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Nighttime instabilities of neurophysiological, cardiovascular, and respiratory activity: integrative modeling and preliminary results

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Abstract

Unstable (cyclical alternating pattern, or CAP) sleep is associated with surges of sympathetic nervous system activity, increased blood pressure and vasoconstriction, heightened baroreflex sensitivity, and unstable heart rhythm and breathing. In susceptible persons, CAP sleep provokes clinically significant events, including hypertensive crises, sleep-disordered breathing, and cardiac arrhythmias. Here we explore the neurophysiology of CAP sleep and its impact on cardiovascular and respiratory functions. We show that: (i) an increase in neurophysiological recovery rate can explain the emergence of slow, self-sustained, hypersynchronized A1 CAP-sleep pattern and its transition to the faster A2-A3 CAP-sleep patterns; (ii) in a two-dimensional, continuous model of cardiac tissue with heterogeneous action potential duration (APD) distribution, heart rate accelerations during CAP sleep may encounter incompletely recovered electrical excitability in cell clusters with longer APD. If the interaction between short cycle length and incomplete, spatially heterogeneous repolarization persists over multiple cycles, irregularities and asymmetry of depolarization front may accumulate and ultimately lead to a conduction block, retrograde conduction, breakup of activation waves, reentrant activity, and arrhythmias; and (iii) these modeling results are consistent with the nighttime data obtained from patients with structural heart disease (N=13) that show clusters of atrial and ventricular premature beats occurring during the periods of unstable heart rhythm and respiration that accompany CAP sleep. In these patients, CAP sleep is also accompanied by delayed adaptation of QT intervals and T-wave alternans.

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Keywords

sleep; computational modeling; neurophysiology; cardiac electrophysiology; baroreflex; arrhythmias

Introduction

There are at least two motivations for studying nighttime patterns of autonomic nervous system (ANS) activity and their effects on cardiovascular and respiratory functions. First, sleep is a pure “autonomic stress test;” [1] it exposes intrinsic ANS activity in the absence of environmental triggers and daytime perturbations. Second, unstable sleep (cyclical alternating pattern or CAP sleep [2]) is accompanied by abrupt changes in ANS activity, surges of blood pressure and vasoconstriction, increased baroreflex sensitivity, and unstable heart rhythm and breathing. In susceptible persons, these physiological instabilities can provoke clinically significant cardiovascular and respiratory events, including hypertensive crises, sleep-disordered breathing (SDB), and cardiac arrhythmias.[1] Indeed, in a large, multicenter clinical study of patients with implantable devices, occurrences of atrial arrhythmias (atrial tachycardia and atrial fibrillation, AT/AF) peaked during the nighttime. [3] Moreover, nighttime predominance of AT/AF was found to be most prominent in subjects with frequent AT/AF events. However, the mechanisms and triggers of such a strong nocturnal predominance of AT/AF episodes remain unclear.[3] Similarly, the triggers of ventricular arrhythmias that occur at night are unclear, although their daytime triggers are well established. [4]

It has been shown that changes in cardiac rhythm and respiration can be used to identify periods of unstable CAP sleep, [5] because high electroencephalographic (EEG) activity (CAP period A) is associated with unstable breathing and heart rate accelerations. [6] Period A can be subdivided into periods with slow, high-amplitude oscillations (pattern A1), fast and lower-amplitude oscillations (pattern A3), and combinations of the two (pattern A2).[2] A typical sequence of events involves transitions from A1 to A2 to A3, with pattern A3 eliciting more pronounced heart rate acceleration than patterns A1 and A2.[2]

Here we explore the mechanisms linking the neurophysiology of unstable sleep to the instabilities of cardiovascular and respiratory functions using computational modeling of neurophysiological and cardiac electrophysiological (EP) activity. We also present pilot data on nighttime patterns of cardiac rhythm, repolarization, and respiration, as well as the occurrence of cardiac arrhythmias.

Methods

Large-scale model of EEG activity during CAP sleep

We used the mean-field approach to modeling neuronal activity that was introduced into neuroscience by Wilson and Cowan. [7] The Wilson-Cowan (WC) approach has been shown to provide an accurate representation of the brain's EP activity on a large scale, corresponding closely to the EP data obtained by direct electrocorticographic recordings

from the surface of the brain. [8] Examples of model-generated EP activity in the brain and cardiac tissue are shown in Fig. 1. Specific details are provided in the Appendix.

