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Electroencephalogram Characteristics of Autonomic Arousals During Sleep in Healthy Men

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Abstract

Objective—Many sleep disorders involve frequent, brief arousals, not appreciated during conventional sleep stage scoring due to lack of electroencephalogram (EEG) desynchronization. We evaluated the temporal relation between heart rate (HR) changes, an index of autonomic activation, and EEG in seven healthy subjects during sleep.

Methods—We identified bouts of tachycardia-bradycardia and performed spectral analysis of EEG during these. We also identified cortical arousals by the appearance of EEG alpha activity. This allowed us to dichotomize bouts of tachycardia-bradycardia by presence or absence of cortical arousal.

Results—During non-rapid eye movement (REM) sleep, bouts with or without cortical arousal occurred with approximately equal frequency. Those with cortical arousals usually preceded onset of EEG changes. Those without cortical arousals were followed by increases in delta but not alpha power. EEG did not change during bouts in REM sleep.

Conclusions—Capturing bouts of tachycardia-bradycardia is relatively easy via computerized algorithm. Bouts occur with cortical arousal or with slow wave synchronization suggestive of subcortical arousal. Thus, changes in HR may be useful index of arousal.

Significance—These brief bursts of tachycardia-bradycardia are consistent with autonomic arousal. Such a measure may be among the first in a continuum of arousal ending with frank awakening.

Keywords

arousal; autonomic; delta waves; alpha waves; EEG

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Introduction

Many sleep disorders involve frequent, brief arousals that are not appreciated during conventional sleep stage scoring because they do not cause electroencephalogram (EEG) desynchronization. Such arousals are a common feature of normal aging and may be clinically relevant as well. Hence analysis of the microstructure of the sleep profile has become more important not only in developing more sensitive measures of arousal but also in understanding the mechanisms for their occurrence (Halász et al., 2004).

A task force of the American Sleep Disorders Association (ASDA) has defined a set of scoring rules and has provided examples for coding EEG arousals during sleep (ASDA, 1992). On the other hand, (Pitson and Stradling 1998) suggested that non-EEG markers might be important and even more reliable signs of arousals than the EEG. For example, it is known that somatosensory and auditory stimulation during sleep can produce alterations in cardiac, respiratory, and somatic measures without overt EEG desynchronization (Halász, 1993; Carley et al., 1997; Winkelman, 1999). These changes are thought to reflect activation of the brainstem or subcortical arousal system without affecting the cortex. The fact that arousals can begin from subcortical as well as cortical loci supports the idea that there may be a continuum of arousals (Halász et al., 2004) – perhaps beginning with primitive subcortical arousals and extending to clear-cut cortical EEG desynchronization, indicative of the wakeful state (Giovani et al., 2000; Sforza et al., 2000, 2002).

Sforza et al. (2000) showed that bursts of K-complexes and delta waves probably reflect activation of a subcortical arousal system. Of interest is the fact that the same cardiac activation is seen during these bursts as during brief cortical arousals [“microarousals” (Martin et al., 1997) and “phases of transitory activation” (Schieber, 1971)]. In addition, temporal analysis of cerebral and autonomic variations across arousals shows a stereotyped pattern consisting of a rise in heart rate (HR) (Bonnet and Arand, 1997; Sforza et al., 2000) that starts about 1 s before the onset of EEG desynchronization; this finding suggests that at least some arousals start with autonomic activation first. However, the types of EEG patterns that accompany HR change and their relationship in time over a whole night of sleep have not yet been tested and cannot be determined by visual inspection alone because of masking by background EEG activity.

In this study, we examined the relation between brief bursts of tachycardia and EEG patterns, assessed by spectral analysis, over the entire night in seven healthy subjects during spontaneous sleep. The purposes of the study were to determine the EEG response accompanying autonomic activation in order to get further information about arousal mechanisms during sleep, and to ascertain the potential usefulness of changes in HR as an alternative to changes in EEG in assessing and quantifying arousals.

Methods

Subjects

The subjects were 7 healthy, non-medicated males. Their mean age, height, and weight were 27 (range 25–29) yr, 175 (range 172–181) cm, and 71 (range 62–88) kg, respectively. All the subjects were good sleepers and without any history of sleep problems, and none was taking any medication at the time of the sleep studies. All gave their informed consent to participating in this institutionally approved study.

Experimental procedures

Each subject underwent three nights of polysomnographic (PSG) sessions in a soundproof, air-conditioned (22–24 °C), and shaded sleeping room. The first and second night sessions were

for habituation, and the data obtained on the third night were used for analysis. The subjects went to bed at the time they normally do, and got up voluntarily. In addition, they were instructed that on the day of the PSG sessions in the laboratory, they should refrain from alcohol and caffeine ingestion and avoid napping or engaging in prolonged and/or strenuous exercise in the daytime.

