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Coronary Artery and Sleep

Relationship Between Coronary Hemodynamic Changes and the Phasic Events of Rapid Eye Movement Sleep

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Summary: Previous studies in dogs showed dramatic increases in coronary blood flow associated with episodes of sinus tachycardia during rapid eye movement (REM) sleep. The present study demonstrates that 90% of these surges in heart rate and coronary flow are concentrated during periods of phasic REM sleep and only 10% in tonic REM sleep. Intensely phasic REM was distinguished from moderately phasic REM sleep by the degree of phasic eye movement. The surges were three times more frequent during intensely phasic REM than in moderately phasic REM sleep. However, the magnitudes of heart rate (37% ± 3%) and coronary flow (25% ± 3%) surges were unaffected by the specific substage of REM sleep. The incidence of surge events was almost eleven times greater in epochs of phasic REM that also contained a muscle twitch than in those that did not. During REM sleep, muscle twitches accompanying surges were not associated with any additional elevations in coronary flow or myocardial demand. Our data indicate that the sinus tachycardia-associated surges in coronary flow represent integrated autonomic responses intrinsic to phasic periods of REM sleep in dogs. **Key Words:** Coronary flow—Sinus tachycardia—Canine—REM sleep—Phasic activity.

Our present studies were prompted by the observations of Kirby and Verrier of striking increases in coronary blood flow (CBF) coupled with episodes of sinus tachycardia during rapid eye movement (REM) sleep in dogs (1). Elevations in heart rate (HR) and CBF each averaged 35%, but sometimes achieved increases of 100% over prevailing levels without any concurrent effects on blood pressure (BP). Initiation of the bouts of sinus tachycardia involved the sympathetic nervous system, as demonstrated by their elimination after bilateral ablation of the stellate ganglia. The enhanced coronary flow appeared to depend largely on the vasoactive effects of increased myocardial metabolism, as the magnitude of the increases in CBF paralleled the changes in HR. During the next series of experiments (2), a stenosis was induced to maintain a 60% decrement in flow in the left circumflex coronary artery. In this group of dogs, a paradoxical reduction in CBF accompanied the episodes of sinus tachycardia during REM sleep. These observations provide support for a canine model of nocturnal angina, which occurs in humans most often during REM sleep (3).

Phasic periods of REM sleep are marked by a high frequency of eye movements, occasional muscle twitches and, in cats, by pontogeniculo-occipital (PGO) waves (4). These external indicators of phasic REM sleep are correlated with significant changes in neuronal excitability in widespread regions of the central nervous system (CNS) (5,6), including areas of the parabrachial pons involved with sleep state dependent changes in cardiovascular function (7). In both cats and humans, substantial fluctuations in heart rate and/or blood pressure are associated with those epochs of REM sleep characterized by intensely phasic central activation (8–11). An increased frequency of sleep-disordered breathing (12) and marked differences in reflex responses to respiratory challenges occur during phasic REM sleep in dogs (13). Thus, across a variety of reflex systems in several species, there is evidence of substantial variation in the properties of autonomic regulation in phasic REM compared to tonic REM sleep.

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We hypothesized that the sinus tachycardia-associated surges in coronary flow observed during canine sleep would be predominantly associated with phasic episodes of REM sleep and that there might be differences in coronary hemodynamic function during phasic REM compared to tonic REM sleep. In addition, we proposed that the incidence and the magnitude of CBF surges during phasic REM sleep would be significantly related to the occurrence of muscle twitches.

METHODS

Experimental protocols were approved by the Georgetown University Animal Care and Use Committee and complied with standards set by the scientific community (14,15). The six mongrel beagles (3 males, 3 females) and 1 mongrel labrador (female) in this study were maintained in the vivarium on a 12:12 light–dark cycle. The following procedures have been described previously in more detail (16).

Surgical preparation

Each dog was sedated with Acepromazine (0.05 mg/kg, i.m.) and anesthetized initially with pentobarbital sodium (20–30 mg/kg, i.v.). The animal was then given Halothane anesthesia throughout the aseptic thoracotomy. Teflon-insulated stainless steel electrodes were inserted in the heart for electrocardiographic (ECG) monitoring. A Doppler flow probe was secured around the left anterior descending coronary artery in the labrador and on the left circumflex coronary artery in the beagles. Microwire electrodes for recording electromyograms (EMG) were implanted in the dorsal neck muscles. To facilitate access for percutaneous arterial blood pressure monitoring, the carotid arteries were exteriorized bilaterally within skin neck tubes. Antibiotics (Amoxicillin, 10 mg/kg, p.o. b.i.d.) were administered for 7–10 days following surgery.

Approximately 1 week after the thoracic surgery, each animal was given Acepromazine (0.05 mg/kg, i.m.), followed by Nembutal (30 mg/kg, i.v.) to maintain a surgical plane of anesthesia for implantation of cephalic electrodes. In order to record electrooculograms (EOG) and electroencephalograms (EEG), stainless steel electrodes were placed in the skull. Concentric bipolar electrodes were implanted in each beagle bilaterally at stereotactic coordinates (17) corresponding to the lateral geniculate nuclei for recording PGO waves. The previously implanted thoracic leads were retrieved from a subcutaneous mesh pouch and, along with the cephalic leads, were attached to a female 36-pin connector. The base of the connector and all wires were covered with methyl methacrylate. Animals were given prophylactic antibiotics as before. Each dog participated in four sessions of behavioral acclimation to the laboratory during this 2-week recovery period.