Simplified model of cardiac EP activity

The modified Morris-Lecar model used in this study has been described in detail; [9] the model equations are provided in the Appendix. The simulations were performed with isotropic and anisotropic (4:1) propagation. A 40×40 cell matrix was paced from the center of the top row. The interval between the earliest depolarization and the latest recovery divided by the square root of the cycle length was 0.4 s. A delayed adaptation of repolarization times to changes in pacing cycle length was modeled by a scaling restitution parameter. Differences in recovery times (i.e., heterogeneity of action potential durations, APD) were assigned in random order and kept constant.

Nighttime data collection and analysis

Nighttime data from 13 patients with cardiomyopathy (ischemic or nonischemic) who were recruited from a Yale University EP practice were used in this study. Clinical variables were collected through chart review. The study was approved by the Yale Human Investigation Committee, and all patients provided written informed consent. The protocol for nighttime data collection from healthy subjects was approved by Salus IRB. Here we show samples of preliminary data that include time series of cardiac rhythm, repolarization, and respiration, as well as vectorcardiographic data (Fig. 2-3).

Repolarization analysis—Methods for repolarization analysis have been described in detail previously. [10], [11] Twenty-four-hour recording of 12-lead electrocardiogram (ECG; Mason-Likar electrode positions), body position, and respiratory movements in the midabdominal region was performed at 250 Hz/channel and 16-bit resolution using multisensor, ambulatory monitors (PinMed, Inc., Pittsburgh, PA). The monitors provide diagnostic-quality ECG data with high-pass filters set at 0.05 and low-pass filters at 500 Hz. The data were upsampled to 1 kHz/channel using cubic spline interpolation. Orthogonal (x, y, z) ECG vectors were constructed using the inverse Dower transformation, [12] and the vector which had the best signal quality was analyzed for each subject throughout.

A previously validated program for adaptive baseline correction [13] was applied to ensure accurate detection of the isoelectrical line. QRS complexes were classified using custom software and verified by an experienced technician. After exclusion of ectopics, series of consecutive sinus beats were processed to identify fiducial points.[10] The dynamics of T-wave alternans (TWA) were examined using two independent time-domain techniques: intrabeat average and modified moving average analyses.[10],[14] Because the correlation coefficient between modified moving average-derived and intrabeat average-derived TWA was 0.72 and results of analyses were similar, only intrabeat analysis results are presented. [15]

Results

Here we show how the slow, circadian-scale changes in the brainstem neuronal recovery properties (experiment 1) influence nighttime cardiac EP dynamics and arrhythmogenesis (experiment 2).

Experiment 1. Computational experiments in a large-scale, continuous, two-dimensional model of a neuronal network

Our computational experiments show that an increase in neurophysiological recovery rate (β) and the resulting shortening of recovery time can explain two essential dynamical properties of unstable CAP sleep[2]: (i) how high-amplitude, self-sustained oscillations of hypersynchronized EEG activity (A1 patterns) emerge from a strong stimulus (e.g., K complex) or a series of such stimuli, and (ii) why A1 patterns are replaced by faster oscillations (A2-A3 patterns) as sleep progresses.[2]

Initially, when the recovery rate is low, a strong stimulus (e.g., K complex) evokes nonsustained waves of activity but no self-sustained oscillations (Fig. 1, Pattern 0). However, as β rises, the same stimulus initiates slow, self-sustained, spatially synchronized oscillations, which are a hallmark of A1 CAP activity (Fig. 1, Pattern 1). As β continues to rise, the recovery interval shortens even further, the frequency of self-sustained oscillations increases; and the faster oscillatory activity becomes similar to the A2-A3 patterns of CAP sleep (Fig. 1, Pattern 2). Fig. 1D shows the initial stimulus and subsequent evolution of neurophysiological activity in the corresponding two-dimensional space.

Experiment 2. Computational experiments in a continuous, two-dimensional model of cardiac tissue

The emergence of A1-A3 CAP sleep patterns described above is associated with heart rate instabilities and accelerations.[2],[6] Computational experiments were performed to examine EP effects of such instabilities in the presence of heterogeneous cardiac repolarization (APD dispersion range: 10-100% in different experiments) and to gain insight into potential mechanisms of nighttime cardiac arrhythmias. To simulate surges of sympathetic activity and accompanying heart rate elevations that occur during CAP sleep, pacing started at a long cycle length (CL=1 sec) and gradually (linearly) decreased to a value at which the propagating repolarization wave encountered incomplete recovery in the areas with longest APD.

