, slow wave sleep, and REM sleep have behavioral, polygraphic, and psychological manifestations. Sample tracings of 3 variables used to distinguish state are shown: electromyogram (EMG), electroencephalogram (EEG) and electrooculogram (EOG). Three lower panels describe other subjective and objective state variables. (Reproduced with permission from American Physiological Society from reference [83].) (B) Histogram of sleep stages, body movements, and transient arousals, during the sleep period of a young adult and an older adult. (Reproduced with permission from W.B. Saunders from [264,265].)

waking, also decrease their output at sleep onset. As their activity declines, there is a progressive increase in depth of sleep, over four discrete phases, as reflected by quantitative changes in EEG voltage and frequency, as well as by discrete EEG patterns including K complexes and sleep spindles. At approximately 90-min intervals, sleep lightens and REM sleep is initiated, due to increased activity in the brain stem reticular formation. As the inhibition from serotonin-containing neurones of the raphe is withdrawn, the cholinergic neurones of the anterodorsal pons are reactivated and their excitability is markedly increased over waking levels, so that they come to fire in intense bursts. The noradrenergic locus coeruleus also ceases to discharge in REM. The net result is a major shift in the modulatory chemistry of the brain. REM sleep is characterized by low-voltage, high-frequency EEG activity, and bursts of rapid saccade-like eye movements. Skeletal muscle tension, already significantly disfacilitated during slow wave sleep, is actively inhibited, causing the frank atonia of REM sleep [76,78,80–82,94]. The neurons activating respiratory muscles normally escape the generalized inhibition [84,95,96]. However, during sleep apnea, there may be cessation of central activity or peripheral obstruction several hundred times each night, with dire consequences in terms of the cardiorespiratory system, as will be discussed.

There are 4 to 6 REM periods per night, with increasing duration and intensity toward morning. Each REM period is characterized by tonic and phasic epochs, the latter being marked by more intense eye movements, by muscle twitches [97], and by bursting discharge of neurones, especially the pontine cholinergic elements [80,82,83,85,91]. Total REM time per night is approximately 90 min or 20 to 25% of total sleep time. It is significant that after middle age there is a progressive fragmentation of the sleep pattern, which can exert a significant impact on cardiovascular health (Fig. 5B).

While dreams can occur during either REM or slow wave sleep, subjects awakened from REM report dreaming 80 to 85% of the time, while those awakened from slow wave sleep report dreaming in only 10 to 15% of cases. REM-sleep dreams are not only longer but also more vivid, bizarre, emotionally intense, and illogical than those which occur during slow wave sleep [98]. Subjects, especially children, may awaken from slow wave sleep in a state of pure terror. These sleep terrors may be accompanied by tachycardia, polypnea, sweating, and dramatic elevations in blood pressure secondary to intense alterations in autonomic activity [99].

The visual imagery which occurs during REM sleep may result from internal activation of the oculomotor centers which command the bursts of rapid eye movement and project specific information to the lateral geniculate body and visual cortex [100]. The internally stimulated forebrain then synthesizes the neurophysiologic barrage into episodic dream stories. These may be coupled with surges in autonomic activity resulting in the increases in heart and respiratory rate and in blood pressure and reflecting activation of central circuits which mediate emotion. A possible mechanism is the direct and prominent projection from the pontine cholinergic neurones to the amygdala. During dreams, other motor systems are also activated, but the accompanying commands are not enacted because of active inhibition of spinal outflow at the level of the anterior horn cells.

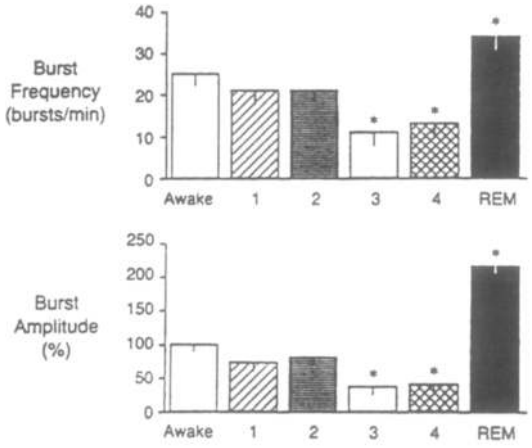

Fig. 6. Sympathetic-burst frequency and amplitude during wakefulness, nonREM sleep (8 subjects) and REM sleep (6 subjects). Sympathetic activity was significantly lower during stages 3 and 4 (* $P < 0.001$). During REM sleep, sympathetic activity increased significantly ($P < 0.001$). Values are means ± s.e.m. (Reproduced with permission from Massachusetts Medical Society from [102].)

It is relevant that during dreaming, the emotions of anger and fear are so commonly generated [83,101]. Fifty-seven per cent of all dreams express one or both of these emotions, which have been linked in wakefulness to the genesis of myocardial infarction and sudden death. The intensity of the emotional states achieved during dreaming may be as strong as or stronger than those which are experienced during wakefulness, and thus to the extent that behavioral stress is an acute risk factor for sudden death [36–41], it is reasonable to hypothesize that REM sleep and dreaming may be capable of precipitating life-threatening arrhythmias.

4.2. Autonomic nervous system activity and circulatory adjustments

The dramatic changes in autonomic nervous system activity which occur as a result of sleep-state changes are well documented [5,78,80,82,102–107] (Fig. 6). These autonomic alterations are particularly evident during REM or active sleep, when the central nervous system may operate with reduced baroreceptor gain [108], with reduced moderation of blood pressure fluctuations. By contrast, during slow wave sleep, the system operates under conditions of heightened baroreceptor gain. These alterations are thought to account for the greater stability in blood pressure regulation during slow wave sleep and for the greater

instability during REM. The significant increase in baroreceptor gain during slow wave sleep is also likely to play an important role in cardiovascular homeostasis in health and disease [109]. Baroreceptor alterations may account for the fact that blood pressure during sleep may exhibit a normal decrease in some hypertensive patients (who are therefore referred to as "dippers") and remain significantly elevated in others (known as "nondippers"). The latter typically show evidence of central hypersympathetic activity with an increased number of microarousals, reduced length and depth of slow wave sleep, and a shortened REM latency [110].

REM sleep, in subserving brain neurochemical functions and behavioral adaptations, can disrupt cardiorespiratory homeostasis [111]. The brain's increased excitability during REM sleep can result in major surges in cardiac sympathetic activity to the coronary and skeletal muscular vessels, accompanied by muscular twitching, and in decreased blood flow to the renal and splanchnic beds. Cardiac efferent vagal tone is generally suppressed during REM [5], and breathing patterns are highly irregular, leading to oxygen reduction [95,96,111,112] (Fig. 7). Such effects can significantly impact cardiovascular functioning, as is evident in changes in heart rate and arterial blood pressure in normal subjects and in the development of arrhythmias in patients whose myocardium is compromised.

Slow wave sleep is associated with marked stability of autonomic regulation [80]. Respiratory sinus arrhythmia is prominent, indicating a high degree of parasympathetic tone [78,80,111], a finding supported by heart rate variability analysis with and without autonomic blockade [103,104]. Slow wave sleep is accompanied by hypotension, bradycardia, and reductions in cardiac output and systemic vascular resistance [5,78,80]. The bradycardias appear to be due mainly to an increase in vagal activation, whereas the hypotension is primarily attributable to a reduction in sympathetic vasomotor tone [113]. During transitions from slow wave to REM sleep, bursts of vagus nerve activity may result in pauses in heart rhythm and frank asystole [114].

Sympathetic nervous system activity appears to be relatively stable during slow wave sleep and its cardiovascular input is reduced [80,102]. Somers and colleagues performed direct peroneal sympathetic nerve recording studies in human subjects during natural sleep and found that sympathetic activity was reduced by more than half from wakefulness to stage 4 of slow wave sleep [102]. These findings appear to be at variance with those of Baust and Bohnert, who suggested that sympathetic activity was not reduced during sleep in cats [106]. However, the results were highly inferential, because direct nerve recordings were not performed and heart rate following vagotomy and stellectomy was the sole indicator of neural autonomic activity during sleep. Other important study limitations resulted from acute cervical vagotomy. This procedure could have artificially increased sympathetic tone by denervating aortic baroreceptors and by causing physical discomfort. Cervical vagotomy also disrupts the pulmonary inflation reflex by interrupting a major afferent component of respiratory control.

In summary, there is strong evidence of heightened cardiac vagal tone during slow wave sleep. With respect to sympathetic nervous system activity, the weight of the literature suggests that this component of peripheral autonomic control is reduced during slow wave sleep. However, definitive demonstration will require direct measurement of cardiac-bound sympathetic nerve activity, a tech-

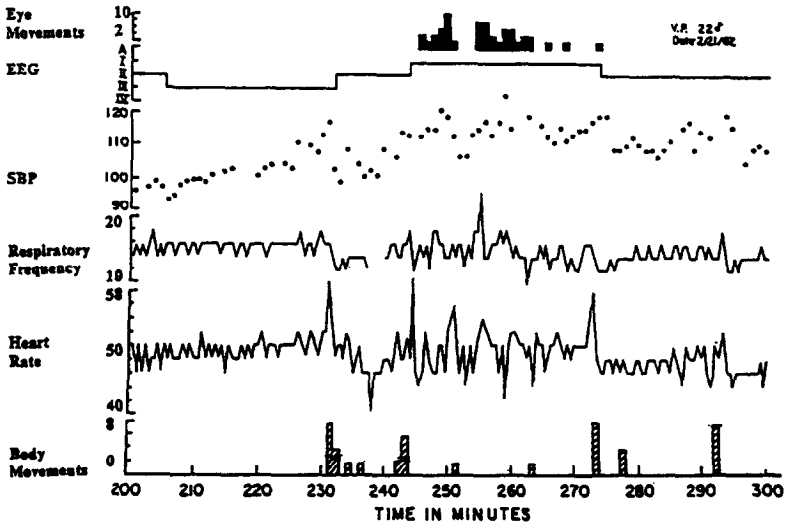

Fig. 7. Minute-by-minute fluctuations in cardiorespiratory variables during 100 min of uninterrupted sleep in a healthy subject. EEG, electroencephalogram; SBP, systolic blood pressure. Note that during REM sleep (min 242–273), two sustained bursts of eye movements (filled bars, top line) were associated with marked irregularities in SBP, respiratory frequency, and heart rate. (Reproduced with permission from American Physiological Society from [112].)

nique which is not presently available. In general, the collective data suggest that peripheral changes in autonomic nervous system activity are reciprocal to those in the central nervous system. Namely, in REM sleep, during which central cholinergic activity prevails [82,83], there is enhanced sympathetic discharge to the cardiovascular system [80,97,102,115,116], whereas in slow wave sleep, during which central aminergic factors are predominant [82,83], there is increased cardiac vagal tone [80,103,104,114].

