Primary vagally mediated decelerations in heart rate during tonic rapid eye movement sleep in cats

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METHODS

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

Surgical preparation. Seven adult male cats weighing between 2 and 2.5 kg were anesthetized with halothane (1–2%) and chronically implanted with electrodes to monitor electroencephalogram (EEG), pontogeniculooccipital (PGO) wave activity in lateral geniculate nucleus (LGN) [6.5 anterior (A), 10.0 lateral (L), +12.0 ventral (V)], hippocampal CA1 theta activity (3.3 A, 5.5 L, +17.0 V), electromyogram (EMG), electrooculogram (EOG), respiration, and electrocardiogram (ECG). The stereotaxic coordinates are according to Berman (4). EMG and EOG were monitored from electrodes placed in the nuchal muscle and posterior wall of the orbit, respectively. Respiratory was monitored with a pair of diaphragmatic electrodes inserted through a midline incision in the peritoneum and sutured directly onto the costal margin of the muscle. Precordial ECG electrodes were placed subcutaneously. The nonchephalic electrode leads were tunnelled subcutaneously to emerge with the cephalic leads in an ammonel pin connector at the top of the head. In three animals, a jugular intravenous catheter was inserted subcutaneously for later autonomic blockade. In two additional animals, a cath-

IT HAS LONG BEEN KNOWN that sleep results in profound state-dependent alterations in heart rate (2, 9, 12, 19, 29, 32). Slow-wave sleep (SWS) is associated with a relatively stable pattern of reduced heart rate characterized by respiratory sinus arrhythmia. Rapid eye movement (REM) sleep results in more labile heart rate and is characterized by abrupt fluctuations (2, 8, 9, 14–16, 23). The most common is a surge in heart rate that is generally accompanied by the baroreflex-mediated deceleration in rate in response to the initial tachycardia (2, 8, 9, 23).

The REM sleep-induced increases in heart rate are accompanied by a striking increase in coronary arterial blood flow that, in canines, achieves 35% over baseline and lasts for 15–20 s (15). These heart rate surges occur mainly during phasic REM sleep (8) and appear to be mediated by the sympathetic nervous system because they are abolished by chronic stellectomy (15). In canines with coronary stenosis, the surge in heart rate results in a decrease in coronary flow through the stenosed vessel (16). REM sleep may have an important impact on arrhythmogenesis clinically, because ventricular arrhythmias (6, 32, 33) and angina (19, 21) are more pronounced during this phase of sleep. The importance of changing autonomic tone to cardiac vulnerability during sleep is further underscored by the recent clinical evidence of a nonuniform distribution of atrial fibrillation (25), sudden death, myocardial infarction, and implantable cardioverter/defibrillator discharge (18).

In the present study, we describe a novel phenomenon of a primary deceleration in heart rate that occurs predominantly during tonic REM sleep. This pattern is distinct from the previously described baroreflex-mediated decelerations in that it is characterized by an abrupt decrease in heart rate without antecedent or subsequent changes in rate.

The main goals of our study were to characterize the primary decelerations in heart rate and to shed light on the underlying central and peripheral autonomic mechanisms. These objectives were accomplished by recording from several CNS structures and by administration of selective autonomic blocking agents that do not cross the blood-brain barrier.

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Heart rate decelerations during tonic REM sleep

Statistical methods. The two-way ANOVA was used to calculate differences in the relative incidence of events by sleep stage. Bonferroni post-test was used to compare the results among the sleep states. Values are means ± SE (P < 0.05).

