SYMPATHETIC-NERVE ACTIVITY DURING SLEEP IN NORMAL SUBJECTS

VIREND K. SOMERS, M.D., D.PHIL., MARK E. DYKEN, M.D., ALLYN L. MARK, M.D., AND FRANÇOIS M. ABBOUD, M.D.

Abstract *Background.* The early hours of the morning after awakening are associated with an increased frequency of events such as myocardial infarction and ischemic stroke. The triggering mechanisms for these events are not clear. We investigated whether autonomic changes occurring during sleep, particularly rapid-eye-movement (REM) sleep, contribute to the initiation of such events.

Methods. We measured blood pressure, heart rate, and sympathetic-nerve activity (using microneurography, which provides direct measurements of efferent sympathetic-nerve activity related to muscle blood vessels) in eight normal subjects while they were awake and while in the five stages of sleep.

Results. The mean (±SE) amplitude of bursts of sympathetic-nerve activity and levels of blood pressure and heart rate declined significantly ($P<0.001$), from 100±9 percent, 90±4 mm Hg, and 64±2 beats per minute, respectively, during wakefulness to 41±9 percent, 80±4 mm Hg, and 59±2 beats per minute, respectively, during stage 4 of non-REM sleep. Arousal stimuli during stage 2 sleep elicited high-amplitude deflections on the electroencephalogram (called "K complexes"), which were frequently associated with bursts of sympathetic-nerve activity and transient increases in blood pressure. During REM sleep, sympathetic-nerve activity increased significantly (to 215±11 percent; $P<0.001$) and the blood pressure and heart rate returned to levels similar to those during wakefulness. Momentary restorations of muscle tone during REM sleep (REM twitches) were associated with cessation of sympathetic-nerve discharge and surges in blood pressure.

Conclusions. REM sleep is associated with profound sympathetic activation in normal subjects, possibly linked to changes in muscle tone. The hemodynamic and sympathetic changes during REM sleep could play a part in triggering ischemic events in patients with vascular disease. (N Engl J Med 1993;328:303-7.)

THE early morning hours after awakening (approximately 6 to 11 a.m.) are associated with a higher-than-expected incidence of cardiovascular events, such as myocardial infarction and ischemic stroke.[1-3] The relation between sleep and these events is not clear. Ischemic events can occur during sleep, especially in patients with severe coronary artery disease[4] and vasospastic angina.[5] REM, or rapid-eye-movement, sleep is especially associated with myocardial ischemia.[4,5] In animals with coronary-artery stenosis, REM sleep causes further decreases in coronary-artery blood flow,[6] possibly due to sympathetic activation during this sleep stage. Surprisingly, although there have been extensive investigations in animals, there have been few studies of autonomic control of the circulation during sleep in humans.[7,8] Microneurography allows direct recording of peripheral sympathetic-nerve traffic to the skeletal-muscle vascular bed.[9,10] We therefore studied sympathetic-nerve activity and hemodynamic changes occurring during the different stages of sleep in normal subjects.

METHODS

We studied 14 normal subjects (10 men and 4 women) after obtaining their informed written consent. These studies were approved by our institution's committee on experimentation in human subjects.

We obtained technically excellent recordings of sympathetic-nerve activity during quiet wakefulness and non-REM sleep (stages 1 through 4) in eight subjects (seven men and one woman, whose mean [±SD] age was 25±5 years). Sympathetic-nerve activity was also recorded during REM sleep in six of these eight subjects. We were unable to measure nerve activity in two of the remaining six subjects. In three subjects, electrodes were shifted repeatedly, with loss of nerve recording, while the subjects were awake or in stage 1 or early stage 2 sleep; studies were therefore abandoned in these subjects. One additional subject was excluded from the analysis because inadequate time markings on separate microneurographic and polysomnographic records precluded precise synchronization of the microneurographic with the polysomnographic recordings.

We obtained direct multiunit (involving multiple nerve fibers) intraneural recordings of efferent sympathetic-nerve activity involving muscle blood vessels, using tungsten microelectrodes (shaft diameter, 200 μm; tip length, 1 to 5 μm). One electrode was inserted into the sympathetic-nerve fascicles of the peroneal nerve posterior to the fibular head (for microneurographic recording).[9,10] A reference electrode was inserted subcutaneously about 3 cm away. The neural electrical signals were amplified, filtered, rectified, and integrated to produce a display of sympathetic-nerve activity at a mean voltage.