4.3. Coronary blood flow regulation during sleep

Striking changes in coronary blood flow occur during REM and sleep-state transitions [97,114–117]. Vatner and coworkers [117] used baboons to study the effects of the sleep/wake cycle on coronary function. During the nocturnal period, when the animals were judged to be asleep by behavioral indicators, coronary artery blood flow fluctuated by as much as twofold. The periodic oscillations in blood flow were not associated with alterations in heart rate or arterial blood pressure and occurred while the animals remained motionless with eyes closed. Since the baboons were not instrumented for electroencephalographic recordings, no information was obtained regarding sleep stage, nor was the mechanism for the coronary blood flow surge defined.

We studied these sleep-related coronary blood flow changes in experiments in dogs chronically instrumented for the recording of sleep stage and of systemic and coronary hemodynamic function [97,115]. The observations were made during natural sleep, and the results were scored according to quiet wakefulness, slow wave sleep, or REM sleep. During slow wave sleep there were moderate but significant reductions in heart rate and coronary blood flow and elevations in coronary vascular resistance. During REM, the coronary blood flow baseline was moderately elevated compared to slow wave sleep, reflecting increased cardiac metabolic activity, and there were remarkable, episodic surges in flow with corresponding decreases in coronary vascular resistance (Fig. 8). There were no significant changes in mean arterial pressure. Heart rate was elevated during the flow surges, suggesting an increase in cardiac metabolic activity as the basis for the coronary vasodilation. In fact, the close coupling between rate–pressure product, an index of metabolic demand, and the magnitude of the flow surge, indicates that the surges do not constitute a state of myocardial hyperperfusion. The

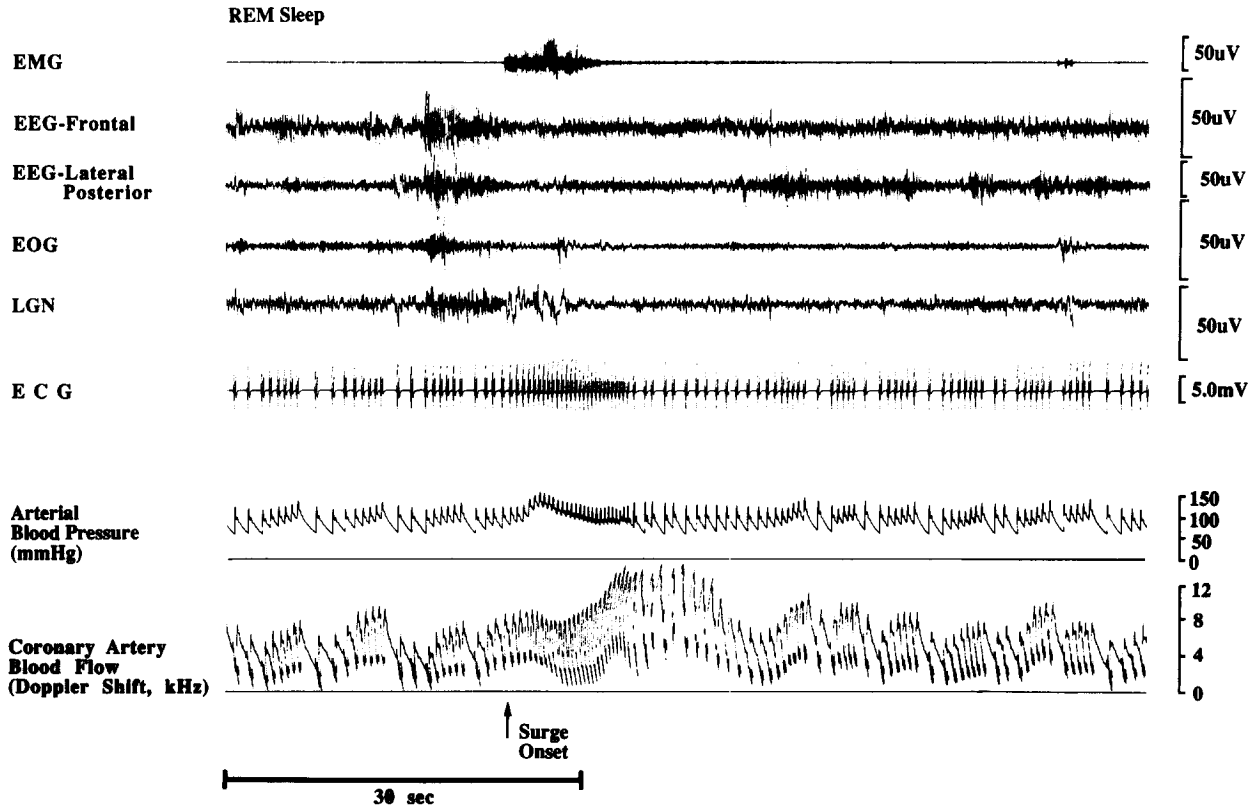

Fig. 8. Surges in heart rate, blood pressure and coronary flow during REM sleep with phasic muscle twitch. Cardiac metabolic demand (HR×SPB) increased by 110% and average coronary flow increased by 32.5% during the first 12 seconds of the surge. The maximum coronary flow achieved by the end of the 12-second period represents an increase of 87% over baseline values preceding the surge. There was no behavioral evidence of arousal. Brief elevations in blood pressure (as shown here) were rarely observed during episodes of phasic REM. Group data indicate that no significant changes in baseline blood pressure were associated with HR surges in any of the substages of REM sleep. (Reproduced with permission from American Sleep Disorders Association and Sleep Research Society from [97].)

surges in coronary blood flow appeared to be due to enhanced adrenergic discharge, since they were abolished by bilateral stellectomy, and not to nonspecific effects of somatic activity or respiratory fluctuations.

During severe coronary artery stenosis, with baseline flow reduced by 60%, phasic decreases in coronary arterial blood flow, rather than increases, were observed during REM sleep coincident with these heart rate surges [116] (Fig. 9). These phenomena occurred predominantly during periods of REM marked by intense phasic activity, as defined by the frequency of eye movements [97]. We have proposed that the increase in adrenergic discharge could lead to a coronary blood flow decrement by at least two possible mechanisms. The first is by the stimulation of alpha-adrenergic receptors on the coronary vascular smooth muscle. Such an effect, however, could only be transitory, as alpha-adrenergic stimulation results in brief (10–15 seconds) coronary constriction, even during sympathetic nervous system stimulation in anesthetized animals [118] or during intense arousal associated with aversive behavioral conditioning [119]. The second possibility for REM-induced reduction in coronary flow during stenosis is mechanical, namely a decrease in diastolic coronary perfusion time due to the surges in heart rate. In support of this explanation, we found a strong correlation ($r^2 = 0.96$) between the magnitude of the increase in heart rate and the decrease in coronary blood flow [116]. The link between REM-induced changes in heart rate and the occurrence of coronary insufficiency in patients with advanced coronary artery disease is consistent with the clinical experience of Nowlin and coworkers [120].

Identification of the central nervous system sites responsible for integrating the REM-induced changes in coronary and systemic blood flow will be challenging. However, some clues are available from the literature [80,82]. Particularly germane are the observations that phasic changes in heart rate, blood pressure, and respiration accompany bursts of eye movements and large phasic potentials which originate in the peribrachial region of the dorsolateral pons. The activity of this area is associated with changes in respiratory and cardiovascular effects [121]; in the past it has been called the apneustic center.

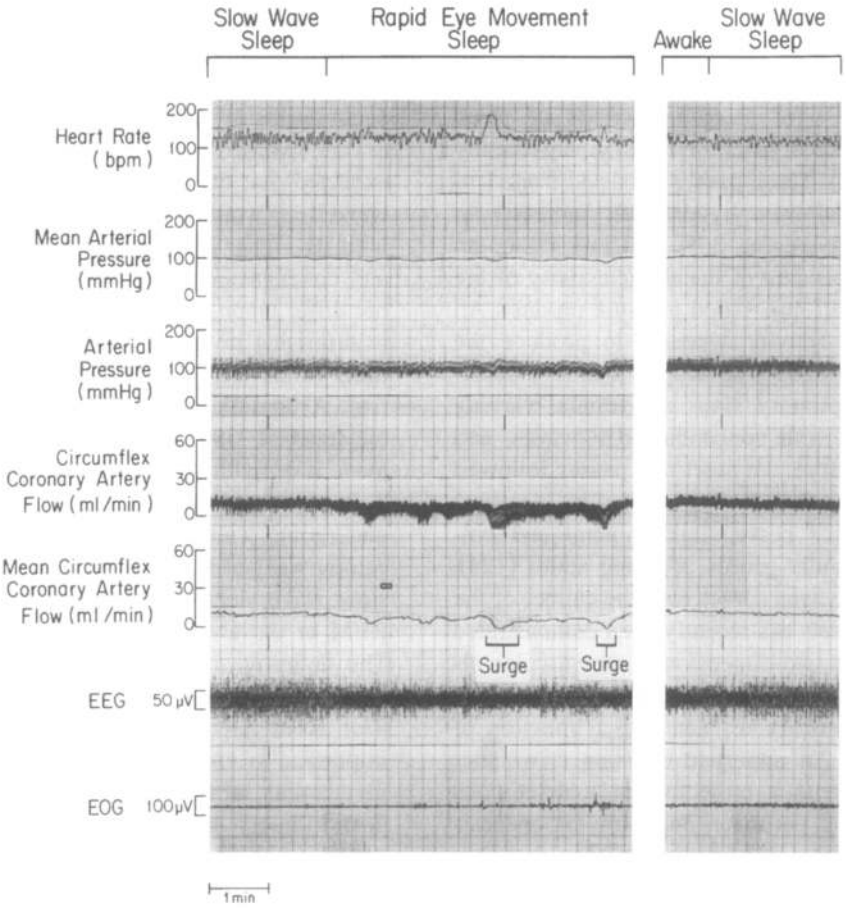

Fig. 9. Effects of sleep stage on heart rate, mean and phasic arterial pressures, and mean and phasic left circumflex coronary artery blood flow in a typical dog during stenosis. Note phasic decreases in coronary flow occurring during heart rate surges while the dog is in REM sleep. EEG, electroencephalogram; EOG, electrooculogram. (Reproduced with permission from Pergamon Press from [116].)

It is now clear that the various phenomena of phasic REM sleep involve profound and widespread episodic changes in fundamental levels of excitability in many neuron populations within the central nervous system, but none is more intensely activated than the central cholinergic neurones of the dorsolateral pons. As noted above, these cells are known to project both to the amygdala, where they may trigger emotion, and to the pons and medulla, where they could excite reticular neurones projecting to the spinal sympathetic chain. One intriguing paradox that could be resolved by such a mechanism is the dissociation between the central aminergic neurones, which are completely silent in REM, while the peripheral sympathetic system is both tonically and phasically activated. The increases in metabolic demands of the brain, in concert with increased neuronal activity during REM sleep, apparently result in a corresponding increase in cerebral blood flow [122,123]. In support of this view, Townsend and coworkers [123] have shown that cerebral blood flow during REM sleep exceeds that which occurs during slow wave sleep and quiet waking and approaches the level observed during intense mental effort.