RESULTS

Our findings demonstrate that tonic REM sleep is associated with marked, transient reductions in heart rate that are not preceded by increases in heart rate (Fig. 1). This event is characterized as an R-R interval increase >20% over the R-R mean value for the preceding 6 s. A second criterion was a duration of ≥1.4 s. The 44 h of control records analyzed yielded 27.4 h of sleep, with 18.5 h of SWS and 8.8 h of REM sleep. There were 179 heart rate events during sleep that satisfied the deceleration criteria. The mean R-R interval decrease was 34 ± 9%, and the greatest increase was 58%. The return to normal rhythm after the deceleration episode was unremarkable, showing no significant alteration in rate compared with the predeceleration rate (Fig. 2). The great majority (86%) of all decelerations lasted between 1.5 and 3 s, with a mean duration of 2.25 ± 0.7 s.

The two cats instrumented for arterial blood pressure measurement, we found that this parameter was relatively stable before and after the heart rate decelerations of tonic REM (Fig. 3). On cessation of PGO activity and concomitant with the heart rate deceleration, there was a moderate but statistically significant reduction in arterial blood pressure, which returned to the predeceleration value on resumption of PGO wave firing. The fact that the pressure change was relatively minor probably accounts for the absence of an appreciable reflex compensatory heart rate increase.

All heart rate decelerations included in this analysis are distinct from respiratory sinus arrhythmia. Examination of respiratory-linked decelerations detected through the diaphragmatic tracing during both REM and SWS revealed that the mean R-R increase for sinus

Fig. 1. Representative polygraphic recording of a primary heart rate deceleration during tonic rapid eye movement sleep (T-REM). During this deceleration, heart rate decreased from 150 to 105 beats/min, or 30%. Deceleration occurred during a period devoid of pontogeniculocerebellar (PGO) spikes in lateral geniculate nucleus (LGN) or theta rhythm in hippocampal (CA1) leads. Deceleration is not a respiratory arrhythmia, because it is independent of diaphragmatic movement. Abrupt decreases in amplitude of CA1, PGO waves (LGN), and respiratory amplitude and rate (DIA) are typical of transitions from phasic to tonic REM. EKG, electrocardiogram; EMG, electromyogram; DIA, diaphragm.

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Arrhythmia was 18%, with a mean duration <1.4 s. Furthermore, heart rate decelerations coinciding with expiratory diaphragmatic inflections or appearing in close rhythmic series were excluded from the analyses. The criteria used in selecting decelerations thus excluded most heart rate decelerations linked to respiratory sinus arrhythmia.

The relationship between heart rate decelerations and sleep states was also explored. SWS composed 42% of the total recording time and 68% of the total sleep period. REM sleep composed 20% of the total recording time and 32% of the total sleep period. The mean proportion of REM sleep spent in tonic activity was ~30%. SWS averaged 1 deceleration per 43.5 min; phasic REM sleep averaged 1 deceleration per 16 min. During tonic REM sleep, decelerations occurred at a rate of 1 per 74 s, a 13-fold increase over phasic REM sleep (P = 0.0002) (Fig. 4). Significantly more decelerations occurred during tonic REM compared with either phasic REM or SWS (P < 0.001, Bonferroni multiple-comparison test). The difference between the number of decelerations during phasic REM and SWS was not significant (P > 0.05).

Peripheral autonomic blockade with the mixed muscarinic antagonist glycopyrrolate both alone (Fig. 5) and 90–120 min after β-blockade with atenolol immediately abolished heart rate decelerations during REM sleep. At the dosage used, glycopyrrolate produced a mean rate elevation of 49% and atenolol caused a mean heart rate depression of 16%. The effect of glycopyrrolate at this dose also persisted beyond one half-life of the drug. Administration of the β-adrenergic antagonist atenolol did not affect the frequency of decelerations (Fig. 6). In two cats, we compared the proportion of recording time spent in REM sleep and the mean duration of REM epochs during 2 h before and after glycopyrrolate and/or atenolol administration. These
lack of lipophilicity of the two agents.