Measurements

EEG's (P4–A2, C3–A2), bilateral electrooculograms (EOG's; left, right), the mental electromyogram (EMG_M), the tibialis anterior electromyograms (EMG_{TA}'s; left, right), and electrocardiogram (ECG; standard bipolar leads) were monitored continuously throughout the night. Analog signals for EEG's, EOG's, EMG_M, EMG_{TA}'s, and ECG were processed on a real-time basis at a sampling frequency of 200 Hz, using a personal computer (IBM ThinkPad A30). The sleep stages were manually scored from the PSG recordings every 30 s by two investigators in accordance with standard criteria (Rechtschaffen and Kales, 1968), and all cortical arousals were identified. A cortical arousal was defined according to standard ASDA criteria (ASDA, 1992) as a return to alpha or fast frequency EEG activity, well differentiated from the background, lasting at least 3 s but no more than 15 s. In doing this, we also used ASDA criteria to identify briefer cortical arousals (i.e. microarousals), lasting at least 1.5 s (Martin et al., 1997). In identifying microarousals during REM sleep, we also required an increase in EMG_M amplitude.

RR interval data correction

The RR interval signal was derived from the ECG. All RR intervals were scanned for extra or missing beats that could affect the results of time domain analysis. The abnormal intervals were corrected by either the insertion (for missing beats) or the omission of beats (for doubled or tripled beats). The number of beats corrected manually in this way was < 0.5 %.

Identifying significant tachycardias

Arousal from sleep has been found to be associated with a characteristic pattern of a rise followed by a fall in HR (Schieber, 1971; Pitson et al., 1994; Winkelman, 1999). We identified episodes of tachycardia-bradycardia per a previously published algorithm (Raymond et al., 2003). The RR interval signal was low-pass filtered to remove respiratory sinus arrhythmia, and then epochs of tachycardia-bradycardia were identified according to the following template: a decrease of at least 60 ms over a 10-s window in the filtered RR interval signal, followed within 20 s by a rise of at least 85 ms over a 10-s window. This template identifies small changes in RR interval, and (Raymond et al. 2003) have successfully used it in detecting arousals occurring during sleep in patients with the apnoea/hypopnoea syndrome. In order to avoid multiple detections from a single arousal, tachycardias detected within 10 s of a previous tachycardia were disregarded. Any tachycardia associated with movement (increasing in EMG_{TA}'s activities) was not included in the analysis.

EEG spectral analysis

Using the P4–A2 lead, we performed Fast Fourier transform (FFT) prior to and during each epoch of tachycardia-bradycardia for all subjects to obtain the power spectrum density. EEG power spectra were estimated for 1 s non-overlapping windows. All spectra were estimated by averaging spectra obtained from 10-time shifted subsets of 128 data points. Four frequency bands were defined: delta (0.75–4.5 Hz), theta (4.5–8.0 Hz), alpha (8.0–13.0 Hz), and beta (13.0–25.0 Hz).

Data analysis and statistics

RR interval signals were ensemble averaged for each subject based on the onset of each cortical arousal and are depicted in Figure 1. Ensemble averaging of RR interval signal was also done based on the onset of each bout of tachycardia-bradycardia in order to detect differences in duration and magnitude between bouts associated with cortical arousal and those without cortical arousal; these are depicted in Figure 3. In addition, we ensemble averaged EEG power based on the onset of each bout of tachycardia-bradycardia to show the differences between epochs followed by cortical arousal compared to those without cortical arousal; data are depicted in Figure 4 and Figure 5.

Differences in RR interval with and without cortical arousals were assessed using two-factor repeated-measures ANOVA (see Figure 3). Post hoc analyses used Tukey student range tests to compare means between pairs of conditions. RR interval and spectral EEG were analyzed with repeated measures ANOVA (Figure 1 & Figure 3 and Figure 4 & Figure 5, respectively). For significant ANOVAs, we performed Dunnett's multiple comparison tests to compare baseline data to those occurring subsequently. Statistical significance was accepted when $P < 0.05$.

Results

All subjects reported sleeping normally on the night of their PSG data collection sessions (Table 1). This was confirmed by the PSG recordings, showing that they had normal sleep patterns without any sleep disturbances. In addition, none had central or obstructive sleep apnea or periodic phasic increases in EMG_{TA} 's during sleep.

