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, electrocuglogram, pontogeniculooccipital (PGO) waves, subcutaneous electrocardiogram, and respiration were recorded. Bouts of sinus tachycardia lasting $\geq 3.5$ 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 $132.5 \pm 2$ beats/min before the surge to $167.5 \pm 2.6$ beats/min ($P < 0.001$) and returned to $130.7 \pm 2.6$ 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 $0.11 \pm 0.03$ 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 $\beta_1$-adrenergically mediated. These findings suggest a coupling between central activation of cardiac sympathetic nerves and the generation of hippocampal theta waves and PGO activity.

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%), 30,000 sudden cardiac deaths (15%), and 15% of implantable defibrillator discharges occur annually in the nighttime hours between midnight 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 stellactomy 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. Vandoli 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 arrhyth-
mic events and sudden death during REM sleep in subjects with prior myocardial infarction. The strong
association between REM sleep and sympathetic dom-
nance 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 associa-
tions of these heart rate phenomena with bursts of eye
movements (3, 8) and single pontogeniculocippital (PGO)
spikes (4). However, they invariably reported average
heart rates rather than addressing the pheno-
menon of surges in heart rate, a practice that tended to
underrepresent cardiac sympathetic activity.

Thus a second goal was more precise characteriza-
tion 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 investi-
gations of this phenomenon (7, 12, 13), has presented
technical difficulties for precise measurement of impor-
tant sleep-related CNS events, including PGO and theta
activity. If such a correlation could be docu-
mented, 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 cardioselec-
tive 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. Electrocardio-
gram (ECG) electrodes for leads I and II were placed subcuta-
neously. 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 admin-
istered 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 × 1 × 1.2-m
recording chamber. The chamber was kept at room tempera-
ture (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, unre-
strained 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 record-
ing 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 β1-adrenergic
blocker atenolol (0.6 mg/kg iv) was administered through the
jugular catheter without disturbing the animal. The inci-
dence 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 activ-
ity, 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 distin-
guished 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 analy-
sis 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
in the ECG R-R intervals was 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
RESULTS

The sleep stages of CNS activity during REM sleep. The sleep stages of CNS activity during REM sleep. The sleep stages of CNS activity during REM sleep. The sleep stages of CNS activity during REM sleep. The sleep stages of CNS activity during REM sleep. The sleep stages of CNS activity during REM sleep. The sleep stages of CNS activity during REM sleep. The sleep stages of CNS activity during REM sleep. The sleep stages of CNS activity during REM sleep. Our findings demonstrate that REM sleep is consistently marked by episodic surges in heart rate averaging $\pm 26\%$ (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 or longer and that were characterized by decreased R-R interval of $\pm 15\%$ compared with the 6 s preceding the event. The data set consisted of 1,288 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 $\pm 7$ min in SWS, 20.2 $\pm 1.4\%$ or 48 $\pm 3$ min in REM sleep, and 33.8 $\pm 3.5\%$ or 81 $\pm 8$ min in wakefulness. There was an average of 8.3 $\pm 0.7$ REM episodes/4-h record; each episode lasted 6.0 $\pm 0.8$ min. The average latency from the beginning of the recording to the beginning of the first sleep episode was 19 $\pm 5$ 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 $\pm 15\%$ 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 $\pm 8.3$ beats/min from 132.5 $\pm 8$ beats/min ($P < 0.001$) during the 6 s before the surge and returned to 130.7 $\pm 8$ 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 $\pm 0.4$ 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
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 ± 1.8% of all REM periods. By comparison, theta activity occupied 81.7 ± 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 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
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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 ± 1.2% of REM, whereas 42.8 ± 1.3% of REM contained one eye movement cluster, 17.5 ± 1.1% contained 2 eye movement clusters, 2.7 ± 1.9% contained 3 eye movement clusters, and 0.9 ± 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.

Fig. 6. Administration of the β₂-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.

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 K aada (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 peripheral 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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