Perhaps due to the remote intravenous access and the indicating that sleep structure had not been disrupted, another distinctive feature is that the deceleration occurs primarily during tonic REM sleep. It is distinct from previously reported sleep state-dependent perturbations in heart rhythm inasmuch as it occurs in the absence of antecedent acceleration or subsequent change in heart rate or arterial blood pressure. In earlier reports by Baust and Bohnert (2) and Dickerson and co-workers (7), decelerations were almost invariably accompanied by prior accelerations in rate, with the likely involvement of baroreceptor activation. Another distinctive feature is that the deceleration occurs primarily during tonic REM sleep. This differs from the previously observed baroreceptor-mediated decelerations, which occur mainly during transition from SWS to desynchronized sleep and more frequently during phasic REM than any other stage of REM sleep (7). It is surprising that this phenomenon of a primary deceleration has not been previously described. This omission may have been in part due to the fact that previous investigations have relied predominantly on ECG recordings with a highly compressed time scale or on tachograph recordings, which have a relatively long time constant and do not provide accurate representation of beat-to-beat changes. In the present study, the customized software, with preprogrammed, objective criteria for acceleration and deceleration, made it possible to track in exquisite detail the subtle dynamics of beat-to-beat fluctuations throughout the recording period.

Comparison of new observations with previous reports of cardiac decelerations in REM. This phenomenon appears to be distinct from the reductions in heart rate observed by Dickerson and co-workers (7). They found heart rate pauses accompanied by increases in coronary blood flow that were concentrated during transition from SWS to desynchronized sleep and in REM sleep, where they occurred more frequently during phasic than tonic REM sleep. Because the heart rhythm pause was almost invariably preceded by tachycardia and elevations in arterial blood pressure, it is likely that the deceleration in rate was the result of reflex vagal activation secondary to baroreceptor stimulation. This differs from the present findings of decelerations that occur primarily during tonic REM sleep and are not associated with any preceding or subsequent change in heart rate or arterial blood pressure. The only point of similarity is that the phenomena appear to have a common mediator, namely enhanced vagal activity. In the heart rhythm pauses described by Dickerson and co-workers (7), however, vagal activity appears to be due to a reflex response after sinus tachycardia and hypertension. In the present study, the involvement of the vagus appears to be directly initiated by central influences, because there is no antecedent or subsequent change in heart rate or arterial blood pressure. The REM sleep-related decelerations reported by Baust and Bohnert (2) in their classic studies were also heralded by rate accelerations and were therefore likely to have been part of a reflex response. These heart rate decelerations in the present study were not preceded by a rise in arterial blood pressure, and therefore the present phenomenon does not appear to be attributable to baroreflex phenomenon. Rather, the main mechanism appears to be central activation of the vagus nerve, which slows the heart directly. This surmise is further supported by the fact that the decelerations were completely eliminated by muscarinic blockade with glycopyrrolate.

The phenomenon that we have observed is more akin to the primary, vagally mediated deceleration in heart rhythm described by Guilleminault and co-workers (13).
in human subjects. They observed striking periods of sinus arrest during REM sleep in young adults who were apparently normal with respect to cardiac function. Two of the four subjects studied had infrequent syncpe while ambulatory at night and experienced periods of asystole of up to 9 s during REM sleep. Administration of muscarinic blockers, either atropine or protriptyline, significantly reduced the duration of the nocturnal asystoles but did not prevent them. The authors concluded that the nocturnal asystoles were the result of exaggerated, if not abnormally elevated, vagal tone. However, given the present observations of significant increases in vagal tone during sleep, the patients may have represented an extreme portion of a continuum of vagal activation during REM sleep.

An important difference between the phenomena reported by Guilleminault (13) and the present findings in cats is that in the human subjects, the decelerations were concentrated during phasic, rather than tonic, REM sleep. Thus it remains to be determined whether the phenomena differ fundamentally or are species specific. Although the predominant number of decelerations in the cats occurred during tonic REM sleep, nevertheless 14% occurred during phasic REM sleep. Thus it is possible that the distribution of decelerations in humans may favor phasic rather than tonic REM sleep.

Autonomic pathology, as suggested by Guilleminault (13), may also impact on the magnitude and presentation of the phenomenon in human subjects.