Sympathetic bursts were identified by inspecting the mean-voltage neurogram, and sympathetic activity was calculated by counting the number of bursts per minute, as well as by measuring the total amplitude of the burst per minute, which is expressed in arbitrary units.[9] In the present study, burst amplitude is expressed as a percentage of the activity during wakefulness.

For measurements of sympathetic-nerve activity, the data were normalized so that the mean value recorded during wakefulness was 100 percent. The mean of the absolute values for sympathetic-nerve activity during three four-minute segments of wakefulness was used as a denominator for all measures of sympathetic activity (including the wakefulness segments), thus expressing all measures of nerve activity within each subject as a percentage of average values recorded during wakefulness. In comparisons of multiunit nerve recordings in subjects, when differences between subjects in gain can greatly affect absolute values for nerve activity, this percentage is a more appropriate measure of changes in nerve activity.

The heart rate was measured by electrocardiography, and blood pressure by the FINAPRES (FINger Arterial PRESsure) system, allowing continuous indirect, noninvasive measurements of beat-by-beat blood pressure.[11] FINAPRES measurements of blood pressure correspond closely to intraarterial measurements, both at rest and during physiologic rapid changes in blood pressure[12]; we did not compare these two types of measurements, and we therefore cannot confirm the accuracy of FINAPRES measurements of abso-

From the Department of Medicine, the Department of Physiology and Biophysics, and the Cardiovascular Center (V.K.S., A.L.M., F.M.A.) and the Department of Neurology (M.E.D.), University of Iowa College of Medicine, Iowa City. Address reprint requests to Dr. Somers at the Department of Internal Medicine, College of Medicine, University of Iowa, Iowa City, IA 52242.

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lute levels of blood pressure in our study group. Each subject was fitted with a FINAPRES cuff appropriate for the size of the finger tested. The FINAPRES system was switched off for 5 to 10 minutes approximately every 2 hours, for the subject's comfort. Blood-pressure measurements obtained before and after temporary cessation of FINAPRES recording were similar. To ensure consistency among these recordings, the position of the recording arm was fixed with the aid of sandbags and an arm board. Complete polysomnographic monitoring was carried out, including measurements of oxygen saturation, air flow, and chest movement and electromyography, electroencephalography, and electro-oculography. All variables were measured continuously.

The stages of sleep were scored according to the recommendations of Rechtstaffen and Kales.[13] In brief, the stages of sleep have been characterized electroencephalographically as slow-wave (non-REM) sleep or desynchronized (REM) sleep.[14-16] Non-REM sleep consists of stages 1 to 4, characterized by a progressively slower frequency and increased voltage activity on the electroencephalogram; these changes correspond to progressive increases in the depth of sleep. Muscle relaxation occurs, with preservation of muscle tone. REM sleep is characterized by sudden, low voltage and fast activity on the electroencephalogram, which are associated with loss of muscle tone. Slow, rolling eye movements occur during this phase, with intermittent discrete episodes of rapid eye movement. REM sleep is associated with irregular respiration and increases in blood pressure and heart rate, and is the stage of sleep when dreaming is likely to occur.[14-16]

Because of the extended periods of sleep recordings in each subject (averaging approximately five hours per subject), all data were initially visually analyzed to establish trends or associations between autonomic, hemodynamic, and polysomnographic findings (qualitative analysis). Representative four-minute periods of wakefulness, stage 2 sleep, stage 4 sleep, and REM sleep were examined by quantitative analysis. Three randomly selected four-minute segments were analyzed from each of these stages. In one subject, only two 4-minute segments from the REM stage could be analyzed, because this stage persisted for only 10 minutes. For each subject, the longest duration of continuous recording of REM sleep obtained during this study ranged from 10 to 23 minutes (mean [±SE], 17.7±2.0). Only two-minute periods of stage 2 and stage 3 sleep were analyzed because of the relatively short duration of these transitional stages.

Initial studies indicated that non-REM sleep (especially stage 4 sleep) was associated with reductions in blood pressure, as well as in heart rate and sympathetic-nerve activity. This was surprising, since baroreceptor-reflex mechanisms would be expected to counter the fall in the blood pressure by increasing the heart rate and sympathetic-nerve discharge. We therefore attempted to simulate the hypotension observed during stage 4 sleep in six subjects (in three of whom sleep recordings were obtained as described above) while they were awake. Hypotension was induced by the infusion of sodium nitroprusside, initially at a rate of 0.5 μg per kilogram of body weight per minute. The rate was increased by 0.5 μg per kilogram per minute every four minutes until the mean blood pressure fell by approximately 15 mm Hg. The blood pressure, heart rate, and sympathetic-nerve activity were measured for three minutes before and during the nitroprusside infusion.

