

Heart rate surges during REM sleep are associated with theta rhythm and PGO activity in cats

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Rowe, Katharine, Ricardo Moreno, T. Rern Lau, Umesha Wallooppillai, Bruce D. Nearing, Bernat Kocsis, James Quattrochi, J. Allan Hobson, and Richard L. Verrier. Heart rate surges during REM sleep are associated with theta rhythm and PGO activity in cats. *Am. J. Physiol.* 277 (Regulatory Integrative Comp. Physiol. 46): R843–R849, 1999.—Rapid eye movement (REM) sleep is characterized by periods of profound cardiac autonomic activation evident in heart rate surges in humans and canines. Our goals were to determine whether or not the heart rate surge phenomenon occurs in cats and to characterize concurrent central nervous system activity. Cortical and hippocampal electroencephalogram, electromyogram, electrooculogram, pontogeniculoccipital (PGO) waves, subcutaneous electrocardiogram, and respiration were recorded. Bouts of sinus tachycardia lasting ≥ 3.5 s achieved a rate of 210 beats/min and were present predominantly during REM sleep. Heart rate during the surges rose an average of 26.4% from 132.5 ± 2.0 beats/min before the surge to 167.5 ± 2.6 beats/min ($P < 0.001$) and returned to 130.7 ± 2.6 beats/min ($P < 0.001$). The heart rate surges were invariably accompanied by increased incidence and frequency of hippocampal theta waves and increased PGO wave frequency and incidence of PGO wave clusters and eye movement clusters. The occurrence of surges was dramatically reduced from 0.11 ± 0.03 to $0.01 \pm 0.01/15$ s of REM sleep ($P = 0.02$) by atenolol (0.6 mg/kg iv), indicating that the phenomenon is β_1 -adrenergically mediated. These findings suggest a coupling between central activation of cardiac sympathetic nerves and the generation of hippocampal theta waves and PGO activity.

cardiovascular regulation; sympathetic control; hippocampus; eye movements; lateral geniculate nucleus; rapid eye movement; pontogeniculoccipital waves

THE ASSOCIATION OF rapid eye movement (REM) sleep with significant perturbations in autonomic nervous system activity is well established (2, 20, 21, 24, 34, 35, 42). However, the potential impact of sleep state-dependent autonomic surges on cardiac vulnerability is not fully appreciated. A recent review of studies based on over 70,000 patients revealed that 250,000 myocardial infarctions (20%), 38,000 sudden cardiac deaths (15%), and 15% of implantable defibrillator discharges occur annually in the nighttime hours between mid-

night and 6:00 AM (17). The distribution of deaths at night is nonuniform, suggesting that the events are nonrandom and probably attributable to physiological triggers. These observations underscore the great need to improve understanding of the autonomic mechanisms responsible for cardiac morbidity and mortality during sleep.

A probable mechanism that could account for the nonrandom distribution of cardiac events during sleep is surges in sympathetic nerve activity that have sufficient magnitude to stimulate thrombotic processes (37), increasing hemodynamic stress on vessel walls conducive to plaque rupture, and to alter cardiac electrophysiological properties (29). These autonomic surges could be responsible for myocardial ischemia and angina pectoris (20, 23, 42) and arrhythmias (6, 42) witnessed during REM sleep in humans. Such significant REM-induced increases in cardiac sympathetic activity have recently been documented only indirectly in humans (19, 35, 40). Suggestive evidence has been provided in canines by Kirby and Verrier (12, 13) and Dickerson et al. (7), who demonstrated that REM-induced heart rate increases of 35% are accompanied by substantial increases in coronary artery blood flow that rise 35% above baseline and persist for 15–20 s. During coronary stenosis, the heart rate surges are accompanied by a decrease rather than an increase in coronary flow, a condition that could be conducive to impaired myocardial perfusion (13). Because chronic stellectomy abolished the REM-induced surges in heart rate, the effect appears to be due to centrally induced sympathetic nerve activation (12).