Recording procedures

The dogs slept spontaneously in a 3 × 3 × 4-foot chamber with a window for behavioral monitoring. A 20-MHz pulsed Doppler transducer amplifier system was used to record CBF from the implanted flow probe. An 18-gauge angiocatheter line was installed in a carotid artery on the day of experiment so that arterial blood pressure could be measured. All data were recorded by a Grass Model 78 polygraph employing 7P511 amplifiers for A.C. channels and 7P1/7DA amplifiers for D.C. channels.

Sleep states were determined for each 15-second epoch, as has been described (16). Assessment of deep slow wave sleep (SWS), light SWS, REM sleep, and quiet waking was performed employing the scoring atlas of Ursin and Sterman (18) with adjustments for the difference in species (19,20). We arbitrarily defined substages of REM sleep according to the amount of phasic activation displayed in the EOG record for each 15-second epoch: tonic REM (0–2 eye movements/epoch), moderately phasic REM (3–10 eye movements/epoch) and intensely phasic REM (>10 eye movements/epoch).

Data analysis

The criteria for selecting a heart rate surge for analysis included a minimum increase of 10% over the prevailing HR and CBF baseline values during a 12-second period and without any preceding disruptions of normal ECG rhythm. Responses were classified according to sleep stage and the incidence of responses per minute of each state was calculated for each dog. The presence or absence of muscle twitches was noted and scored (twitch present = 1, absent = 0).

In order to analyze the CBF response to the heart rate surges, we measured the average HR, average peak systolic blood pressure (BP) and average peak CBF for a 12-second pre-surge period and then compared these values to those in the first 12 seconds of the heart rate surge. Prior to statistical analysis, all parameters were normalized to a per minute basis. Post mortem calibration of the Doppler flow probe in situ was possible in only two of the dogs, and therefore CBF values are given as Doppler frequency shift (kHz). The heart rate-systolic blood pressure product (HR × SBP) was calculated as an indicator of cardiac metabolic demand (21). Summary values were calculated for each dog, for each hemodynamic parameter, under pre-surge and surge conditions within each substage of REM sleep. Paired *t* tests were used to compare pre-surge and surge

TABLE 1. *Comparison of baseline and surge values in rapid eye movement (REM) sleep*

	HR × SBP (mm Hg × beats/min)		Coronary Blood Flow (kHz Doppler shift)	
Tonic REM				
Baseline	9,798 ± 499		5.85 ± 0.85	
Surge	13,170 ± 752		6.88 ± 1.04	
Significance[a]		$p < 0.006$ $t = -5.35$		$p < 0.034$ $t = -3.17$
Moderately phasic REM				
Baseline	10,399 ± 709		5.46 ± 0.63	
Surge	14,234 ± 842		6.82 ± 0.93	
Significance[a]		$p < 0.0001$ $t = -18.08$		$p < 0.005$ $t = -4.32$
Intensely phasic REM				
Baseline	10,424 ± 647		5.47 ± 0.62	
Surge	14,910 ± 703		7.03 ± 0.95	
Significance[a]		$p < 0.0001$ $t = -17.89$		$p < 0.005$ $t = -4.38$

Abbreviations: HR = heart rate, SBP = systolic blood pressure.

[a] Surge values significantly different from baseline values, based on paired t test comparisons of summary values for each condition in each of 7 animals (df = 6 in the comparisons above, except in tonic REM, where df = 4 because two of the dogs had no surges during tonic REM sleep).

responses. When appropriate, t tests or one-way analysis of variation (ANOVA) procedures included the Bonferroni correction applied to tests of significance for repeated comparisons. All data values are expressed as means ± SEM. Portions of these data have been presented at meetings in preliminary form (22,23).

RESULTS

We first studied surges in heart rate that exceeded baseline levels by at least 10% during a total of 1,370 minutes of sleep recorded from five dogs. Of these 158 heart rate surges, 12% occurred during slow wave sleep, 15% during tonic REM sleep and 73% during phasic REM sleep. The incidence of heart rate surges was 2.1 ± 0.4 surges/100 minutes of slow wave sleep and 32.6 ± 3.5 surges/100 minutes of REM sleep ($p < 0.001$, df = 4, $t = -8.95$). Because of this highly significant difference, our present analysis focused on events occurring during REM sleep. Three of these dogs were then instrumented for acquisition of the arterial blood pressure and coronary hemodynamic data.

Our data set for the study of coronary hemodynamic function was comprised of 2,178 minutes of total sleep time recorded between 4:00 p.m. and midnight from seven dogs. Of the sleep periods, 901 minutes (41%) were spent in REM sleep. The dogs displayed considerable respiratory sinus arrhythmia and low average heart rates during all stages of sleep, consistent with prior descriptions of enhanced vagal tone during sleep (8,24).