Two-way analysis of variance was used to evaluate two factors, subject and sleep stage, with more than one observation per stage for each subject. Comparisons of interest between the stages were tested by defining contrasts between stage means. These were then tested with the t-test statistic; standard errors for the test were computed from variance estimates derived from the analysis of variance.[17] P values reported are based on a two-tailed test; a P value below 0.05 was assumed to indicate statistical significance. Results are expressed as means ±SE.

Results

Qualitative analysis revealed a decline in heart rate and sympathetic-nerve activity during non-REM sleep, most marked during stage 4, as compared with measurements obtained during quiet wakefulness. Associated with this was a decrease in the level and variability of arterial pressure. During REM sleep, however, there was a marked increase in both the frequency and height of sympathetic bursts (Fig. 1 and 2), associated with intermittent increases in blood pressure (Fig. 1). The increase in sympathetic-nerve activity during REM sleep was more striking during periods of rapid eye movement.

An analysis of consistent associations between polysomnographic and autonomic measurements and hemodynamic measurements showed that during non-REM sleep, arousal stimuli such as a knock on the door frequently elicited K complexes (which are sharp deflections of high amplitude on the electroencephalogram during stage 2 sleep associated with arousal from sleep). These were associated with momentary increases in sympathetic-nerve activity and increases in blood pressure (Fig. 1, stage 2 sleep). No clear association was observed between sleep spindles (which are synchronized waves of frequency between 7 and 14 Hz, occurring during stages 2 and 3 of non-REM sleep) and sympathetic-nerve activity. With momentary restoration of muscle tone during periods of REM sleep (REM twitches), there were often surges in blood pressure and abrupt cessations of sympathetic-nerve discharge (Fig. 1).

The heart rate fell slightly, from 64±2 beats per minute during wakefulness to 59±2 beats per minute during stage 4 sleep ($P<0.001$). During REM sleep, the heart rate was 63±2 beats per minute, similar to the rates recorded during consciousness (Fig. 3). Both systolic and diastolic blood pressure fell during non-REM sleep. The mean blood pressure fell from 90±4 mm Hg during wakefulness to 80±4 mm Hg during stage 4 ($P<0.001$), but averaged 91±4 mm Hg during REM sleep (Fig. 3). The frequency of sympathetic bursts averaged 25±3 per minute during wakefulness, then decreased between stage 1 and stage 4, reaching 13±3 bursts per minute in stage 4 sleep ($P<0.001$) (Fig. 3). During REM sleep, however, burst frequency increased markedly, to 34±3 bursts per minute ($P<0.001$, as compared with wakefulness). Like burst frequency, the amplitude of sympathetic bursts was influenced by sleep stages; the total amplitude fell from 100±9 percent during wakefulness to 41±9 percent during stage 4 ($P<0.001$) and increased to 215±11 percent during REM sleep ($P<0.001$) (Fig. 3). The blood pressure and sympathetic-burst amplitude and frequency (but not the heart rate) were lower in stage 3 and stage 4 sleep than in stage 2 sleep ($P\leq0.005$).

Nitroprusside Studies

Infusion of nitroprusside when the subjects were awake reduced the mean blood pressure and elicited profound increases in sympathetic-nerve activity and heart rate in all subjects. In the three subjects in whom complete sleep recordings were obtained, nitroprusside reduced the mean blood pressure from 85±3 to 78±3 mm Hg and increased the heart rate from 61±7 to 75±7 beats per minute, the sympathetic-burst frequency from 22±2 to 47±7 bursts per minute,