Because of the inherent challenge in monitoring cardiac sympathetic nerve activity in humans, muscle nerve activity recording and heart rate variability (HRV) analysis have been employed as surrogates. Somers and co-workers (35) reported a marked increase in muscle (peroneal) sympathetic nerve burst frequency and amplitude during REM sleep in normal human volunteers. Vanoli and co-workers (40) demonstrated a significant increase in the low- to high-frequency ratio of HRV in normal subjects during REM compared with non-REM sleep, indicating state-dependent predominance in sympathetic activity. The REM-induced cardiac sympathetic dominance was markedly enhanced in individuals with recent myocardial infarction. The latter observation is especially important as it would imply increased risk of arrhythm-

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mic events and sudden death during REM sleep in subjects with prior myocardial infarction. The strong association between REM sleep and sympathetic dominance has been recently observed by Lovett and co-workers (19), who found a 1:1 coupling between the timing of REM onset and increases in low- to high-frequency ratio.

The present study was undertaken to characterize the phenomenon of heart rate surges as indicators of cardiac sympathetic nerve activity in the feline model, which is well-suited to investigation of central nervous system (CNS) physiology. Increases and irregularities in heart rate have long been noted during REM sleep in humans (1, 20, 23, 34, 35) and in felines (2–4, 8, 10). In the latter studies, some investigators observed associations of these heart rate phenomena with bursts of eye movements (3, 8) and single pontogeniculooccipital (PGO) spikes (4). However, they invariably reported average heart rates rather than addressing the phenomenon of surges in heart rate, a practice that tended to underrepresent cardiac sympathetic activity.

Thus a second goal was more precise characterization of the CNS activity during heart rate surges. Progress in determining concurrent CNS activity has been limited by the fact that the irregular shape of the canine skull, the species employed in previous investigations of this phenomenon (7, 12, 13), has presented technical difficulties for precise measurement of important sleep-related CNS events, including PGO and theta activity. If such a correlation could be documented, this would provide important insights into CNS mechanisms responsible for initiating the heart rate surge during REM sleep. To gain further insight into the specific cardiac adrenergic receptors involved in the phenomenon, we administered the cardioselective β_1 -adrenergic blocking agent atenolol, which does not cross the blood-brain barrier. Preliminary findings have been published in abstract form (16, 26, 43).

METHODS

The study was conducted under National Institutes of Health standards, and the protocols were approved by the Harvard Medical Area Standing Committee on Animal Use. The animals were housed in 1.2×1.2 -m cages subject to a 12:12-h light-dark cycle with food and water provided ad libitum.

Surgical Preparation

Five adult male cats weighing between 2.0 and 2.5 kg were anesthetized with halothane (1–2%) and were implanted with electrodes to monitor the electroencephalogram (EEG), transcortical activity, PGO wave activity in lateral geniculate nucleus [LGN; 6.5 anterior (A), 10.0 lateral (L), +12.0 vertical (V)], and theta activity of the hippocampus (3.3 A, 5.5 L, +17.0 V). The stereotaxic coordinates were according to Berman (26). Electromyogram (EMG) was recorded from the nuchal muscle, and electrooculogram was recorded from the posterior wall of the orbit. Respiration was monitored with a pair of subcutaneous electrodes sutured unilaterally in the muscle of the costal diaphragmatic margin. Electrocardiogram (ECG) electrodes for leads I and II were placed subcutaneously. The noncephalic leads were tunneled subcutane-

ously to emerge with the cephalic leads in an amphenol connector secured to the top of the skull with dental acrylic. Approximately 3 wk after surgery, a jugular intravenous catheter was inserted for later peripheral autonomic blockade in four animals. Postsurgical antibiotic treatment was administered as needed after daily monitoring by a veterinarian.

Recording Procedures

Recordings began 10–14 days after surgery and after 7 days of acclimatization to the sound-attenuated $1 \times 1 \times 1.2$ -m recording chamber. The chamber was kept at room temperature (23°C) and was outfitted with a window for behavioral observation. Polygraphic recording was performed for 4-h sessions between noon and 4:00 PM. A counterweight cable/connector assembly allowed recording of freely moving, unrestrained cats. A Grass 78 multichannel polygraph with 7P511 amplifiers was used for the paper tracing, whereas a Compaq 386SX computer was used to acquire and store digitized data (sampling rate = 333 Hz/channel) on magneto-optical media. The data set for control recordings consisted of eight recording sessions obtained from five animals, one in each of three cats, two in one cat, and three in one cat. We found no significant variability among cats in percentage and duration of REM, number of REM episodes, or number of surges ($P = 0.13$). The small intercat variability in surge-related heart rate change and theta and PGO frequency is indicated by the low SEs.