4.4. Heart rhythm pauses and arrhythmogenesis during sleep

We observed prolonged pauses in heart rate during transitions from slow wave sleep to periods of sleep marked by desynchronized EEG rhythms in chronically instrumented dogs [114]. These pauses persisted from 1 to 8 seconds and were followed by dramatic increases in coronary blood flow, averaging 30% and ranging up to 84%, which were independent of metabolic activity of the heart as reflected in heart rate–blood pressure product. An intense burst of vagal activity appeared to produce the phenomenon, since the pauses developed against a background of marked respiratory sinus arrhythmia, varying degrees of heart block with nonconducted P waves, and low heart rate. Furthermore, the heart rate pauses followed by the surge in coronary flow were emulated by electrical stimulation of the vagus nerve. Guilleminault and colleagues documented similar pauses in young adults [124].

Tonic control of the vagus nerves over the caliber of the epicardial coronary vessels has recently been demonstrated in our laboratory using two-dimensional intravascular ultrasound [125]. This could be an important factor in dynamic regulation of coronary resistance as a function of the sleep–wake cycle. An important question is whether tonic vagal activity exerts a protective or a deleterious influence on myocardial perfusion and arrhythmogenesis in individuals with atherosclerotic disease. The fact that acetylcholine produces coronary vasoconstriction rather than dilation in atherosclerotic segments due to impaired release of endothelium-derived relaxing factor [126], suggests a mechanism by which nocturnal surges in vagus nerve activity could precipitate myocardial ischemia and arrhythmias.

4.5. Effect of sleep states on ventricular arrhythmias during acute myocardial ischemia and infarction

There is a paucity of information regarding the effects of sleep states on susceptibility to arrhythmias during coronary artery occlusion in experimental animals. Data available to-date derive mainly from the investigations of Skinner and coworkers, who examined the influences of sleep state on the occurrence of ventricular arrhythmias during left anterior descending coronary artery occlusion in pigs [65]. Two groups of animals were investigated, one during the early phase of infarction (2 h or 2 days), and the second during acute myocardial ischemia, within the first 20 min of coronary artery occlusion.

In the animals undergoing myocardial infarction, it was found that during intervals in which transitional and slow wave sleep alternated, ventricular arrhythmias were significantly more prevalent than in the awake state [65]. The maximum increase in arrhythmias was during the sustained period of slow wave sleep, and REM sleep was associated with a reduction in the incidence of ventricular arrhythmias. The authors maintained that the sleep-state dependent changes in ventricular arrhythmogenesis were not due to the well-established phenomenon of rate-overdrive suppression of latent ectopic pacemakers, which is known to occur during myocardial infarction [23] (Fig. 2). According to rate-overdrive suppression mechanisms, it would be expected that the slower heart rates associated with slow wave sleep would expose the latent pacemakers, and REM, with its higher heart rates, would suppress them. Skinner and colleagues cited the evidence that the heart rates did not differ among the states of wakefulness and sleep. This is surprising in view of the extensive experimental literature, which suggests that slow wave sleep lowers heart rate. A possible explanation is that in the infarcted pigs, the level of ventricular ectopic activity and tachycardias made it difficult to ascertain the actual sinus rate (see Fig. 2 in reference [65]). In fact, in the group of animals undergoing acute myocardial ischemia, when ventricular ectopy was not as prevalent, the investigators did find that slow wave sleep resulted in a lower heart rate than did REM or the awake state (see Table 2 in reference [65]). The definitive method to resolve this issue of rate-overdrive suppression of latent ectopic pacemakers would have been fixed rate pacing, but this was not performed. It is important to emphasize that the effects observed during myocardial infarction related to proarrhythmic and not profibrillatory influences, since ventricular fibrillation did not occur in any of the pigs.

In the second group of pigs, Skinner and colleagues examined the effects of sleep states on the time of onset of ventricular fibrillation following total coronary artery occlusion, a measure referred to as "ventricular fibrillation

latency'' (VFL) [65]. This endpoint, rather than incidence of fibrillation, was employed because all of the pigs succumbed to fibrillation within 20 min following coronary obstruction, regardless of whether the occlusion was performed during wakefulness or sleep. It is important to note that the occlusion awakened all of the 8 pigs studied, and that they were awake at the time of onset of fibrillation. In 5 of the pigs, in which occlusion was initiated during slow wave sleep, the VFL significantly decreased from 17 to 6 min compared to the previous occlusion, which was carried out during wakefulness. Only 3 pigs were occluded during REM sleep. In these subjects, there was an increase in VFL from 10 to 19 min, but only one animal could be defibrillated. These results were interpreted as indicating that slow wave sleep reduces susceptibility to fibrillation, whereas REM sleep is protective.

Given the small number of animals, the fact that all of the animals fibrillated and were awake at the time of fibrillation, that REM typically lasts only 3 min in this species [127] as compared to 15 min in humans, and that fibrillation latency, as opposed to incidence, was increased, this conclusion must be viewed with caution. The significance of fibrillation latency as a marker of vulnerability to fibrillation is not well established, and a major determinant of this parameter in the pig may be its well-known lack of collateralization. Thus, the hypotension typically associated with slow wave sleep could serve to extend ischemic injury and predispose to rapid onset of fibrillation. The converse is potentially true about REM sleep. As Skinner and coworkers did not measure blood pressure or indices of myocardial perfusion or extent of ischemic injury, these questions remain unresolved.

The view that slow wave sleep is profibrillatory during acute coronary artery occlusion is at variance with a substantial body of experimental and clinical literature. In animal studies, it is well established that enhanced vagal activity is antifibrillatory during acute ischemia [68–75]. Thus, it would seem inconsistent that slow wave sleep, which is characterized by a high degree of vagal tone and reduced sympathetic activity, should be more conducive to fibrillation than wakefulness or REM sleep. That slow wave sleep has a generally deleterious effect on heart rhythm is also puzzling on clinical grounds. If slow wave sleep, which occupies at least 6 h of sleep, were profibrillatory, as Skinner suggests, then the nocturnal period should account for at least 25% of sudden deaths. This is not the case, as only 12% of sudden deaths occur at night [1].

In summary, the limited information available indicates that slow wave sleep may be proarrhythmic during infarction but not that it is profibrillatory. During acute ischemia, slow wave sleep may increase fibrillation latency, but whether this finding indicates an enhancement in vulnerability to that arrhythmia remains to be determined. Certainly, this possibility seems unlikely in view of the low incidence of sudden death at night. Clearly, there is an important need to obtain more extensive information in experimental models regarding the impact of sleep states on susceptibility to sudden arrhythmic death.

5. Clinical studies of the diurnal pattern of myocardial infarction and sudden cardiac death

5.1. Ischemic heart disease

A series of studies initiated in the early 1980s demonstrated an important diurnal pattern of myocardial infarction and sudden cardiac death [1,128]. Examination of death certificates of 2203 patients who sustained out-of-hospital cardiac arrest in Massachusetts during 1983 revealed a peak incidence from 7 to 11 o'clock A.M. [1] (Fig. 10). A similar pattern was subsequently identified in the Framingham Heart Study [129] and for nonfatal myocardial infarction [130]. The morning increase in incidence of myocardial infarction, sudden cardiac death, transient myocardial ischemia, and stroke was further corroborated in numerous studies throughout the world [131]. The work served to focus attention on triggers associated with arousal, since the data suggest that the increases are not determined primarily by time of day but by activities in the hours after awakening. In terms of the evening hours, there is a suggestive moderate peak in coronary events in the late afternoon or early evening and another minor peak in the incidence of sudden death at 2 o'clock A.M., followed by a general trough [1,129]. However, these apparent increases have not been validated statisti-

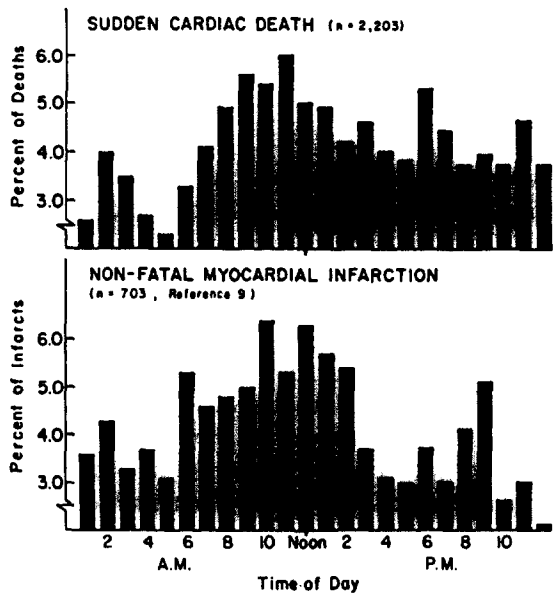

Fig. 10. Bar graphs of time of day of onset of myocardial infarction, sudden cardiac death. Number of events is shown on the *y*-axis and hour of day on the *x*-axis. Both disorders exhibit a prominent increase in frequency of onset from 6 o'clock A.M. to noon. (Reproduced with permission from the American Heart Association from [1].)

cally. It is unknown whether the 2 o'clock A.M. rise is related to changes in sleep physiology, such as deep slow wave sleep, with attendant decreases in arterial blood pressure, or to the proarrhythmic effects of a REM-induced surge in sympathetic activity. A significant incidence of nocturnal non-Q-wave (subendocardial) infarction in the 2-h period between 2 and 4 o'clock A.M. has been documented but the mechanism remains unknown [132]. This is also a common time for arousal [133]. These more subtle changes in the diurnal pattern of sudden death and infarction during the evening and night merit further study as they could provide important clues into neural mechanisms for coronary events.

These analyses may underestimate the number of events which are initiated during sleep and express themselves upon arousal in the form of plaque disruption or life-threatening arrhythmias. REM sleep and dreams, with the attendant surges in sympathetic activity and decreases in parasympathetic activity [5,78,80,82,97,102–106,115,116], are particularly intense just prior to awakening [76,80–83]. These could impact an already unstable myocardium or initiate disruption of vulnerable plaques, leading to ischemia- and reperfusion-induced ventricular tachyarrhythmias. Studies which could determine whether the early morning peak in mortality is initiated by a final surge of REM sleep or results from activities following awakening would provide important information. A further consideration is that sleep is fragmented with advancing age, so that it becomes difficult to ascertain at what time of the morning patients actually awaken. Finally, it remains unknown what percentage of nocturnal sudden death is the result of an ischemic episode or is due to primary ventricular fibrillation.

5.2. Heart failure

Sudden death in patients with heart failure also follows a diurnal pattern [134]. The overall hourly frequency distribution of time of death is remarkably similar to that for myocardial infarction and death in patients with ischemic heart disease. Specifically, sudden death occurred 2.5 times more frequently between 6 o'clock A.M. and noon than in the three other 6-h intervals ($P < 0.005$). The morning peak occurred both in patients with heart failure due to coronary artery disease and in those with nonischemic causes. Approximately 14% of the deaths occurred during the nocturnal period, a proportion comparable to that observed for myocardial infarction and sudden death due to ischemic heart disease.