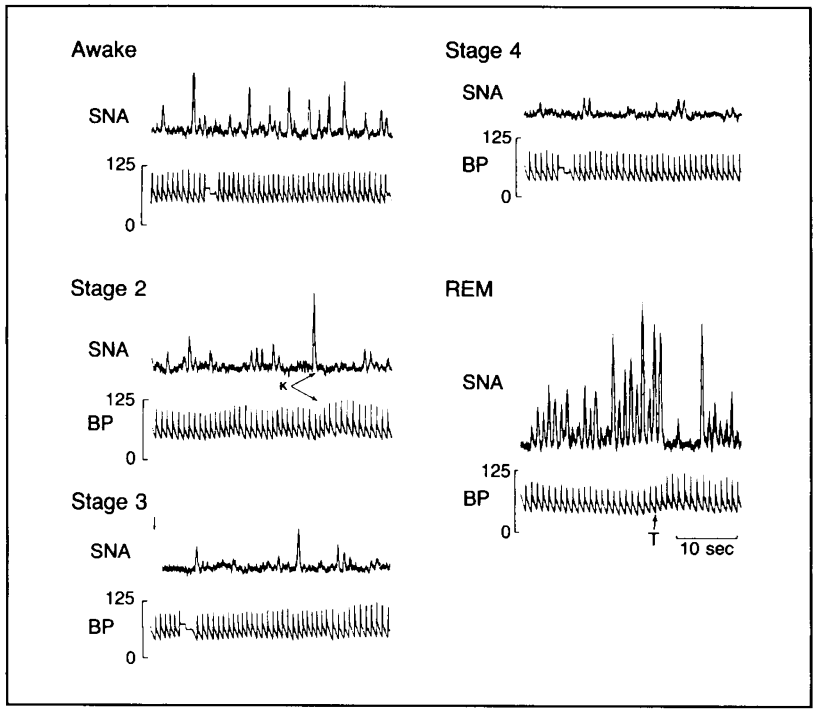

Figure 1. Recordings of Sympathetic-Nerve Activity (SNA) and Mean Blood Pressure (BP) in a Single Subject while Awake and while in Stages 2, 3, 4, and REM Sleep.

As non-REM sleep deepens (stages 2 through 4), sympathetic-nerve activity gradually decreases and blood pressure (measured in millimeters of mercury) 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 non-REM 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.

and the total amplitude to 239±88 percent. In these three subjects stage 4 sleep was associated with a greater fall in the mean blood pressure, from 84±6 to 71±7 mm Hg, than the fall induced by nitroprusside. In contrast, however, during the period from wakefulness to stage 4 sleep, the heart rate decreased from 61±4 to 57±3 beats per minute, the sympathetic-burst frequency from 28±4 to 11±3 bursts per minute, and the total amplitude to 35±14 percent of levels recorded during wakefulness.

Discussion

Our data indicate that sympathetic-nerve activity, blood pressure, and heart rate are lower in normal subjects while they are in deep non-REM sleep than while they are awake. Arousal stimuli during non-REM sleep elicit K complexes, which are accompanied by bursts of sympathetic-nerve activity and transient increases in blood pressure. During REM sleep, sympathetic-nerve activity increases above the levels recorded during wakefulness, and the values for blood pressure and heart rate return to those recorded during wakefulness. Momentary restoration of muscle tone during REM sleep (REM twitch) is frequently