Peripheral Autonomic Blockade

Pharmacological blockade was performed in a separate protocol in four cats. On the day of the experiment, at least one complete REM episode occurred before the β_1 -adrenergic blocker atenolol (0.6 mg/kg iv) was administered through the jugular catheter without disturbing the animal. The incidence of heart rate surges during REM was compared before and after the administration of atenolol for each animal. After atenolol, the cats were observed until the end of the 4-h recording period. The dosage was calculated to ensure a relatively high degree of receptor blockade without affecting sleep state. Atenolol does not cross the blood-brain barrier (9, 14) and had no observable effects on sleep architecture. The appearance of eye movements, theta waves, PGO activity, and EEG signs of phasic REM were unchanged by the drug. The data set for pharmacological blockade studies was compiled from a 4-h recording session in each of four cats.

Data Analysis

Heart rate surge identification. The following criteria distinguished heart rate surges: 1) 15% decrease in the interval between successive R waves compared with the mean for the preceding 6 s and 2) duration ≥ 3.5 s. The polygraphic records were employed for visual inspection and reference, whereas the magneto-optical media were used for quantitative analysis of digitized data. The digitized ECG was transformed into R-R intervals. The sequence of ECG R-R intervals was imported into Excel, and two running means were compared, 1 of 20 followed by 1 of 6 R-R intervals, to identify the surges according to the above criteria. The polygraphic records were examined to exclude from analysis any surges associated with movement, a change of sleep state, increased respiratory activity, or a preceding change in heart rate. The criterion of duration ≥ 3.5 s eliminated surges attributable to respiratory sinus arrhythmia, in which heart rate increases lasted < 1.4 s. After these exclusions, 62 surges remained for analysis.

The total number of surges during REM was tabulated, and the magnitude of heart rate increase and surge durations

was determined. The R-R intervals for 6 s preceding and after the event were also tabulated. The surges were then analyzed for associations with theta and PGO activity, and eye movements. The incidence of heart rate surges before and after administration of the β -adrenergic receptor blocking agent atenolol (0.6 mg/kg) was compared.

Theta wave analysis. Theta activity, a synchronized pattern of activity of 4–8 Hz of rhythmic slow waves recorded from the hippocampus, was analyzed before, during, and after the heart rate surges in three cats. Baseline theta activity was calculated as the percentage of time spent in theta activity. This baseline was determined and compared with percentage of time spent in theta activity during heart rate surges. Additionally, theta frequency was quantified and compared for 6 s before and after the heart rate surges.

PGO activity measurement. The frequency and cluster type of PGO wave activity recorded in the LGN in association with heart rate surges were assessed in five cats. PGO frequency was calculated as the number of PGO wave spikes, regardless of clustering, per unit of time. Single PGO spikes are referred to as type I. Clusters of two, three, and greater than or equal to four PGO waves, each ≤ 150 ms apart, are referred to as types II, III, and IV, respectively (22). PGO activity was determined by calculating the mean PGO spike frequency before, during, and after the heart rate surges and was compared with the mean baseline PGO frequency during REM. The incidence of type IV PGO waves in association with heart rate surges was also calculated.

Eye movement analysis. The distribution of eye movements and eye movement clusters was determined for all of REM sleep, and their association with heart rate surges was analyzed in three cats.

Sleep Scoring

The 4-h recordings were divided into 15-s epochs and then hand scored as slow-wave sleep (SWS), REM sleep, or waking, according to common practice (38). SWS was characterized by delta waves and synchronized, low-frequency, high-voltage EEG activity. These SWS characteristics, when accompanied by ≥ 3 PGO waves/15 s, defined the transition state from SWS to REM sleep. REM sleep was distinguished by low-voltage, high-frequency, desynchronized EEG activity, atonia, theta rhythm, PGO waves, bursts of eye movements, and an absence of delta and spindle activity. The presence of EMG activity without PGO waves distinguished quiet waking from REM sleep. The sleep stages of CNS activity during heart rate surges were identified.