Thus, in view of the large number of nocturnal sudden deaths in ischemic heart disease or heart failure patients, there is a great need to increase our understanding of the triggers responsible for precipitating nocturnal arrhythmic death and myocardial infarction.

5.3. Daily activities and physiologic processes implicated in precipitation of myocardial infarction during wakefulness

Because the sleeping brain is capable of eliciting diverse emotions including anger [101], autonomic changes [80,82,102], and major cardiovascular alterations [5,78,103–105], it is useful to review daytime activities and physiologic processes which have been linked to myocardial infarction. Mittleman and colleagues employed a case-crossover study design to estimate the relative risk of myocardial infarction in response to exertion [135] and anger [136]. The risk was calculated as the observed frequency of the activity during a 1-h hazard period prior to the event, and the result was compared to the expected frequency based on the individual's usual frequency of the activity. It was found that heavy exertion (estimated to be ≥ 6 metabolic equivalents [METs]) yielded a 5.9-fold increase in risk (95% confidence interval: 4.6 to 7.7) of myocardial infarction in the subsequent hour. The risk of myocardial infarction onset during heavy exertion was markedly higher in those who had been sedentary (107-fold) compared with those who had exercised regularly (2-fold).

The same epidemiological design was employed to study the triggers of infarction associated with outbursts of anger [136]. Anger corresponding to levels greater than 4 on a 7-level self-report anger scale was noted by 14% of patients within 26 h prior to myocardial infarction onset. The risk of myocardial infarction was significantly elevated in the 2 h following an outburst of anger and there was a relative risk of 2.0 (95% confidence interval: 1.7 to 3.2). These findings are consistent with mounting evidence from experimental [39] and clinical [137–139] studies demonstrating that anger is capable of provoking ischemia.

A variety of mechanisms, alone or in combination, have been implicated in triggering of myocardial infarction during wakefulness [140]. These include surges in sympathetic activity and withdrawal of parasympathetic tone resulting in elevations in arterial blood pressure. When these occur in combination with transitory coronary vasoconstriction, they may lead to increased shear stress against the endothelium and resultant disruption of vulnerable plaque. If significant myocardial ischemia ensues, ventricular tachyarrhythmias could be triggered, resulting in an adverse positive feedback on coronary hemodynamic function. Contributory prothrombotic processes including increased platelet adhesion, blood viscosity and platelet aggregability, appear to play a role in morning increases in ischemic events. Finally, reduction in fibrinolytic activity is likely to lead to the growth of a mural thrombus overlying a plaque fissure, thereby causing obstruction of the coronary lumen. Similarly, the established nocturnal surges in sympathetic activity which occur particularly during REM sleep [97,102–106,115,116] could precipitate myocardial infarction by stimulating thrombotic and inhibiting fibrinolytic

processes, or by increasing hemodynamic stress on the vessel walls. While the frequency of myocardial infarction onset is significantly reduced ($P < 0.01$) between midnight and 6 o'clock A.M., sleep is not a protected period, as 14% of myocardial infarctions occur during sleep [141].

6. Patients at risk for nocturnal sudden death and myocardial infarction

The pivotal question is not whether sudden death occurs during sleep, as it has been shown that 12% of cardiovascular deaths and 14% of myocardial infarctions do occur during the nocturnal period. Rather, the main issue is why cardiovascular events should occur at all during a time of relative inactivity of the organism. The challenge is to identify physiologic events during sleep that actively conduce to myocardial infarction and arrhythmic death.

Insights into this question can be derived from several subsets of patients who are at increased risk for premature cardiac demise. These include individuals with ischemic heart disease, acute post-myocardial infarction, heart failure, or apnea, and a subset of patients with pause-dependent long QT syndrome, near miss or siblings of sudden infant death (SIDS) victims, and young Southeast Asian men. Whereas there are likely to be significant differences in the pathophysiologic mechanisms responsible for sudden death in each of these syndromes, they also share important common elements, namely a vulnerable cardiac substrate upon which sleep activates the autonomic nervous system and/or disrupts breathing, leading to cardiac demise. The complexity of neurocardiac interactions during sleep has been discussed in detail in an excellent review by Gillis and Flemons [142]. This section focuses on conditions in which coronary artery disease is a predisposing factor and thus will not deal with the long QT syndrome [143] and SIDS [144], for which excellent reviews are available.

6.1. Ischemic heart disease

Precipitation of life-threatening arrhythmias in patients with ischemic heart disease may occur as a direct result of influences on the stability of cardiac rhythm or through a change in myocardial blood flow, such as can occur during a thrombotic event involving plaque disruption and platelet aggregation. To gain insights into this issue, we will review the literature relating to arrhythmogenesis during sleep and nocturnal angina.

6.1.1. Sleep and ventricular arrhythmias

The prevailing view from the clinical literature is that there is a reduction in ventricular arrhythmias during the nocturnal period [142,145–153]. In some cases, arrhythmia frequency may be enhanced, and this may be due in part to the fact that latent foci may be exposed by the generalized reduction in heart rate associated with sleep. Lown and coworkers [147] found that in 35 of 45 patients with ventricular ectopy during 24-h ambulatory monitoring, sleep was associated with a 25–50% reduction in frequency of ventricular ectopic activity; grade was likewise reduced. After many hours of sleep, ventricular premature beats decreased at low heart rates. Further analysis with polysomnographic monitoring revealed that the abatement in arrhythmia was attributable to slow wave sleep, with the maximum reduction occurring during stages 3 and 4 [154]. During REM sleep, ventricular premature beats increased in frequency and grade and were comparable to that observed during wakefulness. The fact that 80% of sleep time is spent during slow wave sleep, as opposed to REM, probably accounts for the general but not complete reduction in arrhythmias in the nocturnal period.

As will be discussed in greater detail below, the impact of sleep states on arrhythmogenesis is more complex when there are respiratory abnormalities and/or changes in cardiac mechanical function, as occurs in patients with sleep apnea or heart failure. In patients with these conditions, reduction in oxygen saturation due to respiratory impairment occurring either during slow wave or REM sleep can lead to significant brady- or tachyarrhythmias. In patients recovering from myocardial infarction, in whom there may be impairment of pump function, the hypotension which attends slow wave sleep exacerbates ischemia and arrhythmias [150,155].

6.1.2. Nocturnal ischemia and angina

Although detailed studies of patient activity from several laboratories indicate that mental arousal is a common trigger mechanism of transient myocardial ischemia [156–159], it is widely acknowledged that there is a significant frequency of spontaneous ischemia and angina [3,120,148,160–166] during the nocturnal period. It has been estimated that 8 to 10% of ischemic attacks and angina occur during sleep [167,168]. The REM phase of sleep is particularly conducive to angina and ST-segment abnormalities [120,148,163]. This stage is characterized by increased heart rate and blood pressure [5,112,169], sympathetic nervous system activity [102–105], and plasma catecholamines [170]. Thus, this period could be particularly hazardous in angina-prone patients [171].

Nocturnal ischemia and angina in patients with severe coronary disease has been attributed both to a reduction in perfusion [161,172] due to the generalized hypotension of slow wave sleep, and to a REM-induced increase in heart rate and blood pressure and, therefore, metabolic demand [120,164,165,173,174]. Figueras and colleagues [175] demonstrated a decline in the ischemic threshold (defined as ≥ 1.0 mm ST segment shift) with atrial pacing in patients with significant coronary artery stenosis ($> 70\%$). The pacing rates which met the ST-segment shift criterion were substantially lower at night (125 ± 3 beats/min) compared to those observed in the morning or afternoon (138 ± 3 and 139 ± 2 beats/min, respectively, both $P <$

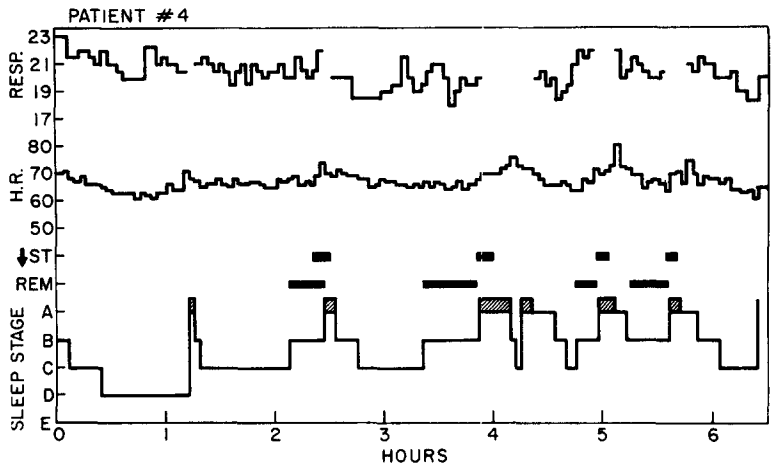

Fig. 11. Composite graph of a night of sleep in a patient with nocturnal angina pectoris. Note association between REM-related surges in heart rate and occurrence of ST-segment changes. Resp, respirations; HR, heart rate; ST, periods of significant ST segment depression on electrocardiogram. (Reproduced with permission from the American College of Physicians from [120].)

0.005). Nowlin and coworkers [120] found in patients with advanced coronary artery disease that attacks of nocturnal angina occurred predominantly (32 of 39 episodes in 4 patients) during REM sleep and were associated with heart rate acceleration (Fig. 11). Selwyn and colleagues [176] found that ST-segment depression occurred more often ($P < 0.001$) between 4 and 6 o'clock A.M. than at any other 2-h nocturnal period in patients with frequent angina.

In patients with Prinzmetal's variant angina, REM sleep is associated with coronary spasm, leading to nocturnal ischemia and angina [160,163,165,177–186]. Anginal attacks in these patients were twice as prevalent during the second half of the sleep period, when REM is more frequent [178–185]. In a study of 8 Prinzmetal's angina patients over an 18-day period, Otsuka and colleagues [186] observed that the episodes of nocturnal angina occurred exclusively during REM and were accompanied by ventricular premature beats and ventricular tachycardia.

Thus, most studies indicate that in the absence of significant mechanical compromise of the heart, nocturnal ischemic events occur primarily during REM sleep. There is evidence to suggest that this may be due largely to sympathetically mediated surges in rate–pressure product and metabolic demands in flow-limited, stenosed coronary arteries.