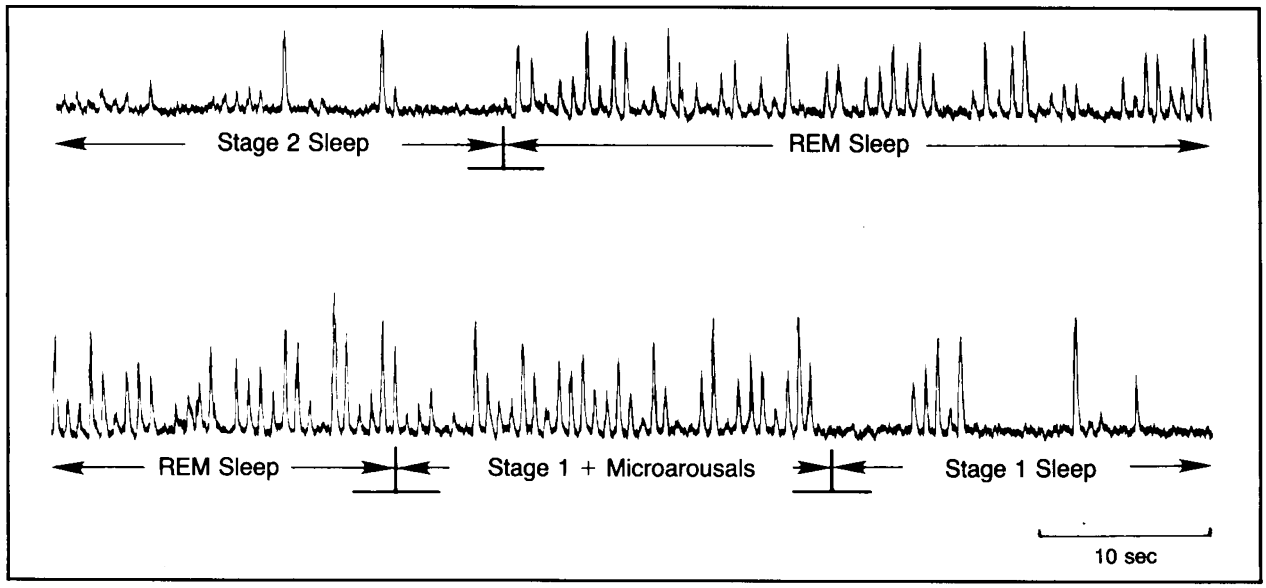

Figure 2. Sympathetic-Nerve Activity during Sleep Stages.

Changes in discharge frequency and amplitude are shown during the transition from stage 2 sleep to REM sleep (upper tracing) and the transition from REM sleep to stage 1 sleep with frequent "microarousals" and then to established stage 1 sleep (lower tracing).

associated with cessation of sympathetic-nerve discharge and increases in blood pressure.

Studies in animals have shown that the mechanisms underlying the fall in blood pressure during non-REM sleep include a reduction in cardiac output and a decrease in total peripheral resistance.[18] During REM sleep, distinct and profound mesenteric and renal vasodilation and skeletal-muscle vasoconstriction occur. Reis et al.[19] demonstrated that vasoconstriction during REM sleep involved only the red, tonic muscles (which are involved in postural support). Interestingly, REM sleep is associated with a complete loss of postural muscle tone. Furthermore, this muscle vasoconstriction appears to depend on an intact sympathetic innervation as well as intact afferent impulses from the skeletal muscles,[20] suggesting that the loss of muscle tone during REM sleep is a disinhibitory (or excitatory) stimulus to sympathetic-nerve activation of muscle, but not mesenteric or renal blood vessels. REM-sleep "twitches," or brief periods of return of muscle tone, induce surges in blood pressure that are due to even greater vasoconstriction of skeletal muscle.[16]

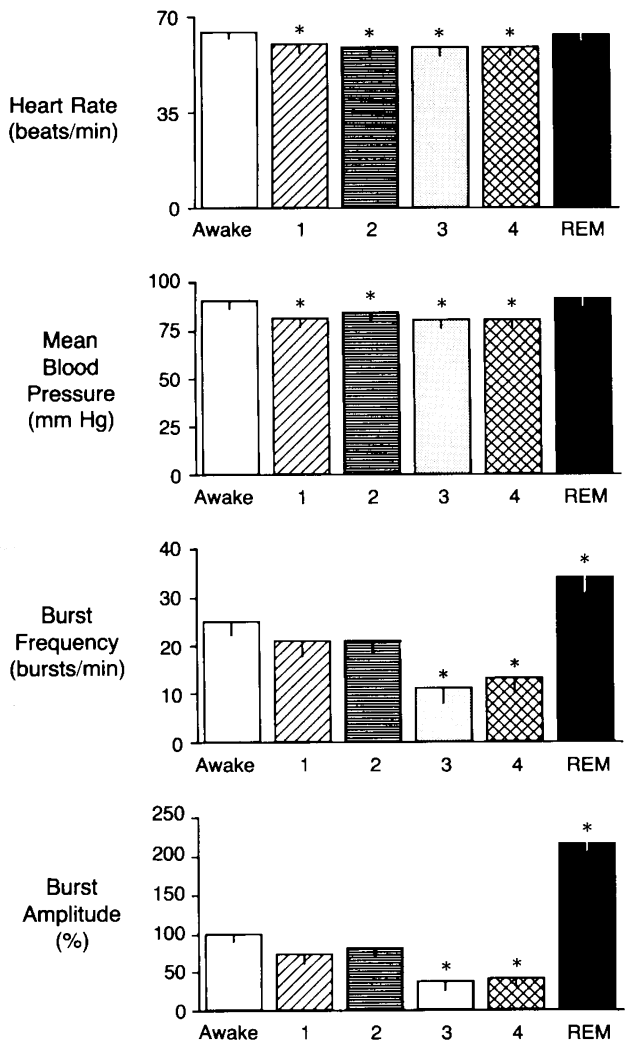

Figure 3. Heart Rate, Mean Blood Pressure, Sympathetic-Burst Frequency, and Burst Amplitude during Wakefulness and Non-REM Sleep (Eight Subjects) and REM Sleep (Six Subjects).