Statistical Methods

The two-way ANOVA and Bonferroni posttest were employed to calculate differences in heart rates, in the frequencies of theta and PGO waves before, during, and after the surges, and in the distribution of eye movement clusters. A paired *t*-test was used to analyze the incidence of surge events before and after atenolol injection. A multivariate ANOVA with Bonferroni posttest was employed to determine variability among cats. Values are means \pm SE ($P < 0.05$).

RESULTS

Our findings demonstrate that REM sleep is consistently marked by episodic surges in heart rate averaging $\geq 26\%$ (Fig. 1) and that these events are in close temporal association with hippocampal theta activity, PGO waves, and clusters of eye movements. Our analysis focused on heart rate accelerations that lasted 3.5 s

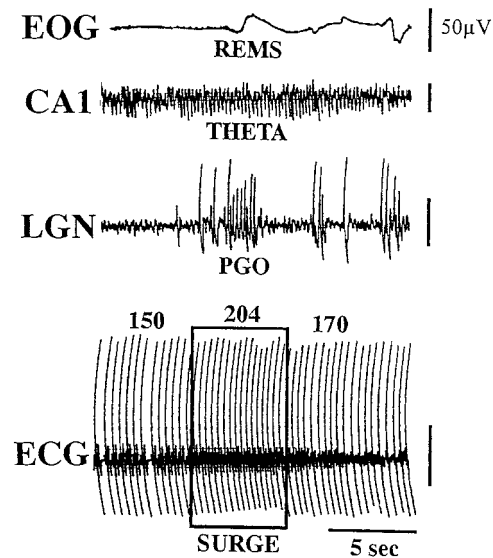


Fig. 1. Representative polygraphic recording of a heart rate surge during rapid eye movement (REM) sleep associated with eye movements, fast theta activity in the hippocampus, and a burst of pontogeniculooccipital (PGO) spikes. Before and after this heart rate surge, hippocampal field potentials, although exhibiting rhythmic activity in the theta range, were of variable amplitude and frequency. In contrast, hippocampal theta activity stabilized, and its frequency increased in association with the surge. There was also an augmentation in PGO frequency from 0.17 to 2.16 spikes/s, which started with 2–3 single spikes followed by a type IV burst. No PGO spikes occurred during the 6 s preceding the surge, and single spikes dominated the control period after the surge. The channels recorded were electromyogram, electrooculogram (EOG), transcortical, hippocampal theta rhythm (CA1), electrocardiogram (ECG), and PGO waves of the lateral geniculate nucleus (LGN). During this surge, heart rate increased from 150 to 204 beats/min or 26.4%. Calibration marks represent 50 μ V and a paper speed of 5 mm/s.

or longer and that were characterized by decreased R-R interval of $\geq 15\%$ compared with the 6 s preceding the event. The data set consisted of 1,282 min of total sleep time compiled from five cats during a total recorded session time of 1,920 min. On average, each 4-h record comprised $46.3 \pm 3.0\%$ or 111 ± 7 min in SWS, $20.2 \pm 1.4\%$ or 48 ± 3 min in REM sleep, and $33.8 \pm 3.5\%$ or 81 ± 8 min in wakefulness. There was an average of 8.3 ± 0.7 REM episodes/4-h record; each episode lasted 6.0 ± 0.8 min. The average latency from the beginning of the recording to the beginning of the first sleep episode was 19 ± 5 min.

Our analyses focused on the 62 surges in heart rate recorded during REM sleep that lasted 3.5 s or longer and that were characterized by decreased R-R interval of $\geq 15\%$ compared with the 6 s preceding the event. The average incidence was one surge per 6.1 min of REM sleep. Heart rate during surges rose an average 26.4% to 167.5 ± 2.6 beats/min from 132.5 ± 2.0 beats/min ($P < 0.001$) during the 6 s before the surge and returned to 130.7 ± 2.6 beats/min ($P < 0.001$) during the 6 s after the accelerations (Fig. 2). The surge durations ranged from 3.5 to 16.1 s, with 95% of the surges lasting 4.2–10.0 s; mean duration was 7.1 ± 0.4 s. The greatest heart rate increase was from 140 to 210 beats/min (33%); this surge lasted 15.6 s. All of these heart rate surges were accompanied by PGO