As expected, the template identified distinct phasic changes in RR interval during sleep in the form of tachycardia-bradycardia. Bouts of tachycardia-bradycardia occurred at different rates during the different stages of sleep (Table 2), being less common during stages III and IV than stages I and II. Most of the episodes identified, both with and without cortical arousals, occurred during stages I, II, and REM. Number of bouts occurring per hour during a whole night of sleep was approximately the same whether or not they were associated with cortical arousals (Table 2). The distribution of these bouts was however somewhat different: A larger percentage of bouts associated with cortical arousal occurred during stages I/II and a smaller percentage during REM compared to bouts occurring in absence of cortical arousals. The interval between the start of two consecutive bouts of tachycardia-bradycardia for all subjects showed no significant difference between bouts with and without cortical arousals (5.8 ± 10.0 min and 5.6 ± 8.7 min, respectively).

Figure 1 shows ensemble-averaged RR intervals before and during every cortical arousal for every subject (dotted lines) as well as grouped data (solid line). We assessed the relation of RR interval response to cortical arousals by examining the RR interval response before and after onset of each epoch of cortical arousal. Each subject showed a similar pattern of RR interval decreasing and increasing related to cortical arousals. Evaluation of grouped ensemble-averaged data revealed that the tachycardia started 8 beats before the onset of cortical arousals (shown by arrow in Fig. 1). The decrease in RR interval attained statistical significance 1 beat before cortical arousals, and bradycardia started 4 beats later. There was relatively little difference in the timing of RR interval changes for individual subjects.

Figure 2 depicts the probability of the beginning of cortical arousals relative to the onset of tachycardia-bradycardia. The start of the change in RR interval preceded most cortical arousals (92.4 %): cortical arousals began an average of $5.6 [\pm 3.4 (SD)]$ beats after the first beat of tachycardia-bradycardia.

Figure 3 compares ensemble-averaged RR intervals for epochs of tachycardia-bradycardia occurring with and without cortical arousals. In both conditions, RR intervals monotonically decreased from 1 to 11 beats after the start of the epoch, reaching statistical significance 3 beats after the start of the epoch. RR intervals then monotonically increased over a period of 12 to 27 beats. However, the duration of tachycardia was shorter for those epochs without cortical arousals than those with cortical arousals (note in Fig. 3 fewer beats with significantly shorter RR interval from baseline as depicted by asterisks for epochs without cortical arousal than with cortical arousal). In addition, the magnitude of tachycardia was less for epochs without cortical arousal than with cortical arousal (significant differences between groups depicted by †).

Figure 4 and Figure 5 depict the relation between RR interval changes and EEG power in the delta, theta, alpha, and beta ranges. Time 0 indicates the first beat of the ensemble-averaged bouts of tachycardia-bradycardia. Figure 4 includes data from bouts of tachycardia-bradycardia associated with cortical arousals and shows that there are significant increases in all ranges of powers. Increases in delta power begin approximately 6 s after the onset of the epoch of tachycardia-bradycardia while alpha power increased 2 s later. Figures 5A and B show that epochs of tachycardia-bradycardia occur without cortical arousal as is evident by the lack of change for both alpha and beta powers during stages I/II and III/IV, respectively. However, as in Fig. 4, delta power increased after the onset of the RR interval changes. EEG power did not change for bouts of tachycardia-bradycardia during REM sleep (Fig. 5C).

Discussion

Brain activity during sleep is controlled by pons, basal forebrain areas, and other subcortical structures. In addition, during sleep, activities in the thalamocortical, reticular activating, and limbic systems change dramatically (Hobson et al., 1986). Changes of neuronal dynamics in these brain centers as reflected in the EEG are closely linked to RR interval dynamics (Otzenberger et al., 1997, 1998; Togo and Yamamoto, 2001). The key neurotransmitters involved are norepinephrine, serotonin, and acetylcholine (Hobson, 1989). The neuronal populations that produce and distribute these three neuromodulators throughout the brain, together constitute the central representation of the sympathetic and parasympathetic subdivisions of the autonomic nervous system.

We used a computer-based algorithm to identify short bouts of tachycardia-bradycardia representing bursts of autonomic activity consistent with autonomic arousals. These occurred in association with cortical arousal as well as in its absence (Fig. 4 and Fig 5), indicating that the occurrence of bursts of autonomic activity is not dependent on cortical arousals. RR interval changed significantly less and for a shorter duration for epochs without cortical arousal than for those with them, indicating less autonomic activation in the former condition (Fig. 3)

We examined the relationship between RR interval and EEG responses over a whole night of normal sleep using both temporal and frequency analysis. By using short time FFT, we have demonstrated that not all bouts of tachycardia-bradycardia are associated with the alpha and beta wave changes characteristic of cortical arousals (Fig. 4 and Fig 5). During those bouts not associated with cortical arousal in non-REM sleep, we observed increases in delta power (Fig. 5A and Fig B). We interpret these increases to be similar to the “synchronization type microarousals” labeled as subtype A1 (periodic appearance of bursts of delta waves and K-complexes) of the cyclic alternating pattern (CAP) (Terzano and Parriono, 2000) and to reflect activation of the subcortical arousal system. (Sforza et al. 2000) made a similar inference when they suggested that bursts of K-complexes and delta waves were expressions of subcortical arousals representing a real arousal response with tachycardia similar to that seen during cortical arousals.