When the cardiac cycle shortens (i.e., heart rate increases), APD adaptation (shortening) is delayed by approximately 60-120 sec. [16] During such transitional periods of accelerating heart rate and incomplete APD adaptation, waves of electrical excitation can encounter cell clusters that are at different stages of repolarization (i.e., refractory, incompletely recovered, and fully recovered cells) due to spatial heterogeneities of APD distribution, which can be further exacerbated by acute ischemia or ischemic cardiomyopathy. [17], [18] Cells that are completely recovered will experience normal excitation. In contrast, excitation of cells that are partially recovered will be impaired (e.g., reduced depolarization amplitude and rate) due to incomplete recovery of the respective ionic channels. [19] Finally, cells that are refractory

(unexcitable) will not respond to the next excitation front, creating a local conduction block. As a result of such spatially different responses of cells with different APD, the form of excitation front becomes distorted and spatially irregular. Initially, these spatial irregularities are small and do not lead to any major changes in the global patterns of depolarization and repolarization (Fig. 1E and 1F). No further changes of electrical activity patterns will occur if any of the following conditions are met: (i) the CL becomes longer than the longest recovery time due to the increase of the pacing cycle length, (ii) the repolarization duration in all areas gradually becomes shorter than the pacing CL as a result of the repolarization adaptation to a shorter pacing CL, or (iii) the pacing CL becomes shorter than the shortest refractory period, and the entire cardiac tissue was unexcitable (refractory) during the next depolarization, which led to a complete conduction block.

However, if the interaction between early excitation waves and incomplete repolarization in the regions with long APD continues over multiple cycles, small irregularities and distortions of depolarization waveforms gradually accumulate. These give rise to large-scale changes, including large areas of conduction block or slowing, asymmetry, and breakup of excitation front (Fig. 1G-1I), and ultimately to retrograde and reentrant excitation and the emergence of spirals, the hallmarks of common cardiac arrhythmias (Fig. 1J-1L). For initial conditions with smaller APD heterogeneity, longer pacing was needed (>100 cycles) than for initial conditions with greater APD heterogeneity to allow gradual accumulation of functional, dynamical APD dispersion and conduction waveform abnormalities.

We note that the S1-S2 and very rapid pacing protocols, which are commonly used for arrhythmia induction, can be considered special cases of evoking very fast disruptions of electrical conduction due to the interaction between premature conduction waves and incomplete, spatially heterogeneous recovery.

However, spontaneous (real-life) initiation of sustained (clinically significant), monomorphic ventricular tachyarrhythmias (MVTA) that are most common in patients with ischemic cardiomyopathy does not resemble the S1-S2 protocols or very rapid pacing. Usually, MVTA is preceded by 5-30 min of gradual, modest heart rate elevation, [20] as well as by gradual increase in proarrhythmic repolarization instability.[11] Furthermore, MVTA is usually not preceded by early-coupled premature ventricular complexes (PVC) that would resemble the S1-S2 protocol. In contrast, the commonly observed PVCs usually have a relatively long coupling interval. [21], [22], [23]

To summarize, the S1-S2 sequences or very rapid heart rate are rarely observed before the onset of real-life MVTA. Instead, real-life events are usually preceded by: (i) gradual and modest heart rate increase and (ii) extrasystolic beats with relatively long coupling intervals. Thus, real-life initiation of sustained MVTA is consistent with gradual accumulation of electrical conduction abnormalities due to incomplete, heterogeneous recovery as shown in our model.

Nighttime instabilities in cardiovascular and respiratory activity in human subjects

Heart rate and respiratory movements—Figs. 2A and 2B show examples of simultaneously recorded RR intervals (top tracing) and respiratory movements in the

midabdominal region (bottom tracing) during deep, non-REM sleep in a healthy subject and in a patient with ischemic cardiomyopathy. Note that RR intervals exhibit both respiratory sinus arrhythmia (faster oscillations) and slower, baroreflex-mediated Mayer waves of vasomotor activity, which are associated with changes in arterial pressure. [24] Periods of unstable heart rhythm were often associated with irregular respiratory movements (Fig. 2C and 2D). We note that clusters of premature atrial and ventricular complexes occurred predominantly during such periods of unstable heart rate and respiration (Fig. 2C and 2D, respectively; ectopic beats are depicted as squares below the tracings).