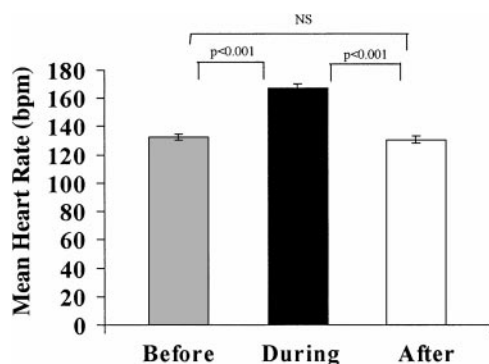


Fig. 2. Mean heart rates before, during, and after surges. Heart rates during the surges (167.5 ± 2.6 beats/min) were significantly elevated compared with the heart rates during the 6 s preceding (132.5 ± 2.0 beats/min) and the 6 s after (130.7 ± 2.6 beats/min) the accelerations ($P < 0.001$ for both comparisons). There was no statistical difference between the heart rates 6 s before and after the surge. NS, not significant; bpm, beats/min.

waves and theta activity, and 93.5% ($n = 58$) was associated with some eye movements.

The heart rate surges were associated with a higher incidence of hippocampal theta waves. Theta activity occupied $46.8 \pm 1.8\%$ of all REM periods. By comparison, theta activity occupied $81.7 \pm 2.9\%$ of time spent in heart rate surges ($P < 0.001$). Furthermore, theta frequency increased 16.7% during the surges from 4.8 ± 0.1 waves/s during the 6-s interval before the surges to 5.6 ± 0.1 waves/s during the surge ($P < 0.001$) and decreased after the surges (to 4.9 ± 0.1 waves/s, $P < 0.001$; Fig. 3).

The mean frequency of PGO waves and the occurrence of clusters of PGO waves increased significantly during the heart rate surges. The mean PGO frequency for all time spent in REM averaged 1.0 ± 0.1 spikes/s. During the surges, the mean PGO frequency rose 58.3% (from an average 1.2 ± 0.1 spikes/s during the 3-s interval before the surge to 1.9 ± 0.1 spikes/s during the surge, $P < 0.001$) and then returned to 1.2 ± 0.1 spikes/s during the 3-s interval after the surge ($P < 0.001$; Fig. 4). Type IV PGO clusters, those consisting of four or more spikes each < 150 ms apart, occurred more

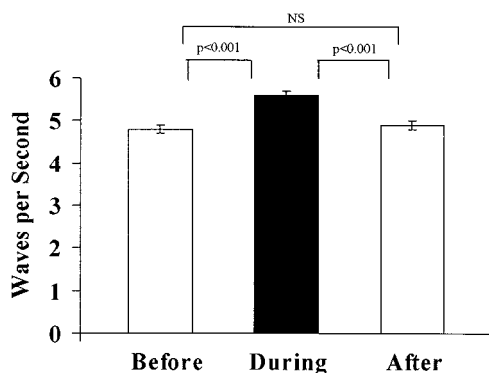


Fig. 3. Mean frequency of theta waves before, during, and after surges. Theta frequency during the surges of 5.6 ± 0.1 spikes/s was greater than the frequencies during the 6-s intervals both before (4.8 ± 0.1 spikes/s) and after the surges (4.9 ± 0.1 spikes/s; $P < 0.001$ for both comparisons). Theta frequencies during the 6 s before and the 6 s after the heart rate surges were not significantly different.

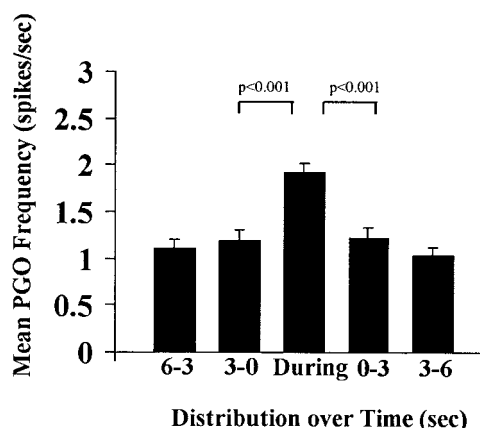


Fig. 4. Mean PGO frequency before, during, and after the surges. The mean PGO frequency was 1.1 ± 0.1 spikes/s during the interval from 6 to 3 s before the surge and 1.2 ± 0.1 spikes/s during the interval from 3 to 0 s before the surge (NS). During the surge itself, the mean PGO frequency rose to 1.9 ± 0.1 spikes/s ($P < 0.001$). During the interval from 0 to 3 s after the surge, mean PGO frequency decreased to 1.2 ± 0.1 spikes/s ($P < 0.001$) and to 1.0 ± 0.1 spikes/s during the interval from 3 to 6 s after the event (NS). The mean PGO frequency for all time spent in REM was found to be 1.0 ± 0.1 spikes/s. This baseline value was not different from the frequency values before and after the heart rate surges.