Probable CNS origins of heart rate decelerations in tonic REM. The primary involvement of CNS activation is demonstrated by the consistent, antecedent abrupt cessation of PGO activity and concomitant interruption of hippocampal theta rhythm, which are salient features of the tonic REM sleep decelerations. This finding had been anticipated based on the established positive relationship between PGO activity and hippocampal theta activity in cats (5, 26). How these changes in CNS activity lead to the tonic REM sleep-induced increase in vagal tone to suppress sinus node activity remains unknown. The literature on the relationship between PGO activity during sleep and cardiac function is sparse. Baust and colleagues (3) found only a relatively minor, baseline rate-dependent, variable response in heart rate (<80 ms R-R interval change) to PGO activity in cats.

In normal human volunteers, Taylor and colleagues (30) observed heart rate decelerations during REM sleep that preceded eye bursts by 3 s and suggested that the phenomenon reflects an orienting response at the onset of dreaming. However, because the decelerations were not illustrated nor their magnitude described, their similarity to those we characterize is debatable. Notwithstanding extensive studies of the physiological and anatomic basis for PGO activity, little is known about the conductivity and functional relationship to heart rhythm control during sleep (1, 10, 27, 28).

Possible mechanisms of heart rate decelerations in tonic REM. The most likely basis for the abrupt deceleration in heart rate during tonic REM sleep is a change in the centrally induced pattern of autonomic activity to the heart. This could be the result of a decrease in sympathetic activity or an enhancement of vagal tone, either alone or in combination. We found that cardioselective β1-adrenergic blockade with atenolol did not affect the incidence or magnitude of decelerations but muscarinic blockade with glycopyrrolate completely abolished the phenomenon. These observations suggest that the tonic REM sleep-induced decelerations are primarily mediated by bursting of cardiac vagal efferent fiber activity. It is well known that enhanced vagal activity can abruptly and markedly affect sinus node firing rate (22). The quaternary ammonium structure of glycopyrrolate limits its passage through the blood-brain barrier, thus minimizing possible confounding CNS effects (11). The agent did not affect REM sleep structure. Therefore, it is unlikely that indirect effects of the drug on brain state contributed to this effect. Because β-adrenergic blockade exerted no effect on the frequency or magnitude of decelerations, it does not appear that withdrawal of cardiac sympathetic tone is an important factor in the observed rate changes. Rather, a primary surge in vagal activity is implicated. This does not preclude the fact that cardiorespiratory interactions may moderate heart rate, because this influence operates throughout sleep (14). However, our results suggest that respiratory interplay is not an essential component of the deceleration, because the phenomenon often occurred in the absence of a temporal association with inspiratory effort, as is evident in Fig. 3.

Perspectives

The present observations carry important clinical as well as scientific implications. They underscore the principle that sleep state-dependent CNS activity is integrally coupled to cardiac-bound autonomic pathways. Improved understanding of the neuroanatomical and functional linkage between the brain and the heart during sleep may provide important information regarding the adaptive control of cardiovascular function in normal subjects. Clinically, the growing realization of the magnitude of sleep-related cardiovascular risk motivates further exploration of control of cardiac function during sleep in patients with heart disease. It has been estimated that 250,000 myocardial infarctions and 38,000 sudden deaths occur at night (18). The nonrandom distribution of these events implicates triggering by autonomic activity. In addition, −40% of episodes of atrial fibrillation, for a total of one million events in the United States alone, are precipitated at night (25). Atrial tissue is particularly sensitive to the profibrillatory influences of acetylcholine, and pronounced surges in vagal activity could be an important factor in the prevalent but poorly understood phenomenon of nocturnal atrial fibrillation. Thus intense vagal activity, as may occur during either tonic REM sleep, as in the present study, phasic REM sleep (7, 13), or SWS has the potential for precipitating not only pause-dependent ventricular arrhythmias and asystole but also atrial arrhythmias.
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