6.2. *Post-myocardial infarction patients*

Nocturnal sleep is significantly disturbed in the acute post-myocardial infarction phase [162,174]. The first week following myocardial infarction is particularly critical, as chronic hypoxemia is common, and there are recurring

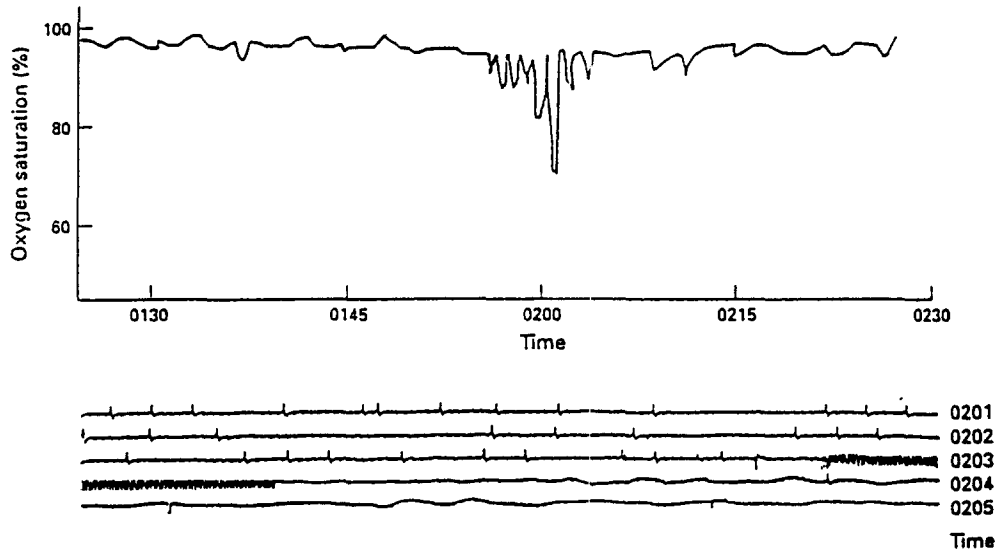

Fig. 12. Importance of monitoring nocturnal oxygen saturation in post-infarction patients. Simultaneously occurring nonsustained ventricular tachycardia and hypoxemia measured by pulse oximetry in a patient on third night after infarction. The individual died on following day of cardiogenic shock. (Reproduced with permission from the British Medical Society from [187].)

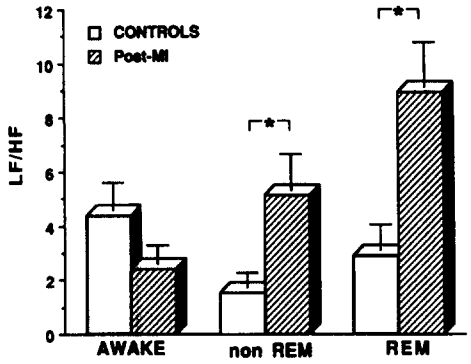

Fig. 13. Bar graphs indicating mean ± s.e.m. of the low- to high-frequency ratio (LF/HF) from spectral analysis of heart rate during the awake state (left), during non-rapid eye movement (nonREM) sleep (middle), and during REM sleep (right) in normal subjects and in post-myocardial infarction (post-MI) patients. * $P < 0.01$ when comparing control subjects versus post-MI patients. (Reproduced with permission from the American Heart Association from [103].)

episodes of oxygen desaturation in association with sinus tachycardia, ventricular premature beats, and ST-segment changes [187,188]. Abnormal oxygen saturation and ventricular tachycardia during sleep are common in patients with impaired left ventricular function [189–192] and in acute post-myocardial infarction patients [187] (Fig. 12). Lack of sleep staging in these studies leaves it inferential that the REM phase is of particular significance. However, Broughton and Baron [174] found that nocturnal angina among post-myocardial infarction patients occurred mainly during slow wave sleep and led to awakening. It was postulated that the hypotension associated with this phase of sleep resulted in a diminution in perfusion pressure in the mechanically compromised myocardium. Decreases in perfusion pressure supplying collateral vessels may also play a role. Thus, during the acute phase of myocardial infarction, nocturnal ischemic attacks may be more common during slow wave sleep, when they result from hypotension, which may exacerbate ischemia by reducing coronary perfusion pressure, and by a reflex increase in sympathetic activity.

The changes in autonomic nervous system activity are crucial in the post-myocardial infarction period. Depression of heart rate variability or baroreceptor sensitivity, markers of vagal influences on the heart, have been correlated with post-myocardial infarction risk for mortality [193,194]. These markers are complementary rather than redundant, as heart rate variability is a measure of tonic vagal activity and baroreceptor sensitivity is a measure of

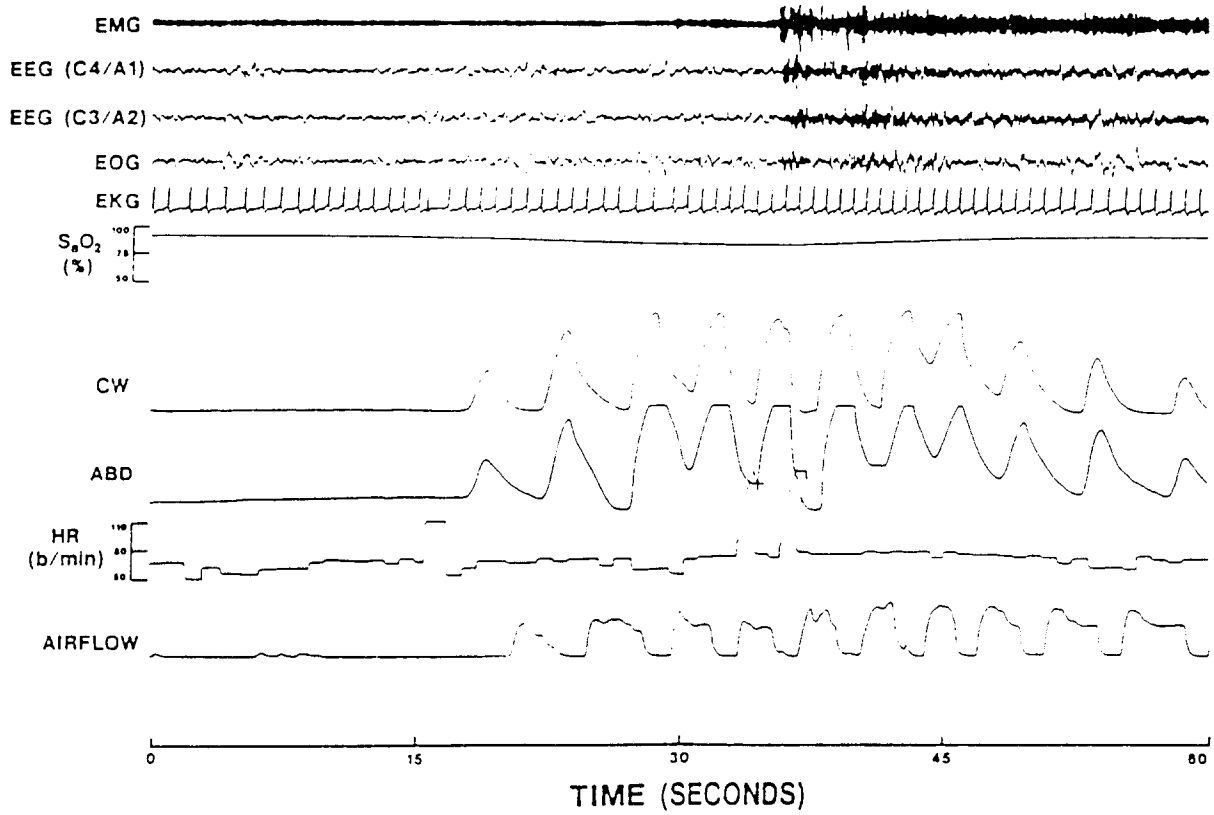

Fig. 14. Tracing of Cheyne-Stokes respiration observed in a patient with heart failure. EMG, electromyogram; EEG, electroencephalogram; EOG, electrooculogram; EKG, electrocardiogram; SaO_2, oxygen saturation; CW, chest wall movement; ABD, abdominal wall movement; HR, heart rate; AIRFLOW, expired carbon dioxide at the nose and mouth. An apneic phase is followed by waxing and waning of chest wall and abdominal wall movement. SaO_2 is lowest at the height of the hyperpneic phase. The arousal manifested by the EEG, EMG, EOG activity is observed at the height of the hyperpneic phase. (Reproduced with permission from the American College of Chest Physicians from [266].)

the capability of this reflex arc to elicit powerful vagal activation with reciprocal suppression of sympathetic nervous system activity. Vanoli and colleagues [103] demonstrated in a recent study using heart rate variability that the acute post-myocardial infarction period is associated with impairment of vagal activation during sleep (Fig. 13). The result was a relative sympathetic dominance, which the authors proposed could be a significant factor in life-threatening arrhythmias.

6.3. Heart failure

Moser and colleagues [134] commented, in view of the high incidence of sleep abnormalities in heart failure patients, that it was surprising that the incidence of sudden death was not higher during the night. Sleep in such patients is highly fragmented, with frequent arousals and stage changes, which may occur at a rate of up to 50 per hour. Stage distribution is also abnormal, with an increased density of stage 1 as opposed to deeper stages of sleep [195]. Breathing during sleep is also markedly disturbed, with the common appearance of Cheyne-Stokes respiration, which can impair cardiac function (Fig. 14). Because polysomnography was not performed in this study, it is impossible to identify the sleep states during which arrhythmic events occurred. However, it is established that high sympathetic tone in heart failure patients is associated with an increased mortality rate [196].

Thus, there is an important need to study the impact of sleep states on cardiac electrical function in patients with heart failure. Investigation of this issue is particularly attractive in light of recent evidence which suggests that noninvasive assessment of QT dispersion is an indicator for arrhythmic events in patients with heart failure [197]. This concept is further underscored by the provocative findings of Smith [198], who discovered that with progressive heart failure, patients experienced dreams of death and separation. These dreams set the stage for significant negative affective states such as depression and loss of will to survive. Finally, it would be worthwhile to determine whether the use of benzodiazepines might exert a beneficial effect on cardiac electrical stability by interrupting a deleterious feedback loop between the brain and the heart. These agents have been reported to improve total sleep time and quality in patients with congestive heart failure without compromising mechanical function [199].