commonly during the heart rate surge itself compared with the 6-s periods before and after this event ($P < 0.001$). In the entire data set, there was a total of 6 type IV clusters during both 3-s intervals before the surge, 30 type IV clusters during the surge, 6 type IV clusters from 0 to 3 s after the surges, and no type IV clusters 3–6 s after the surges.

A strong association was found between surge events and eye movement clusters. In records in which eye movement clusters were apparent, 26 of the 28 (92.9%) surges were associated with eye movement clusters (Fig. 5). This distribution is consistent with the general incidence of eye movements in all of the animals. Thus only two surges (7.1%) were not associated with eye movement clusters, although 33.7% of REM contained no eye movements, indicating a highly nonrandom distribution.

Pharmacological blockade of sympathetic nerve activity with the β -adrenergic antagonist atenolol (0.6 mg/kg) significantly reduced the heart rate surges in subsequent REM episodes. The incidence of heart rate surges decreased from 0.11 ± 0.03 to 0.01 ± 0.01 surges/15 s of REM ($P = 0.02$) immediately after atenolol administration (Fig. 6). At this dosage, atenolol caused a mean heart rate depression of 16%. After atenolol administration, sleep structure showed no significant variation in the proportion of recording time spent in REM or the number and duration of REM epochs.

DISCUSSION

The main goal of the present study was to determine whether consistent, sizeable, REM-induced surges in heart rate occur in the feline, as they do in humans (1, 20, 23, 34, 35) and in canines (7, 12, 13). Heart rate increases of a lesser magnitude than observed in this

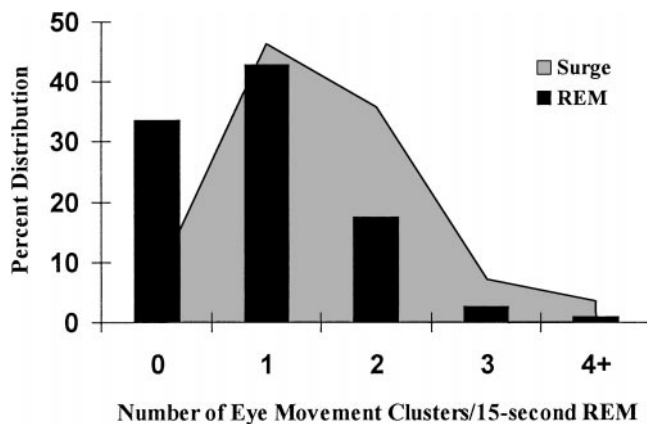


Fig. 5. Distribution of eye movement clusters and heart rate surges during REM sleep. REM percent distribution was calculated as the percentage of 15-s intervals of REM for each of the categories of zero to four eye movement clusters. No eye movement clusters were found during $33.7 \pm 1.2\%$ of REM, whereas $42.8 \pm 1.3\%$ of REM contained one eye movement cluster, $17.5 \pm 1.1\%$ contained 2 eye movement clusters, $2.7 \pm 1.9\%$ contained 3 eye movement clusters, and $0.9 \pm 0.7\%$ contained >3 eye movement clusters. Of the 28 surge events analyzed for association with eye movement clusters, 13 (46.4%) were associated with 1 eye movement cluster, 10 surges (35.7%) with 2 clusters, 2 surges (7.1%) with 3 clusters, 1 surge (3.6%) with >3 clusters, and 2 surges (7.1%) with no eye movement clusters.

study had previously been described in the feline to coincide with phasic bursts of eye movements (3, 8) or the appearance of single PGO spikes (4). Demonstration of the specific heart rate surge phenomenon in this species allowed detailed investigation of the CNS mechanisms because of the feasibility in felines of precise stereotaxic implantation of electrodes in brain sites that could be responsible for increasing cardiac autonomic drive during REM sleep. Our results indicate that REM-induced heart rate surges that average $\geq 26\%$ do in fact occur in normal, unrestrained cats and that these events are typically associated with hippocampal theta activity, PGO activity, and eye movement clusters. Significant reduction in the incidence of the phenomenon by pharmacological blockade of sympathetic nerve inputs to the heart with atenolol indicates that the final common pathway of REM-induced surges