Surges in heart rate during phasic REM sleep were accompanied by substantial elevations in coronary flow (Fig. 1). Of the 180 surge events comprised of increases in both heart rate and CBF during REM sleep, 90% occurred during phasic REM sleep, which made up 56% of total REM sleep. The remaining 10% occurred during tonic REM sleep. Thus, the average incidence of heart rate-coronary flow surges during tonic REM sleep was 4 ± 2 surges per 100 minutes. Within phasic REM sleep, the incidence of heart rate-coronary flow surges was related to the overall degree of phasic eye movement activity, in that moderately phasic REM was characterized by 16 ± 3 surges per 100 minutes, whereas intensely phasic REM was marked by 62 ± 12 surges per 100 minutes (Fig. 2). The incidence of surges within each of these three substages of REM sleep was significantly different from the other two substages.

Both coronary flow and cardiac metabolic demand (HR × SBP) were elevated substantially above baseline values during the heart rate surges in each substage of REM sleep (Table 1). When surge events during tonic REM, moderately phasic REM and intensely phasic REM sleep were compared by one-way ANOVA tests, no significant differences were found among these three groups in the magnitudes of the changes observed in coronary flow, heart rate, blood pressure or cardiac metabolic demand. Therefore, the "moderate" and "intense" subgroups of phasic REM were combined into one group for subsequent analyses of other properties of the surge events.

During the surges of phasic REM sleep but not tonic REM sleep, the increase in coronary flow was significantly correlated with the increase in cardiac metabolic demand ($p < 0.0002$, Pearson correlation coefficient = 0.29). This result is due to the correspondence between the increases in coronary flow and heart rate (p

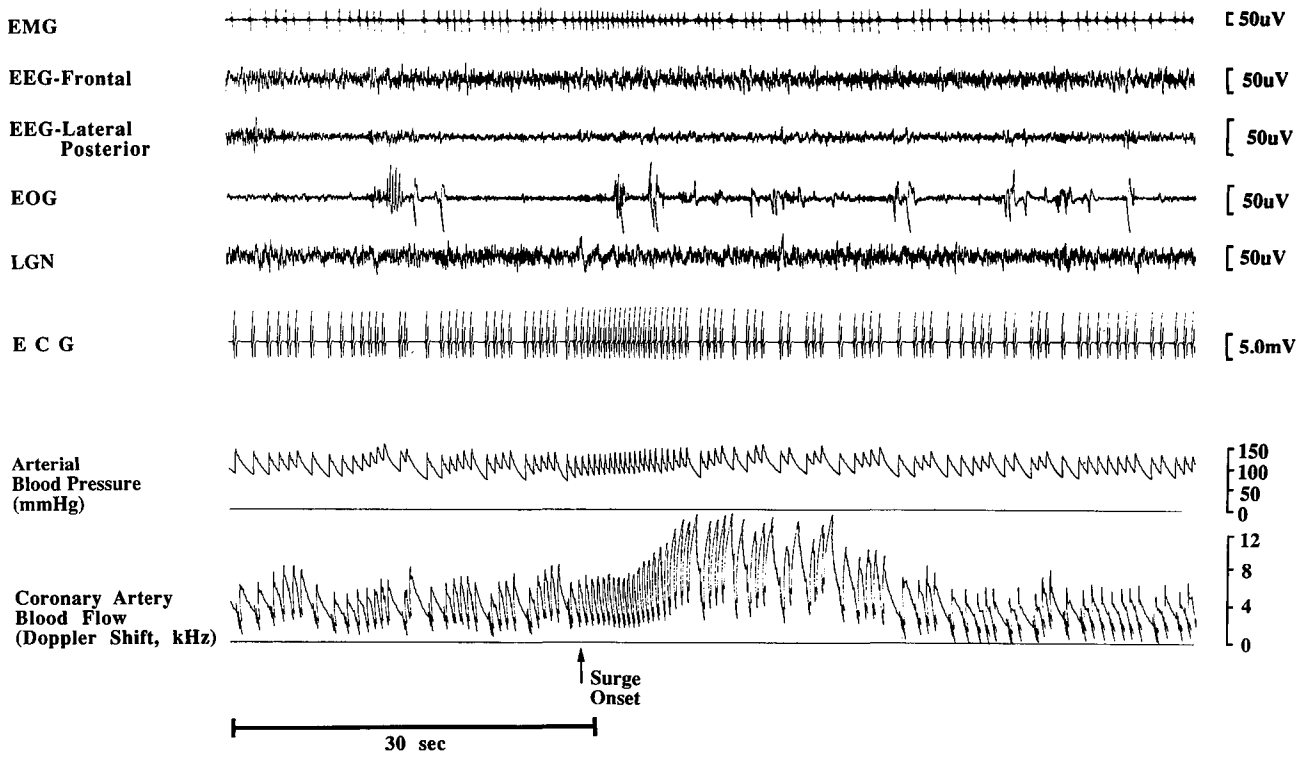

FIG. 1. Illustration of HR and CBF surge during a period of REM sleep marked by frequent bursts of phasic eye activity. The arrow indicating surge onset also indicates the beginning of the 12-second period for measurement and calculation of hemodynamic variables. During the first 12 seconds of the surge in HR, cardiac metabolic demand (HR × SBP) increased by 64% and average coronary flow increased by 26%. The maximum coronary flow achieved by the end of the 12-second period represents an increase of 100% over baseline values preceding the surge. EMG: electromyogram. EEG: electroencephalogram. EOG: electrooculogram. LGN: lateral geniculate nucleus field potential recordings. ECG: electrocardiogram. μV: microvolts. mV: millivolts.