6.4. Apnea, chronic obstructive lung disease, and snoring

Harper and colleagues have emphasized that an important homeostatic aspect of sleep is maintenance of control over two fundamentally different types of musculature

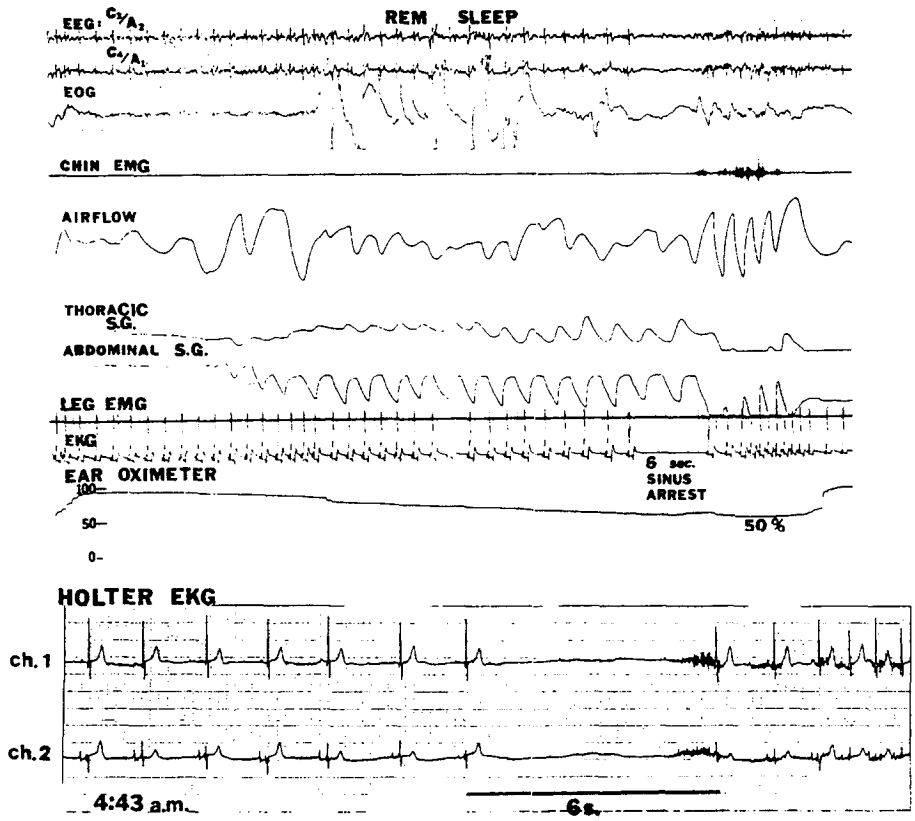

Fig. 15. Simultaneous segments of a polygraphic recording and Holter recording obtained from a patient with obstructive sleep apnea syndrome during REM sleep. Note the progressive bradycardia, sinus arrest, and tachycardia when respiration resumed secondary to arousal from sleep. (Reproduced from American College of Cardiology from [146].)

[111]. One is somatic and is responsible for oxygen exchange; the other is autonomic, involving the heart and vasculature and is responsible for blood transport. A significant breakdown in the regulation of either or both systems can lead to malperfusion of the myocardium, resulting in myocardial infarction and/or sudden death. Whereas considerable attention has been focussed on the mechanisms whereby sleep can disrupt myocardial perfusion and electrophysiologic function, the more subtle and insidious potential role played by derangements in respiratory function — from snoring to apnea and chronic obstructive lung disease — is less well appreciated.

At the most serious end of the sleep–breathing-disorder spectrum is obstructive apnea, which can be treated with continuous positive airway pressure (CPAP), tracheostomy [200,201], or reduction of body weight to a more normal range [202]. The sleep apnea syndrome, which can be due either to airway obstruction or to derangement in central nervous system control of respiration [146], is estimated to affect at least 1% of adults.

Sleep apneic attacks have been shown to be highly conducive to nocturnal ischemia, bradyarrhythmias and tachyarrhythmias in patients with coronary artery disease [146,203–211]. In 6 apneic subjects, 5 of whom had coronary artery disease, Koehler et al. [208] found that 83.5% of the 85 recorded episodes of nocturnal ischemia were precipitated during REM sleep, when apnea activity was high and hypoxemia was cumulative. Severe, chronic oxygen desaturation (to less than 65%) due to apnea is highly conducive to ventricular ectopy [206] and tachycardias [146,203–211]. Shepard postulated that the low ebb of oxygen saturation toward the end of the apneic episode results in a massive surge in sympathetic activity which can trigger ventricular ectopic activity and tachyarrhythmias [207] (Fig. 15). However, apnea does not trigger arrhythmia in patients without serious cardiac or respiratory comorbidity, as Flemons et al. [211] demonstrated in a group of 173 arrhythmia patients.

Sleep apnea has also been strongly implicated in the occurrence of myocardial infarction. Hung and coworkers [210] showed that among patients in the highest quartile of apnea severity, the risk of myocardial infarction was 23.3 times that of patients in the lowest quartile ($P < 0.001$). The precise mechanisms for this relationship remain unknown. Among the major possibilities are reduced myocardial oxygen supply due to bradycardia and asystole and to impaired respiration [209,210]. Vagal–sympathetic interactions during the course of an apneic episode are sometimes expressed in patients as a bradycardia–tachycardia sequence [207]. The bradycardia or asystole may be associated with increases in the QT-interval which have the potential to predispose to serious ventricular arrhythmias such as Torsade de Pointes, particularly if the bradycardia is terminated by a ventricular premature beat [212].

The risk of cardiovascular death is increased by 33% across 8 years when frequency exceeds 20 apneas per hour [213]. Death following a prolonged apnea has been witnessed [214]. While the precise time of death was not identified by Thorpy et al. [215] in their study of 269 apnea patients, 50% of the 43 deaths occurred between midnight and 8 o'clock A.M. Apnea may also have predisposed to lethal daytime events, as 71% of the total deaths were due to cardiovascular causes. Thus, death in apnea patients is predominantly of cardiovascular origin and tends to occur during sleep.

Less studied but at parallel risk are patients with chronic obstructive lung disease [216,217], in whom nocturnal oxygen desaturation is of sufficient magnitude to be arrhythmogenic. The specific findings include ST-segment and T-wave changes, prolonged QT interval, and increased ventricular premature beats at night over daytime.

Increased risk of angina, ischemic heart disease, and sudden death has been attributed to snoring. Koskenvuo and colleagues [218] in a postal questionnaire study of 3847 Finnish men and 3664 women, aged 40 to 69, found a significant association between angina pectoris and habitual snoring in men but not women. This risk did not extend to myocardial infarction. A followup study revealed an association between snoring and ischemic heart disease (risk ratio = 1.71, $P < 0.05$), even after adjustment for age, body mass index, hypertension, smoking, and alcohol use [219]. The relationship between snoring history and occurrence of sudden death was analyzed in 460 consecutive cases of Finnish men, aged 35 to 76 years [220]. It was found that the incidence of cardiovascular death was significantly greater ($P < 0.05$) among those who snored habitually or often, that a greater proportion of habitual snorers died during sleep ($P < 0.05$), and that snoring was a risk factor for sudden death between 4 o'clock A.M. and noon among those dying of cardiovascular causes ($P < 0.01$). Parallel observations have been made in other populations [221]. Snoring has the potential of establishing a positive feedback loop of enhanced autonomic discharge to the heart during sleep, as there is evidence that this condition, especially when accompanied by respiratory pauses, can promote anxiety dreams [222]. These findings are of particular significance because 20% of the adult population snores, including approximately 50% of 50-year-old males [219].

Collectively, this information underscores the importance of assuring that the cardiac patient is not experiencing respiratory distress during sleep due either to snoring or apnea. Because excessive alcohol is an important predisposing factor to both snoring and apnea, it may be useful to monitor patients on a night following their typical consumption of alcohol. Nicotine has also been observed to predispose to sleep apnea [223].

6.5. Nocturnal asystole

Our experimental studies demonstrating the occurrence of pauses in heart rhythm due to bursts of vagus nerve

activity [114] may carry important implications for diagnosing and treating neurogenically induced ischemia and arrhythmias during slow wave sleep. Bradycardias and asystoles of up to 9-seconds duration can occur during sleep in otherwise healthy young adults [124]. In patients with cardiac disease, nocturnal asystolic events could set the stage for arrhythmias, as abrupt changes in cycle length are conducive to early and late afterdepolarizations [224]. This phenomenon may also be germane to a subset of patients with the long QT syndrome, whose syncopal episodes occur almost exclusively either at rest or, more frequently, during sleep, when the QT-interval is further prolonged [143]. Within this subset, most patients appear to have the cardiac sodium channel gene SCNSA linked to chromosome 3 [225]. Another intriguing possibility is that sleep-induced pauses may initiate severe ventricular arrhythmias in individuals sensitized by antiarrhythmic drugs with Class III action, which have the potential to induce Torsade de Pointes. Accordingly, we propose that vagally mediated pauses associated with transition from slow wave to desynchronized sleep as described in our experimental studies [114] could predispose to early and late afterdepolarizations and Torsade de Pointes. In patients with damaged endothelium, vagal surges could result in vasoconstriction due to impaired release of endothelium-derived relaxing factor. This is an important topic for further exploration, as it remains to be determined whether acetylcholine released from the vagus nerve will elicit coronary constriction as it does when this substance is administered through the intracoronary route [126].

7. Dreams and sudden death

The belief that dreams can cause sudden cardiac demise is imbedded in folklore and medical history. This stems from the common experience of being awakened by vivid, frightening dreams, with racing pulse, cold sweat, and other physiologic responses associated with intense distress. MacWilliam [2] documented "extensive rises in blood pressure during sleep, increased heart action, changes in respiration, and various reflex effects" which exhibit a "suddenness of development." These pioneering insights have been bolstered by substantial evidence of heightened autonomic activity associated with dreams [98].

The impact of dreaming on the heart is most dramatic during night terrors and nightmares. In the former case, there is a partial arousal in panic from stages III and IV of slow wave sleep, with marked tachycardia and tachypnea without recall of dreaming [226]. Nightmares can be precipitated during slow wave sleep, when they are characterized by pure fear without visual hallucination, or REM sleep, when vivid and frightening dreams have been reported. It has been postulated that the autonomic surges are due to a failure to synchronize the activation and deactivation of sensory autonomic and motor systems during the transitions between slow wave and REM sleep.

How strong is the evidence linking dreams to sudden death and myocardial infarction? Notwithstanding this presumptive evidence that dreams result in intense activation of the sympathetic nervous system, definitive proof that this brain state can trigger these events has been elusive. This no doubt results from the dual problems of establishing the occurrence of a dream state and witnessing the cardiac event. The overall case implicating dreams as a cause of sudden death or infarction rests on several lines of circumstantial evidence. These include the findings that REM sleep, when most vivid dreams occur, is a potent inducer of ischemic attacks in patients with classical and Prinzmetal's angina [120,148,160,163] and the observation that REM may precipitate ventricular ectopic activity and tachycardias [154].

Ventricular tachycardia or fibrillation has been reported in association with violent or frightening dreams. Lown and coworkers performed a detailed sleep study in a patient with recurring ventricular fibrillation in the absence of coronary heart disease [227]. While being monitored during sleep in a coronary care unit, the patient developed ventricular fibrillation at 4 o'clock A.M. When the patient was interviewed, he recalled dreams with emotionally charged content. During subsequent sleep recording sessions, it was observed that high grade ventricular arrhythmias occurred at the same time of night during REM sleep.

7.1. Night terrors

The most striking association between dreaming and sudden death has been observed in Southeast Asians, in whom there is a high incidence of sudden, unexplained nocturnal deaths in young (age 25–44), apparently healthy males [228–236]. These deaths are named "Lai-tai" ("sleep death") in Laos, "Pokkuri" ("sudden and unexpected death") in Japan, "Bangungut" ("to rise and moan in sleep") in the Philippines and "sudden unexpected nocturnal death (SUNDS)" in the United States, where the phenomenon occurs among immigrants.