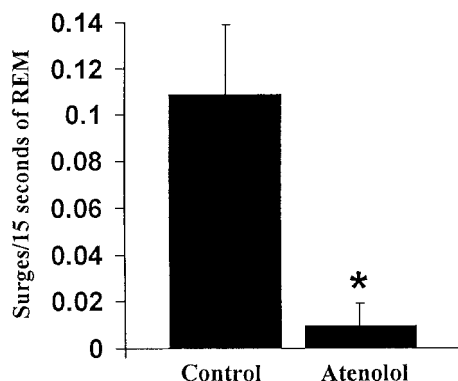


Fig. 6. Administration of the β_1 -adrenergic blocker atenolol (0.6 mg/kg iv) significantly reduced the occurrence of heart rate surges. The incidence of heart rate surges decreased from 0.11 ± 0.03 to 0.01 ± 0.01 surges/15 s of REM (* $P = 0.02$) immediately after atenolol administration.

in heart rate is activation of cardiac β -adrenergic receptors and not withdrawal of parasympathetic tone.

Relationship of Present Observations to Previous Reports of Cardiac Acceleration During REM

Several investigators have reported REM-induced increases in heart rate in experimental animals (2–4, 7, 8, 12, 13). The pattern of the heart rate response observed in the present study is most closely akin to that previously reported in dogs by Kirby and Verrier (12, 13) and Dickerson et al. (7), who found an abrupt although transitory 35–37% increase in rate that is concentrated during phasic REM and that is abolished by interruption of sympathetic neural input to the heart. The phenomenon differs from that observed by Baust and Bohnert (3) in felines in that the heart rate increase observed is more marked and is not dependent on withdrawal of parasympathetic activity. Rather, sympathetic activation appeared to be the predominant influence, as β_1 -adrenergic blockade with atenolol significantly reduced the response. Because muscarinic receptor blockade was not performed in the present study, there is a possibility that some decrease in vagus nerve activity may have played a role in the observed heart rate surges.

The main difference in the pattern of REM-related increase in heart rate from that reported by Kirby and Verrier (12, 13) and Dickerson et al. (7) in dogs is that we found no significant deceleration in rate secondary to the surge. The precise reason for this is unclear. One possibility is that the dogs exhibited a greater baroreceptor sensitivity, as a large proportion of the animals in the Dickerson et al. study (7) were beagles, which are bred for intense physical activity, a factor that increases baroreceptor responsiveness (30, 31).

With respect to humans, there is growing evidence that REM sleep is associated with a major increase in sympathetic activity (19, 35, 40). This view is supported both by direct peroneal nerve recording studies of muscle sympathetic activity in normal volunteers (35) and by HRV analysis (19, 40). Somers and co-workers (35) reported a marked increase in the frequency and amplitude of sympathetic activity in the peroneal nerve during normal REM sleep. Vanoli and co-workers (40) demonstrated that the low- to high-frequency ratio of HRV indicative of sympathetic dominance is significantly enhanced in REM sleep. Recently, Lovett and co-workers (19) demonstrated that there is in fact a 1:1 coupling in human subjects between the increase in low- to high-frequency HRV and the onset of REM sleep. Thus there appears to be a human counterpart to the sympathetically mediated REM-induced surge in autonomic activity as described in the present study in cats.

Probable CNS Events Mediating REM-Induced Heart Rate Acceleration

The primary involvement of CNS activation in the heart rate surges of REM sleep is demonstrated by the concomitant, conspicuous increase in hippocampal theta frequency, PGO activity, and eye movements (Figs. 3–5). Identification of a heart rate surge in felines during REM sleep accompanied by increased theta

frequency is a novel observation. Sei and Morita (32) reported an association between theta activity, eye movements, and increased heart rate and blood pressure in the rat. They demonstrated a significant increase in theta frequency at 1 s before eye movement activity. However, they did not find a consistent correlation with increased mean arterial pressure or heart rate, which, when it occurred, was delayed by 7 s.