< 0.0001, Pearson coefficient = 0.31), as there is no significant correlation with the minimal changes in BP, which averaged less than 4%. Thus, metabolic factors play an important role in the coronary flow increases associated with the heart rate surges (37% ± 3%) of phasic REM sleep. These correlation coefficients indicate only a moderate degree of correspondence between the increases in coronary flow and myocardial metabolism during the surges.

The data (Fig. 3) indicate a partial mismatch between the percent increases in coronary flow (25% ± 3% above baseline) and concomitant cardiac metabolic demand (41% ± 2%). This disparity was significant during the surges of phasic REM sleep ($p < 0.009$, df = 6, $t = -3.82$). Additional data may be required to ascertain the significance of a similar disparity observed in the small number of events in tonic REM sleep, as there was no statistical association between the increases in cardiac metabolic demand (35% ± 7%) and the coronary flow surges (18% ± 4%) in this group (Fig. 3). In summary, although there was a fairly consistent relationship between coronary flow and metabolic demand during the surges of phasic REM sleep, coronary flow did not increase nearly as much as would be expected from the increases in heart rate and cardiac metabolism.

Events within phasic REM sleep were analyzed on the basis of the presence or absence of muscle twitches (Fig. 4). Although brief elevations in blood pressure were occasionally observed during episodes of phasic REM with muscle twitches (Fig. 4), these small increases in BP were quite rare, accompanying only one-sixth of the surges. Also, group data indicated no statistically significant changes in blood pressure associated with HR surges in any of the substages of REM sleep analyzed. Comparison of events within phasic REM on the basis of the presence or absence of muscle twitches showed no significant differences in the percent change in heart rate or myocardial metabolic demand.

The presence or absence of muscle twitch had no significant effect on the temporal relationships of the initiation of sinus tachycardia and the onset and peak of the CBF surges. Within phasic REM sleep, the onset of sinus tachycardia preceded the initiation of the CBF surge by ≤0.5 seconds in 54% of events, but in 46% of events, the CBF surge was delayed by 2.9 ± 0.3 seconds after the onset of sinus tachycardia. The CBF

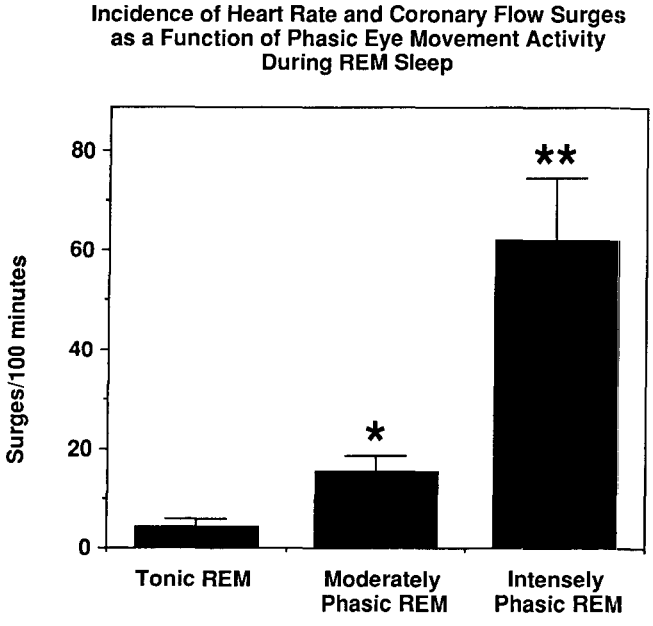

FIG. 2. Summary of the incidence of surges in heart rate and coronary flow, expressed as number of events per 100 minutes of each arbitrarily defined substage of REM sleep. REM: rapid eye movement sleep. Tonic REM: 0–2 eye movements per 15-second epoch. Moderately phasic REM: 3–10 eye movements per 15-second epoch. Intensely phasic REM: >10 eye movements per 15-second epoch. *$p < 0.014$ for comparison of incidence in moderately phasic REM to that of tonic REM sleep ($df = 6$, $t = -3.43$). **$p < 0.007$ for comparison of incidence in moderately phasic REM to that of intensely phasic REM sleep ($df = 6$, $t = -4.03$) and $p < 0.003$ for comparison of incidence in tonic REM to that of intensely phasic REM sleep ($df = 6$, $t = -4.86$). The Bonferroni relationship yields $0.05/3 = 0.017$ as the critical alpha value for significance for these three comparisons.