Death is unexpected, as the victims are in apparent good health. Absence of cardiovascular disease in this syndrome has been established in a number of cases at autopsy. The immediate symptoms are onset of agonal respirations during sleep. Case reports provide varying suggestions of the pathophysiologic basis [232,234]. Some victims were revived by vigorous massage and then reported sensations of airway obstruction, chest discomfort or pressure, and numb and weak limbs. These symptoms recurred within weeks to months and culminated in death [232]. While this presentation does not suggest ventricular fibrillation, case reports were provided by Otto et al. [234], of three victims who were resuscitated from ventricular fibrillation and who experienced recurring fibrillation in

hospital during sleep accompanied by similar moaning vocalizations. In these three patients, there was no evidence of atherosclerosis or structural abnormalities and no sleep apnea, but creatine kinase levels were markedly elevated and potassium depressed. Autopsies suggest that some SUNDS deaths may be associated with developmentally abnormal conduction system pathways [228,230].

The terminal events surrounding these deaths suggest that the victims suffered from night terrors, a sleep disorder which occurs during stages 3 and 4 of slow wave sleep and is characterized by vocalization, violent motor activity, nonarousability, rapid irregular deep breathing, perspiration, and severe autonomic discharge [99,228,237]. Heart rates may reach 160 to 170 beats/min within 15 to 45 seconds of onset of a night terror. There is marked sympathetic discharge as evidenced by pupillary mydriasis and decreased Galvanic skin resistance. Patients awakened from night terrors report nightmares sometimes linked to traumatic experiences [238]. In these individuals, slow wave sleep may be associated with risk of cardiac death because of the potent centrally mediated sympathetic activation and parasympathetic deactivation due to the emotional content of night terrors. This is a variation on the usual autonomic pattern of slow wave sleep, which results in decreased sympathetic activity and increased parasympathetic activity. A psychological component of SUNDS cannot be ruled out, due to the stress of daily life as a refugee or immigrant [228,229,235,236,239,240].

SUNDS may have a dietary basis, as the incidence of this syndrome declines with immigration and altered diet [233,239]. It has been proposed that low thiamine levels [241] or hypokalemia [242] may be predisposing factors. Typical diets of poor Asians include raw, dried, and fermented fish, which contains potent anti-thiamine compounds. In a study of over 100 Laotian refugees in Thailand, the QT interval was found to be prolonged, a symptom associated in individuals at risk for SUNDS with poor thiamine status and a history of seizure-like episodes in sleep [233]. Nimmannit et al. [242] have reported that hypokalemia is related to the diet of sticky rice in the Laotian–Thai plateau. Hypokalemia is associated with lethal arrhythmias and respiratory failure at night, due to sleep-associated dip in potassium levels. Hypokalemic periodic paralysis "attacks" show similarities to SUNDS, with sudden nocturnal onset, muscle weakness, respiratory failure, and potential for death [242]. While SUNDS occurs at a high rate in culturally and genetically distinct groups [232], the phenomenon cannot be viewed as a result of inbreeding, which is severely restricted, even to the third generation [243]. Whereas this syndrome is clearly different from nocturnal sudden death due to ischemic heart disease, it underscores the concept that in a predisposed myocardial substrate, the massive surges in sympathetic activity which occur during intense dreams are potentially capable of triggering life-threatening arrhythmias.

8. Clinical importance of arousal from sleep

A high incidence of ischemic events [133] and arrhythmias [153] is associated with arousal from sleep. It appears that a contributing factor to these events is an increase in platelet aggregability that results from assumption of the upright posture [128,244,245]. There is evidence that cardiac electrical stability can be disrupted during rapid transitions from sleep to wakefulness. Wellens and coworkers [246] reported the case of a 14-year-old female who experienced repeated episodes of life-threatening ventricular tachyarrhythmias when awakened from sleep by a loud auditory stimulus (Fig. 16). The trigger mechanism appeared to be a surge in adrenergic activity, because the syncopal episodes could be prevented by propranolol therapy.

Somers and coworkers [102] have recently provided insights into the potential mechanisms whereby arousal from sleep can result in life-threatening arrhythmias. They

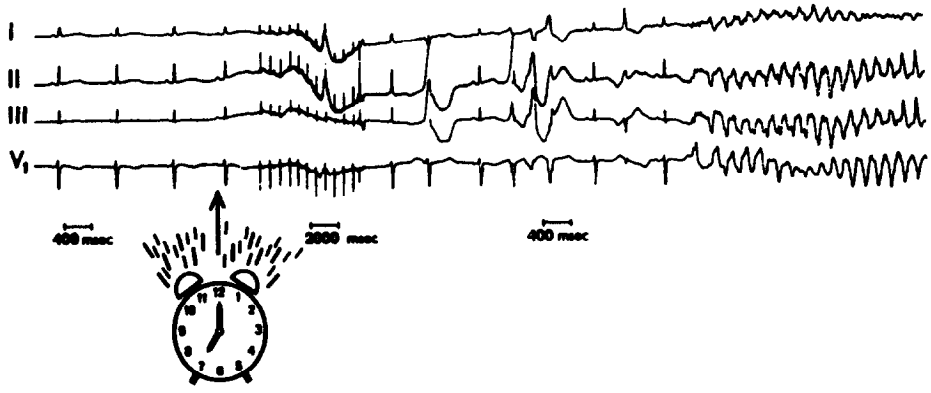

Fig. 16. Initiation of ventricular fibrillation following an auditory stimulus (alarm clock). QT-segment changes are followed by ventricular premature beats and ventricular fibrillation. The middle of the record is taken at slower speed than the beginning and end. (Reproduced with permission from the American Heart Association from [246].)

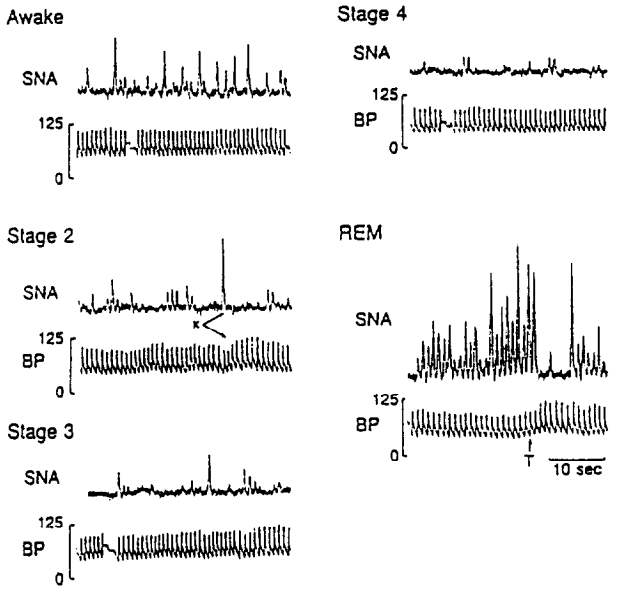

Fig. 17. Recordings of sympathetic nerve activity (SNA) and mean blood pressure (BP) in a single subject while awake and while in slow wave sleep stages 2, 3, 4, and REM sleep. As slow wave sleep deepens (stages 2 through 4), sympathetic nerve activity gradually decreases and blood pressure (mmHg) and variability in blood pressure 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 slow wave sleep, heart rate, blood pressure, and blood pressure variability increased during REM sleep, together with a profound increase in both the frequency and the amplitude of sympathetic nerve activity. 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 blood pressure. (Reproduced with permission from Massachusetts Medical Society from [102].)

measured sympathetic nerve activity using peroneal microneurography in normal subjects undergoing simultaneous polysomnography. They found that arousal stimuli from stage 2 sleep elicited high-amplitude deflections in the electroencephalogram (K complexes), which were frequently associated with bursts of sympathetic activity and transient increases in arterial blood pressure. Interestingly, similar stimuli during wakefulness did not elicit an increase in sympathetic firing rate. It was suggested that the response during sleep is a consequence of central processing of auditory and other arousal stimuli. The postulated adaptive value is to counter hypotension during slow wave sleep by increasing blood pressure to permit adequate cerebral and cardiac perfusion required for the postural changes in preparation to meet a potential confrontation (Fig. 17).

9. New tools for studying neurocardiac interactions during sleep

The impact of sleep states and dreaming on cardiac electrical stability has escaped careful definition, partly because of the melding of complex methodologies from the fields of cardiac electrophysiology and behavioral neurophysiology required to address these issues. While the occurrence of nocturnal ischemic events and arrhythmias is gaining attention, the absence of sleep staging hampers analysis of the results of these studies and limits the amount of information available for possible treatment decisions.

Recent developments provide practical solutions. In terms of predicting risk of sudden cardiac death, substantial evidence has been amassed which indicates that T-wave alternans, a beat-to-beat fluctuation in T-wave area, may provide a noninvasive means for assessing cardiac electrical instability [46] (Fig. 18). In our experimental studies in canines it has been shown that quantification of the magnitude of alternans by spectral analytical techniques is capable of predicting onset of ventricular tachycardia and fibrillation under diverse conditions of myocardial ischemia, reperfusion, autonomic stimulation and blockade, and behavioral stress [48]. In angioplasty patients, T-wave alternans magnitude tracked the timecourse of vulnerability during coronary artery occlusion and reperfusion [46]. The data were obtained during spontaneous rhythm, obviating the need for fixed rate pacing. In a few Holter recording studies in patients with Prinzmetal's angina [247,248] and the long QT syndrome [249], the presence of alternans provided a measure of susceptibility to lethal ventricular tachyarrhythmias. Rosenbaum and colleagues [250] have shown that T-wave alternans is equivalent to

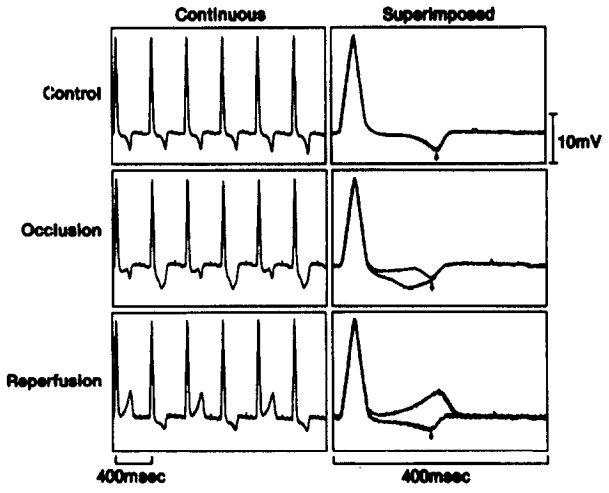

Fig. 18. ECG recorded within the left ventricle before, during, and after coronary artery occlusion in a single representative animal. The pattern shown was observed in all animals studied. Right panels show superimposition of six successive beats. Before occlusion (top), the T waves of each succeeding beat were uniform (arrowhead designates apex of T wave). After 4 min of coronary artery occlusion (middle), there was marked alternation of the first half of the T wave, coinciding with the vulnerable period of the cardiac cycle. The second half of the T wave remained uniform. After release of the occlusion (below), alternans was bidirectional, with T waves alternately inscribed above and below the isoelectric line. (Reproduced with permission from the American Association for the Advancement of Science from [47].)