The appearance of theta waves in cats is characteristic of arousal, orienting activity, alertness, and REM sleep, when it is strongly associated with PGO activity and eye movements (11, 18, 25, 28). Sakai and colleagues (28) reported a positive correlation between theta activity, PGO potentials, and bursts of eye movements during REM sleep in cats. These investigators found theta frequency to be significantly higher during REM sleep than during wakefulness. Kemp and Kaada (11) observed maximum hippocampal theta activity in association with increased eye movements during REM sleep in cats. Lerma and Garcia-Austt (18), using spike-triggered averages in cats, reported that theta rhythm was consistently associated with PGO spikes and spike clusters and that bursts of eye movements appeared in association with clusters of PGO spikes. Other investigators have demonstrated that increased theta activity is characteristic of periods of increased eye movements during REM sleep in dogs (44) and rats (29, 36, 39). Sano and co-workers (29) found an increase in theta frequency during REM sleep in rats to precede eye movements by 0.5 s. Valle and colleagues (39) reported in rats that, during REM sleep, theta waves consistently preceded and were continuous with eye movements and limb twitches.

Observations of PGO activity during sleep associated with heart rate phenomena of any type have been documented only infrequently. Baust and colleagues (4) found only a relatively minor, baseline rate-dependent, variable response in heart rate to PGO activity in cats during REM. Type I PGO wave spikes occur commonly in SWS, when they are independent of eye movements, whereas the more phasic types II, III, and IV PGO wave activity are associated with the eye movement bursts of REM sleep (22). Our new finding of a correlation between theta and PGO activity with heart rate surges during REM is complementary to our recent observation of vagally mediated heart rate decelerations concurrent with the cessation of PGO activity and interruption of theta rhythm during tonic REM sleep (15, 41).

Our documentation of a significant association of heart rate surges with eye movements is in agreement with previous findings of Dickerson and co-workers (7), who reported that the frequency of heart rate surges was increased during periods of REM marked by phasic eye movements in canines. These investigations extend previous descriptive reports of heart rate increases in association with eye movements (3, 8) and provide data on the autonomic nervous system consequences of concurrent theta wave, PGO, and eye movement activation (11, 18, 25, 28).

Alterations in centrally induced autonomic activity constitute the most likely basis for the abrupt accelerations in heart rate during REM sleep. Plausible periph-

eral mechanisms include an increase in sympathetic activity or a diminution of vagal tone, either alone or in combination. Our finding that cardioselective β -adrenergic blockade with atenolol markedly reduced the phenomenon suggests that the REM sleep-induced surges are primarily mediated by bursting of cardiac sympathetic efferent fiber activity, which directly affects heart rate. Atenolol permeates the blood-brain barrier poorly, thus minimizing possible confounding CNS effects (23). We observed no effect of the agent on REM sleep structure. Therefore, it is unlikely that indirect effects of the drug on brain state contributed to its suppression of heart rate surges.

The present findings carry important clinical and scientific implications. They indicate that there is substantial sympathetic nerve activation during REM sleep that impacts on the stability of heart rhythm, resulting in marked surges in rate. Our investigations provide the specific insight that CNS mechanisms that increase theta rhythm and PGO activity may contribute to enhanced cardiac sympathetic tone during REM. Beyond this particular observation is the broader implication that the feline may provide a heuristic model for in-depth exploration of CNS events that result in clinically important cardiac phenomena during normal sleep.

Given the past findings and our present study of sympathetically mediated heart rate surges during REM sleep, it is noteworthy that recent peroneal nerve recording and HRV studies in human subjects reveal a close correlation between REM onset and sympathetic dominance. Under pathophysiological conditions, sympathetic dominance may be an especially important trigger of cardiac events, as Vanoli and co-workers (40) have shown that sympathetic activity is relatively unfettered after myocardial infarction compared with normal individuals. The clinical condition may be further compounded by the fact that myocardial infarction may disrupt sleep structure and establish an additional predisposition for disturbed autonomic activity (33). Thus autonomic triggers during sleep may have a greater than anticipated role in the precipitation of myocardial infarction and sudden death at night and could help to explain why these events, as well as defibrillator discharge (17) and atrial fibrillation (27), are nonrandomly distributed at night.

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