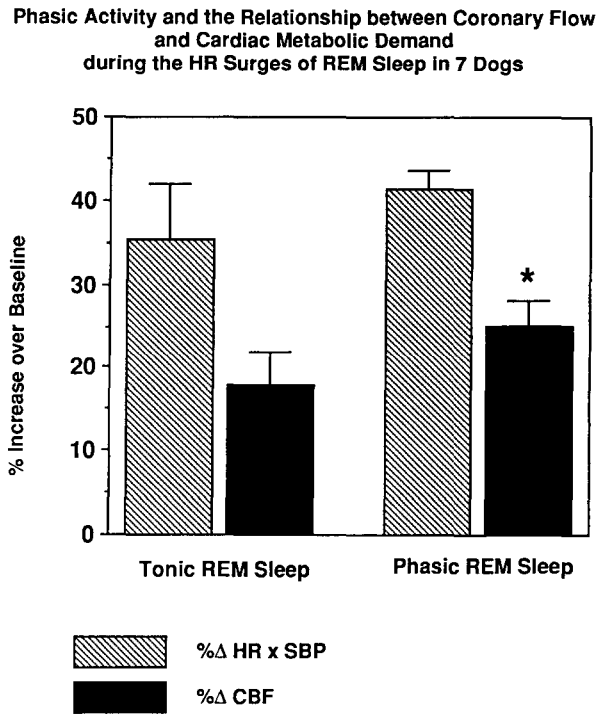

FIG. 3. Phasic activity and the relationship between coronary flow and cardiac metabolic demand during the HR surges of REM sleep. Paired comparisons of the percent increase in coronary flow to the percent increase in cardiac metabolic demand indicated that the mismatch was statistically significant (*$p < 0.009$, $df = 6$, $t = -3.82$) in phasic REM sleep but not during tonic REM sleep ($p < 0.06$, ns; $df = 4$; $t = -2.60$).

surge peaked on average 5.2 ± 0.3 seconds after its onset in 97% of the events. In those events accompanied by a muscle twitch, there was no consistent pattern of twitch initiation either before, after or simultaneous with the beginning of the HR surge.

However, the incidence of surge events (139 ± 28 per 100 min) was almost eleven times greater in those epochs of phasic REM that also contained a muscle twitch than in those that did not (13 ± 5 per 100 min) ($p < 0.006$, $df = 6$, $t = 4.18$) (Fig. 5). The proportion of phasic REM epochs containing muscle twitches ranged from 9% to 38% in the seven dogs, yielding an average value of 20%. Our data suggest that the presence of muscle twitch is a highly significant indicator of the episodic CNS activity that underlies the heart rate and coronary flow surges of phasic REM sleep.

DISCUSSION

We have demonstrated that 90% of the surges in heart rate and coronary flow are concentrated in periods of phasic REM sleep compared to 10% during tonic REM sleep. Increased eye movement activity and the presence of muscle twitches were taken as indicators of the enhanced CNS excitability associated with episodes of phasic REM sleep. The incidence of the flow surges was related in rather striking fashion to the degree of phasic eye movement activity. During intensely phasic REM, the surges were three times more frequent than in moderately phasic REM sleep and 15 times more frequent than in tonic REM sleep. Neither the frequency of eye movements nor the presence of muscle twitch had any effect on the magnitudes of the heart rate and coronary flow surges. However, the incidence of surge events was almost 11 times greater in those epochs of phasic REM sleep that also contained a muscle twitch than in those that did not. The hemodynamic responses of phasic REM sleep were clearly distinct from those during awakening, which typically initiates sustained increases in both blood pressure and heart rate. The REM sleep-associated surges in HR and coronary flow also differ markedly from episodes of coronary vasodilation, which often follow pauses in heart rhythm during transitions from one sleep state to another state (16).

Our data indicate that enhanced cardiac metabolic demand (as indicated by the product of HR × systolic BP) (21) was sufficient to account for the sinus tachy-