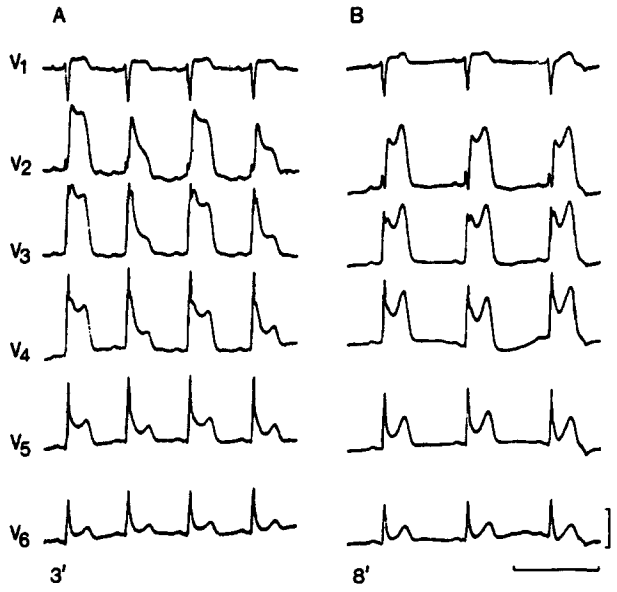

Fig. 19. Alternation in precordial leads V_2 to V_5 3 min after onset of nocturnal angina (A). In B, recorded 8 min after beginning of pain, alternation has disappeared. (Reprinted with permission from the American College of Chest Physicians from [267].)

electrophysiologic testing in predicting arrhythmia-free survival. Fortuitous monitoring of nocturnal angina has provided two illustrations from the literature of T-wave alternans in patients with established electrical instability (Figs. 19 and 20). Thus, a noninvasive marker for tracking cardiac vulnerability is available and is amenable to Holter monitoring during sleep [9]. Another promising noninvasive electrocardiographic technique for monitoring cardiac vulnerability, which has been tested in several laboratories, could be employed, such as QT-interval dispersion [12,197,251–253].

Such noninvasive electrocardiographic techniques for assessing risk of sudden death could be combined with new, at-home sleep monitoring systems, such as the analogue Oxford Medilog or digital Vitalog system or the simpler "Nightcap", which uses eyelid and body movement sensors to discriminate wake, slow wave, and REM sleep automatically [6,254]. The Nightcap's algorithms predicted the results of handscoring of sleep records with a percent agreement of $85.6 \pm 1.7\%$. The eyelid movement component of the device is particularly sensitive to the flurries of REM with which autonomic activity is typically associated.

Two general types of studies would be required to establish the potential diagnostic value of sleep as an autonomic stress test. The first would be to establish normative, age-matched control data for the main parameters of interest. These could include measurements of heart rate variability dynamics including Poincaré plots along with indices of cardiac electrical instability including QT-dispersion and T-wave alternans. In order to obtain these data, subjects would be monitored across 24 h. Nighttime records would include information from an ambulatory sleep device synchronized to the ECG recorder. The computerized analysis of cardiovascular variables could then be compared to the distribution of each of these parameters of interest. The second type of study would be to obtain followup data on high-risk patients in order to establish whether the results of the sleep stress test can predict cardiovascular events including arrhythmia-free survival, myocardial infarction, and sudden death. These studies would establish sensitivity and specificity of the sleep stress test at several predetermined cut-points defining abnormal test results. For T-wave alternans analysis, there is a precedent in the investigations by Estes, Cohen, and coworkers who showed that the presence of alternans during the exercise phase of an exercise stress test was significantly associated with vulnerability to ventricular arrhythmias. Alternans at rest was not predictive. However, the sensitivity of the exercise phase was improved by incorporating the alternans data from the resting state

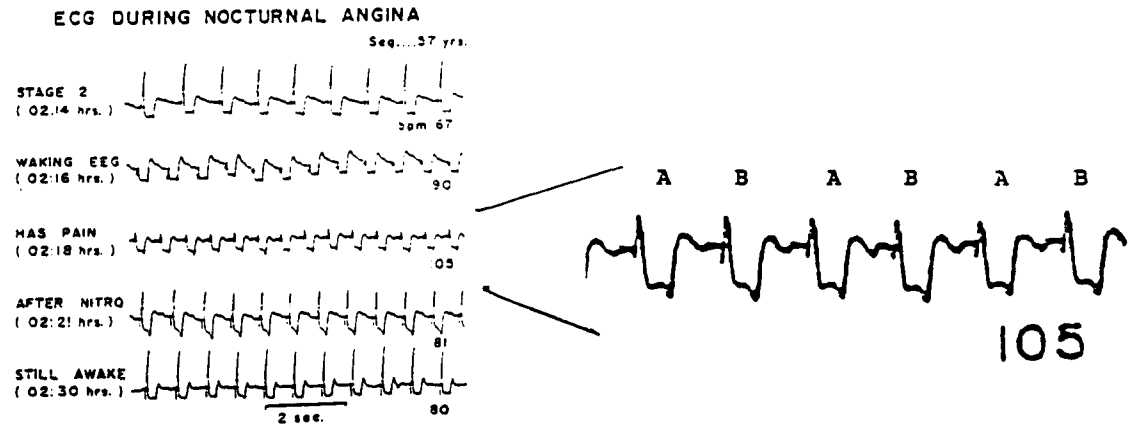

Fig. 20. ECG (precordial to posterior chest wall) showing amplitude decrease during nocturnal angina. The ECG exhibited ST changes and amplitude decrease before awakening (not shown), although the patient did not complain of chest pain until 2 min after the arousal. Note the presence of ST-segment alternans during pain. Nitroglycerin resulted in rapid return towards pre-anginal ECG patterns. (Reprinted with permission from Elsevier/North Holland Scientific Publishers, Ltd., from [174].) In experimental animals nitroglycerin has also been shown to suppress ischemia-induced T-wave alternans [268].

[254]. Similarly, a sleep test, by incorporating both rest and the challenge of autonomic activation associated with changes in sleep state, could detect latent cardiac electrical instability in patients at risk for life-threatening arrhythmias.

More important than the details of the test is the concept that new tools for assessing sleep state at home can be applied simultaneously with noninvasive measures of autonomic function and cardiac vulnerability. Thus, the stage is set for making major inroads in understanding the effect of sleep state on cardiac vulnerability both from a scientific perspective and for advances in diagnosis and therapy.

10. Final comments: the case for sleep as an autonomic stress test for the heart

The literature reviewed points to a functional resemblance between sleep and its apparent antithesis, exercise. Both activities involve motor programs of the central nervous system, and the appropriate central autonomic patterns are activated. Both operations exert a salutary influence on coronary hemodynamic and cardiac electrophysiologic function but are capable of precipitating catastrophic events. Slow wave sleep and exercise conditioning increase cardiac electrical stability by augmenting vagal tone and baroreceptor sensitivity. In contrast, the surges in sympathetic activity and reduction in baroreceptor sensitivity associated with REM sleep and severe exertion during wakefulness may disrupt plaques, precipitate myocardial ischemia, and trigger ventricular tachyarrhythmias. There is an important interaction between the circulatory and respiratory systems in sleep and exercise. The autonomic challenges may be more likely to provoke ischemia, infarction, and arrhythmic death when ventilatory function is impeded by respiratory disease. In the case of sleep, the ventilatory malfunction may take the form of apnea, and during exercise, smoking-induced pulmonary disease may compromise respiratory capacity.

The use of sleep as an autonomic stress test for the heart could prove helpful in identifying individuals at risk for sudden cardiac death. It is proposed that simultaneous assessment of autonomic function using heart rate variability and baroreceptor sensitivity [12,193,194] measures, in conjunction with indicators of abnormal repolarization, in the form of T-wave alternans [46–49] and QT dispersion [251–253], holds considerable promise in this regard. The recent development of a convenient home monitoring system for sleep staging could aid precise identification of the neural and cardiac electrophysiologic mechanisms of arrhythmogenesis during sleep and arousal. The studies reviewed also highlight the relatively unrecognized importance of respiratory derangements, ranging from snoring to apnea, which constitute significant accomplices in nocturnal death and morbidity. There is a strong case for monitoring respiratory parameters and arterial oxygen saturation during sleep in patients at risk for cardiac death. A home oximetry test can effectively rule out (to 3%) the probability of apnea [256].

The potential disruptive effects on sleep pattern of cardiac drugs, such as antihypertensives, beta-blockers which cross the blood–brain barrier, and calcium channel blockers [257] need to be considered. Many pharmacologic agents, including barbiturates, and treatments such as continuous positive airway pressure (CPAP) have the capability of inducing REM deprivation and creating the conditions for a subsequent rebound phenomenon, with intense autonomic activity which could trigger coronary vascular and arrhythmic events. Conversely, the opportunity to prevent cardiac death by improving sleep quality with pharmacologic measures deserves exploration. This concept is supported by the demonstration of a significant beneficial effect of benzodiazepines on sleep quality in heart failure patients who suffer from grossly fragmented sleep [258].

Particular attention should be paid to the 2 o'clock A.M. increase in coronary events and to the last episode of REM before arousal, which is often intense and associated with a marked increase in autonomic discharge. Autonomic surges could stimulate platelet aggregability, disrupt plaques, or precipitate coronary spasm or arrhythmia, which may become manifest only upon arousal and could be inappropriately attributed to events during wakefulness rather than to sleep.

Improved understanding of the circulatory consequences of sleep should lead to a greater appreciation of diurnal variations in drug responsiveness and the need to adjust the therapeutic regimen [78,259–261]. Mancia [78], for example, has suggested that in certain patients with impaired perfusion due to stenotic lesions in the brain or heart, exacerbation of the hypotensive effect of slow wave sleep can constitute a risk for thrombosis and embolism. Floras [261] postulated that the lack of diminution of nocturnal myocardial infarction in patients treated with antihypertensive agents was attributable to an unrecognized increase in nocturnal hypotension. Thus, since antihypertensive and vasodilatory drugs can exacerbate hypotension, there is a rationale for considering their use primarily for daytime.

In summary, the profound autonomic changes which occur during sleep states and transitions exert a significant impact on the cardiovascular system, which can culminate in major cardiovascular events, including myocardial infarction and claims 36 000 lives due to sudden death annually in the United States. Whereas the sheer numbers of events are not as large as those encountered during wakefulness, they are nevertheless of epidemic proportion, amounting to nearly 80% of the number of fatalities due to automobile accidents or 40% more than deaths due to HIV infection. Furthermore, there is an important heuristic corollary that sleep, particularly REM, constitutes an important physiologic challenge or test of the cardiovascular

system. Thus, it is reasonable to exploit the concept that REM sleep provides a diagnostic opportunity to disclose latent cardiac electrical instability, using the new diagnostic noninvasive tools of heart rate variability and T-wave alternans. Though the measurements would be made during sleep, the findings would also be relevant to the awake state. Finally, improved understanding of the impact of sleep on cardiovascular function could result in improved dosing of drugs as indicated by the promising field of chronotherapy.

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