Indices of cardiac repolarization—The decreases in RR interval length (which correspond to surges of heart rate mediated by sympathetic nervous system activity) were accompanied by the shortening of QT intervals with a time delay of approximately 1-2 min (Fig. 2E). The nighttime surges in heart rate (Fig. 2F) were also accompanied by increases in the magnitude of TWAs (Fig. 2G and 2H). The instability of the T-wave amplitude was clearly visible in the three-dimensional space of the three orthogonal ECG vectors obtained from the 12-lead ECG using inverse Dower transformation (Fig. 2I).

Discussion

Here we show that a gradual increase in neurophysiological recovery rate and shortening of recovery time can explain the emergence and evolution of CAP sleep. In particular, this provides a plausible explanation for the fact that CAP sleep does not occur during early sleep stages (which are associated with longer recovery time in our model, Fig. 1A). CAP sleep usually emerges later, during deep sleep stages, and becomes more frequent as total sleep time increases. A gradual increase in neurophysiological recovery rate (Fig. 1B), exhibiting circadian rhythmicity, can explain the emergence of a slow, self-sustained, hypersynchronized A1 CAP-sleep pattern and its transition to faster A2-A3 CAP-sleep patterns. When the recovery rate increases beyond a critical value, slow, self-sustained hypersynchronized neurophysiological activity (CAP-sleep pattern A1) can be triggered by a strong and appropriately timed neurophysiological event (e.g., K complex), which occurs frequently during unstable sleep (sleep-stage transitions) and is associated with vasoconstriction, an increase of sympathetic nervous system activity, and a rise in arterial pressure.[2]

The gradual increase of recovery rate and shortening of recovery time can be attributed to circadian rhythmicity of both central and peripheral molecular clocks, which are associated with changes in the activity of ionic channel and cell EP. [25], [26] While such circadian changes have been reported in separate studies of neuronal cells and cardiomyocytes, our study is the first to link the slow, circadian-scale changes in neuronal recovery properties to nighttime cardiac EP and arrhythmias.

In particular, using a two-dimensional, continuous model of cardiac tissue with heterogeneous APD distribution, we showed that heart rate accelerations during CAP sleep may encounter incompletely recovered electrical excitability in cell clusters with longer APD. If the interaction between short CL and incomplete repolarization persists over multiple cycles, irregularities and asymmetry of depolarization front may accumulate and

ultimately lead to a conduction block, retrograde conduction, breakup of activation waves, reentrant activity, and arrhythmias.

These modeling results are consistent with the nighttime data obtained from patients with structural heart disease that show that clusters of atrial and ventricular premature beats occur during the periods of unstable heart rhythm and respiration accompanying CAP sleep (Fig. 2C and 2D). [2], [6], [5] In these patients, CAP sleep is also accompanied by delayed adaptation of QT intervals and proarrhythmic repolarization instability as manifested by TWA (Fig. 2 and 3).

To the best of our knowledge, this is the first study that explains the emergence and dynamics of slow, self-sustained, hypersynchronous EEG activity during CAP sleep, the transition from slow (A1) to faster (A3) activity, and its proarrhythmic effects. Future studies will determine the prevalence of cardiac repolarization instabilities and the impact of heightened arterial pressure and increased baroreflex sensitivity during CAP sleep.

Limitations

The data were obtained from patients with cardiomyopathy (92% ischemic), and the results may not be generalizable to other populations. Central and obstructive sleep apnea (OSA) and other types of SDB are common in this patient population, in particular during CAP sleep. Diagnostic sleep studies were performed in a small subset (23%) of the study participants, and in this subset, OSA was found in all subjects. Further studies are warranted to examine the prevalence and impact of SDB episodes on the dynamics of cardiovascular activity during CAP sleep.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Fig. 2.

Fig. 3.

Table 1

Demographic and clinical characteristics of study participants (N=13).

Age	63.4 ± 10.4
Sex (male/female)	77% / 23%
Sleep study/sleep disordered breathing	23% / 23%
Etiology:	100%
- Ischemic cardiomyopathy	12 (92%)
- Nonischemic cardiomyopathy	1 (8%)
Patients with frequent ventricular ectopy (>30/hr)	6 (46%)
Premature ventricular beats/hr (median)	
Isolated beats	62 ± 85 (11)
Couples	3.1 ± 4.4 (1.5)
Runs > 4	0.3 ± 0.6 (0)
Total	65 ± 5.0 (0.4)
Sleep study performed / obstructive sleep apnea diagnosed	3 (23%) / 3 (23%)