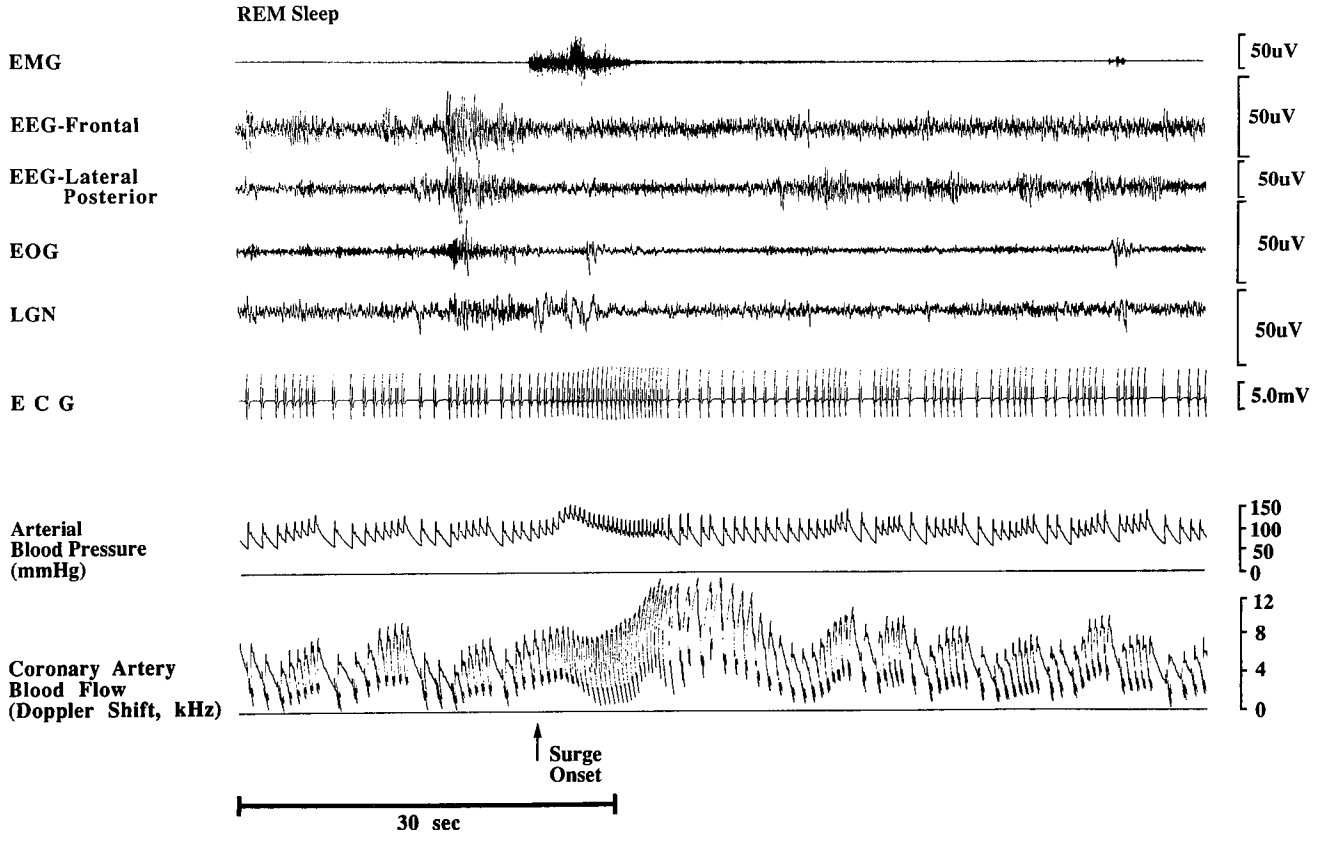

FIG. 4. Illustration of surges in heart rate, blood pressure, and coronary flow during REM sleep with phasic muscle twitch. Cardiac metabolic demand (HR × SBP) increased by 110%, and average coronary flow increased by 32.5% during the first 12 seconds of the surge. The maximum coronary flow achieved 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 during this period of monitoring. Although brief elevations in blood pressure were occasionally observed during episodes of phasic REM (as shown here), these small increases were rare. Group data indicate that no statistically significant changes in blood pressure were associated with HR surges in any of the substages of REM sleep.

cardia-associated increases in coronary flow. However, during the first 12 seconds of the surge events, coronary flow increased by only 25%, which is not as great as would be expected from the increases in heart rate (37%) and cardiac metabolism (41%). Normal coronary circulation exhibits remarkably linear coupling between coronary blood flow and myocardial metabolism (21). The mismatch of these elements during phasic REM sleep suggests involvement of nonmetabolic vasomotor control. For example, this mismatch might be the result of: 1) transient neurally mediated coronary vasoconstriction at the onset of the surges in heart rate or 2) tonic coronary vasoconstriction prevailing throughout the duration of some surge events. Another hypothesis is that sleep might be associated with an additional delay in the normal response of coronary vessel tone to metabolic vasoactive substances.

Studies in conscious dogs by Billman and Randall support the possibility of a delay in vascular response due to neural activation (25). Dogs subjected to Sidman avoidance trials experienced a 12–15-second lag between onset of heart rate increase and the subsequent increase in coronary flow. When this early phase of coronary constriction was blocked by alpha-adrenergic antagonists, the onset of the increase in coronary flow was nearly simultaneous with the surge in heart rate. Thus, in the absence of alpha-adrenergic blockade, vasoactive products of cardiac metabolism require time to build up to levels sufficient to counteract the sympathetically mediated coronary constriction that initially accompanies the increase in heart rate. A similar mechanism may operate during the onset of some of the REM sleep-associated surges in HR and CBF.

Transient fluctuations in heart rate, blood pressure and respiration accompany bursts of eye movements and PGO waves (8–13). During REM sleep, phasic CNS activity apparently provides a physiological substrate for the potential, but not obligatory, expression of episodic variability in autonomic regulation. In our study, increased eye movement activity and the presence of muscle twitches were taken as indicators of the pervasive changes in CNS neuronal excitability associated with episodes of phasic REM sleep. It is likely