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

Our data provide some mechanistic explanations for the above findings in animals. REM sleep (and loss of muscle tone) triggers marked increases in sympathetic-nerve activity involving muscle blood vessels. REM-sleep twitches result in surges in blood pressure, and despite evidence of increased vasoconstriction in animals, we found a suppression of sympathetic-nerve activity in our subjects. The abrupt cessation of sympathetic activity during the REM-sleep twitches is probably due to the restoration of muscle tone, possibly augmented by baroreceptor-reflex–mediated inhibition of sympathetic activity in response to the increase in blood pressure.

The finding of lower blood pressure, heart rate, and sympathetic-nerve activity during non-REM sleep suggests a dramatic modulation of the baroreceptor reflex during sleep, as reflected by the marked tachycardia and sympathetic excitation, with comparatively milder hypotension during wakefulness (as evidenced by the nitroprusside studies). These data do not indicate whether this modulation involves resetting, a change in sensitivity, or both. Other investigators, however, have shown that baroreceptor-reflex gain increases during sleep.[21,22] Power spectral analysis of simultaneous frequencies of variation of the heart rate and blood pressure supports the notion of such an increase during sleep.[23]

Power spectral analysis of blood pressure and heart rate has also suggested that sleep is associated with increased vagal activation and decreased sympathetic activation.[24,25] By direct measurement of sympathetic activity in sleep-deprived subjects, Hornyak et al.[7] found changes in sympathetic activation during sleep that were qualitatively similar to those in our study. The effects were less pronounced than in our study, possibly because of sleep deprivation, which affects both sleep pattern and blood-pressure regulation during sleep.[26] Furthermore, most of their subjects were studied during daytime sleep, and their values for sympathetic-nerve activity during wakefulness also included data recorded during stage 1 sleep. The duration of REM sleep (2 to 13.5 minutes; mean, 7.4) in their study[7] was substantially less than in ours (10 to 23 minutes; mean, 17.7). Simultaneous recording of blood pressure and sympathetic-nerve activity was obtained during all sleep stages in only two subjects.

More recently, Okada et al.[8] have studied changes in the frequency of sympathetic bursts during sleep stages. It is not known whether their volunteers underwent sleep deprivation. Although blood pressure was measured in some subjects, data were not reported for

the group. There was no apparent increase in nerve activity between wakefulness and REM sleep, perhaps because total nerve activity was not measured, although the authors described qualitative increases in burst amplitude during REM sleep.

The association of arousal stimuli and K complexes with increased sympathetic activation and blood pressure has also been noted by Hornyak et al.[7] and Okada et al.,[8] and appears to constitute part of the fight-or-flight response of sleep. Remarkably, arousal stimuli during wakefulness do not increase sympathetic-nerve activity involving muscle, but do increase sympathetic-nerve activity involving skin.[27] Arousal stimuli do, however, increase sympathetic activity in muscle after spinal cord injury[28] or anesthesia of the vagal and glossopharyngeal nerves (which carry baroreceptor-reflex afferent impulses).[29] Therefore, it appears that during sleep, there is a change in the neural processing of auditory and possibly other arousal stimuli. This would be a logical alteration since, because of the hypotension during non-REM sleep, acute increases in blood pressure would be required to allow adequate cerebral and cardiac perfusion during arousal, postural change, or confrontation.

Changes in heart rate and blood pressure during sleep are small, in keeping with findings in earlier studies of sleep in human subjects.[30-33] The increases in sympathetic activity during REM sleep are more pronounced than the changes in heart rate and blood pressure (relative to stage 4 sleep and wakefulness). Thus, measurements of heart rate and blood pressure may underestimate the magnitude of the autonomic cardiovascular adjustments during REM sleep. The less marked change in heart rate may be explained by a dissociation of muscle and cardiac sympathetic activity or alternatively by simultaneous cardiac parasympathetic activation offsetting cardiac sympathetic activation.

REM sleep is most manifest toward the end of sleep, before arousal. Sympathetic and hemodynamic alterations during REM sleep could conceivably initiate increased platelet aggregability, plaque rupture, or coronary vasospasm,[4-6,34,35] thus acting as a triggering mechanism for thrombotic events that may present clinically only after arousal.

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