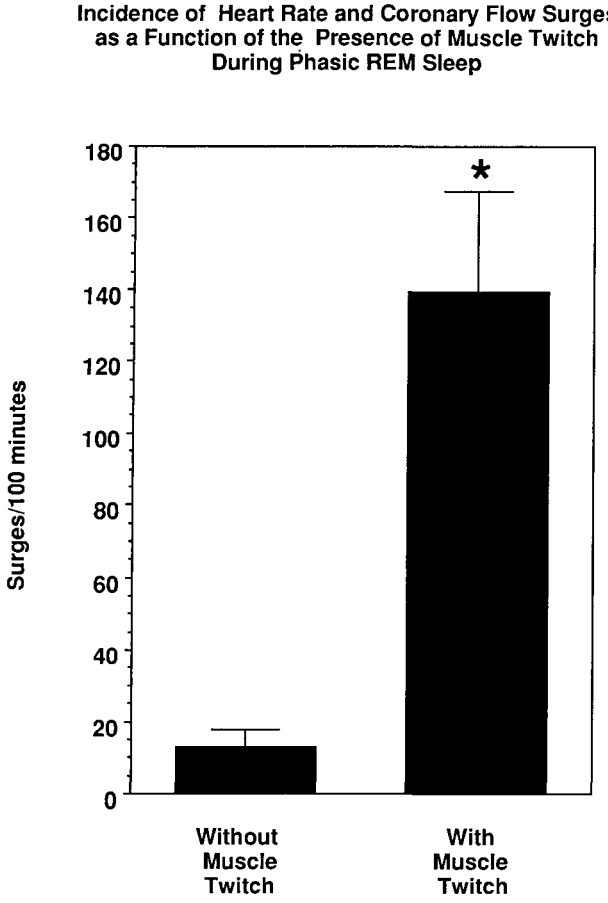

FIG. 5. Association between muscle twitches and the incidence of heart rate and CBF surges during phasic REM sleep. Intensely phasic REM and moderately phasic REM sleep were combined into one group for this analysis. In comparison to REM sleep without muscle twitch, surge events occurred almost eleven times more frequently in 15-second epochs of REM sleep which also included a muscle twitch ($p < 0.006$, $df = 6$, $t = 4.18$).

that the phasic enhancement of CNS excitability is responsible for the increased incidence of sinus tachycardia-associated surges in coronary flow. Other qualitative differences in autonomic regulation during phasic REM compared to tonic REM sleep have been described. The following are but a few illustrative examples. Substantial fluctuations in HR, BP and respiration are associated with phasic episodes of REM sleep in both cats (8,11) and humans (9). In the medulla of sleep-deprived cats, specific patterns of respiratory neuronal activity have been correlated with PGO activity (26,27), another standard indicator of phasic REM sleep. An increased frequency of sleep-disordered breathing (12) and diminished respiratory reflex responses to hypercapnia or lung inflation (13) occur during phasic REM sleep in dogs. Muscle twitches and/or frequent eye movements accompany transient vasoconstriction in regionally specific vascular beds. These episodic changes occur against a background of selective redistribution of blood flow in renal, mesenteric and skeletal muscle beds during REM sleep in cats (10). Our data are consistent with these prior reports to the extent that the frequency of HR and CBF surges, but not their magnitude, was characteristic of the most intensely phasic periods of REM sleep, as evidenced by numerous eye movements and muscle twitches.

Various state-dependent changes in the association of heart rate and/or blood pressure with specific patterns of neuronal discharge have been observed in the parabrachial pons (7), the midbrain periaqueductal gray (28), the amygdala (29) and regions of limbic cortex (30). These regions are involved with the cardiovascular variability observed during REM sleep, but it is not known whether such state-dependent neuronal activity represents a central correlate of autonomic afferent or efferent activity (30). Correlation of sleep-state dependent changes in coronary flow to neural activity in specific CNS regions awaits identification of the CNS sources of vagal influences on coronary vasomotor tone, details of which are still lacking. Sympathetically mediated coronary vasoconstriction is influenced by the medullary reticular formation (31) and the perifornical lateral hypothalamus (32).

In summary, dynamic changes in CBF exhibit characteristic patterns of association with specific sleep state phenomena. The direct implication of our data is that the sinus tachycardia-associated surges in coronary flow represent part of the coordinated repertoire of autonomic responses intrinsic to phasic periods of REM sleep. The phenomena observed during tonic and phasic REM sleep probably are due to fundamental variations in patterns of neural activation of the heart. In terms of providing insights into clinical problems, our experimental model may help to identify the factors involved in the genesis of nocturnal angina and in cardiac arrhythmias during sleep or during episodes of sleep apnea. These and other clinical phenomena have been studied extensively during sleep, but the underlying mechanisms remain to be explored (3,33–35).

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REFERENCES

1. Kirby DA, Verrier RL. Differential effects of sleep stage on coronary hemodynamic function. *Am J Physiol: Heart Circ Physiol* 1989;256:H1378–H1383.
2. Kirby DA, Verrier RL. Differential effects of sleep stage on

coronary hemodynamic function during stenosis. *Physiol Behav* 1989;45:1–4.
3. Nowlin JB, Troyer WG Jr, Collins WS, et al. The association of nocturnal angina pectoris with dreaming. *Ann Intern Med* 1965;63:1040–6.
4. Callaway CW, Lydic R, Baghdoyan HA, Hobson JA. Pontogeniculo-occipital waves: spontaneous visual system activity during rapid eye movement sleep. *Cell Mol Neurobiol* 1987;7: 105–49.
5. Elazar Z, Hobson JA. Neuronal excitability control in health and disease: a neurophysiological comparison of REM sleep and epilepsy. *Prog Neurobiol* 1985;25:141–88.
6. Siegel J, Rogawski MA. A function for REM sleep: regulation of noradrenergic receptor sensitivity. *Brain Res Rev* 1988;13: 213–33.
7. Sieck GC, Harper RM. Discharge of neurons in the parabrachial pons related to the cardiac cycle: changes during different sleep-waking states. *Brain Res* 1980;199:385–99.
8. Baust W, Holzbach E, Zechlin O. Phasic changes in heart rate and respiration correlated with PGO-spike activity during REM sleep. *Pflugers Arch* 1972;331:113–23.
9. Snyder F, Hobson JA, Morrison DF, Goldfrank F. Changes in respiration, heart rate, and systolic blood pressure in human sleep. *J Appl Physiol* 1964;19:417–22.
10. Mancia G, Baccelli G, Adams DB, Zanchetti A. Vasomotor regulation during sleep in the cat. *Am J Physiol* 1971;220:1086–93.
11. Gassel MM, Ghelarducci B, Marchiafava PL, Pompeiano O. Phasic changes in blood pressure and heart rate during the rapid eye movement episodes of desynchronized sleep in unrestrained cats. *Arch Ital Biol* 1964;102:530–44.
12. Hendriks JC, Kovalski RJ, Kline LR. Phasic respiratory muscle patterns and sleep-disordered breathing during rapid eye movement sleep in the English bulldog. *Am Rev Respirat Dis* 1991; 144:1112–20.
13. Sullivan CE, Murphy E, Kozar LF, Phillipson EA. Ventilatory responses to CO_2 and lung inflation in tonic versus phasic REM sleep. *J Appl Physiol: Respirat Environ Exercise Physiol* 1979; 47:1304–10.
14. *Guide for the care and use of laboratory animals,* NIH publication No 86-23, revised 1985.
15. Council of The American Physiological Society. Guiding principles in the care and use of animals. *Am J Physiol* 1992;263: unnumbered page.
16. Dickerson LW, Huang AH, Nearing BD, Verrier RL. Primary coronary vasodilation associated with pauses in heart rhythm during sleep. *Am J Physiol: Regulatory Integrative Comp Physiol* 1993;264:R186–R196.
17. Lim RKS, Liu C-N, Moffitt RL. *A stereotaxic atlas of the dog's brain.* Springfield, IL: Charles C. Thomas, 1960.
18. Ursin R, Sterman MB. *A manual for the standardized scoring of sleep and waking states in the adult cat.* Los Angeles: Brain Information Service/Brain Research Institute, University of California, 1981.
19. Lucas EA, Powell EW, Murphree OD. Baseline sleep–wake patterns in the pointer dog. *Physiol Behav* 1977;19:285–91.
20. Wauquier A, Verheyen JL, van den Broeck WAE, Janssen PA. Visual and computer-based analysis of 24 h sleep-waking patterns in the dog. *Electroencephalogr Clin Neurophysiol* 1979;46: 33–48.
21. Rooke GA, Feigl EO. Work as a correlate of canine left ventricular oxygen consumption, and the problem of catecholamine oxygen wasting. *Circ Res* 1982;50:273–86.
22. Dickerson LW, Huang AH, Schryver T, Nearing BD, Verrier RL. Distribution of heart rate and coronary blood flow surges during tonic and phasic REM sleep. *Sleep Res* 1990;19:37 (abstract).
23. Dickerson LW, Thurnher MM, Verrier RL. Coronary flow surges enhanced during the phasic muscle twitches of REM sleep. *Soc Neurosci Abst* 1992;18:1226 (abstract).
24. Haddad GG, Jeng HJ, Lee SH, Lai TL. Rhythmic variations in R-R interval during sleep and wakefulness in puppies and dogs. *Am J Physiol: Heart Circ Physiol* 1984;247:H67–H73.
25. Billman GE, Randall DC. Mechanisms mediating the coronary vascular response to behavioral stress in the dog. *Circ Res* 1981; 48:214–23.
26. Orem JM. Respiratory neuronal activity in sleep. In: Edelman NH, Santiago TV, eds. *Breathing disorders of sleep.* New York: Churchill Livingstone, 1986:19–44.
27. Orem JM. Medullary respiratory neuron activity: relationship to tonic and phasic REM sleep. *J Appl Physiol* 1980;48:54–65.
28. Ni H, Zhang J, Harper RM. Cardiovascular-related discharge of periaqueductal gray neurons during sleep-waking states. *Brain Res* 1990;532:242–8.
29. Frysinger RC, Zhang J, Harper RM. Cardiovascular and respiratory relationships with neuronal discharge in the central nucleus of the amygdala during sleep-waking states. *Sleep* 1988; 11:317–22.
30. Harper RM, Frysinger RC, Zhang J, Trelease RB, Terreberry RR. Cardiac and respiratory interactions maintaining homeostasis during sleep. In: Lydic R, Biebuyck JF, eds. *Clinical physiology of sleep.* Bethesda: American Physiological Society, 1988: 67–78.
31. Gutterman DD, Bonham AC, Arthur JM, Gebhart GF, Marcus ML, Brody MJ. Characterization of coronary vasoconstrictor site in medullary reticular formation. *Am J Physiol: Heart Circ Physiol* 1989;256:H1218–H1227.
32. Bonham AC, Gutterman DD, Arthur JM, Marcus ML, Gebhart GF, Brody MJ. Electrical stimulation in perifornical lateral hypothalamus decreases coronary blood flow in cats. *Am J Physiol* 1987;252:H474–H484.
33. Gillis AM, MacLean KE, Guilleminault C. The QT interval during wake and sleep in patients with ventricular arrhythmias. *Sleep* 1988;11:333–9.
34. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. *Am J Cardiol* 1983;52:490–4.
35. Verrier RL, Dickerson LW. Autonomic nervous system activity and coronary blood flow changes as a function of the sleep-wake cycle. *Circulation* 1991;83(Suppl. II):II-1–II-9.