Although there is some similarity in EEG characteristics between our observations on the bouts of tachycardia-bradycardia in the absence of cortical arousals and subtype A1 of the CAP, distribution of these events during the whole night sleep is different. While subtype A1 occurs most frequently during the transition from light to deep sleep and stages III and IV, and has been suggested to have a sleep protective function (Terzano and Parrino, 2000), bouts of tachycardia-bradycardia in our study occurred more often in the lighter stages of non-REM and in REM sleep (Table 2). Also there was no difference in rates of bouts with and without cortical arousals occurring during stages III and IV (Table 2). Thus, we cannot tell if bouts of tachycardia-bradycardia not associated with cortical arousal might have a similar protective function as subtype A1. However, some of these differences might be explained by differences in method of detection; we used a computerized algorithm to identify bouts of tachycardia-bradycardia while CAP is identified visually from the EEG.

We found that delta power as determined by spectral analysis of EEG signal increased also in cortical arousals, starting about 2 s before the significant increase in alpha power (Fig. 4). (Sforza et al. 2000) found delta power increasing in a previous study that examined EEG changes during cortical microarousals, although they showed that delta and alpha powers increased concomitantly. The temporal pattern of EEG signals we observed is similar to those seen in subtype A2 of CAP which contains desynchronized EEG patterns preceded by or mixed with synchronized EEG (Terzano and Parrino, 2000). Finding that delta power can increase before alpha suggests the existence of a spectrum of arousals with different EEG manifestations.

Such a spectrum of arousal is probably more complex than previously thought. As shown in Fig. 4 and Fig 5, tachycardias in our study began before the significant increase in power of any sleep-related EEG frequency. Although it has been shown that tachycardia and sympathetic nerve activity increase following subcortical arousal as manifested by the presence of K-complexes (Hornyak et al., 1991; Tank et al., 2003), there is some evidence indicating that autonomic activation could be the cause rather than the result of K-complexes. For example, K-complexes can often occur synchronously with Mayer blood pressure waves and are preceded by onset of tachycardia (Monstad and Guilleminault, 1999). Moreover, Tank et al. (2003) reported that 55 % of large single K-complexes are preceded by baroreflex-mediated changes in muscle sympathetic nerve activity. A previous study (Sforza et al., 2000) found that rises in HR were preceded by onset of bursts of K-complexes and delta waves with latency of about one to two beats. We believe that the difference between this study and our study probably reflects the different approaches used. While the previous study focused on EEG, we in turn have focused on HR. In addition, (Sforza et al. 2000) used an average HR over 10 beats before the onset of bursts of K-complexes and delta waves for their baseline while we evaluated bouts of tachycardia-bradycardia from the first beat identified in each bout. This averaging in the previous study may have hidden the onset of increases in HR during baseline. Therefore, we would posit that autonomic arousals as reflected by these brief HR changes may be one of the earliest or more primitive modes of arousal along a continuum leading to full cortical desynchronization and wakefulness. This is partly supported by the observation that there are more episodes of tachycardia and surges of blood pressures (identified by their surrogate pulse transit time) than there are episodes of EEG desynchronization (Poyares et al., 2002; Adachi et al., 2003).

Unrefreshing sleep is a common patient complaint, but no objective method is currently accepted to evaluate and quantify it (Davies et al., 1997). Although it seems reasonable that sleep quality should diminish as arousals increase, frequency of cortical arousals correlates poorly with this complaint (Bennett et al., 1998; Kingshott et al., 1998). One obvious tactic would be to improve ways of identifying arousals during sleep. Symptoms of unrefreshing sleep are reported to be greater when CAP occupies a greater percent of sleep (Terzano and

Parrino, 2000). Since CAP probably reflects subcortical as well as cortical activation, finding this result suggests that the frequency of both cortical and subcortical arousals together might be better related to sleep quality than either alone. Although primary attention in doing this kind of analysis has focused mostly on EEG signal analysis, the difficulty in doing this may outweigh the simplicity of our approach which focuses on HR, rather than on harder to measure autonomic measures such as pulse wave transit time or pulse amplitude (Pitson and Stradling, 1998; Haba-Rubio et al., 2005). During REM sleep, bouts of tachycardia-bradycardia occur without any detectable change in the EEG power spectrum (Fig. 5C). We cannot determine if these do or do not disrupt sleep at a subcortical level because the EEG during REM sleep is already desynchronized. The dynamics of RR interval changes during REM sleep are similar to those during the awake state (Otzenberger et al., 1997, 1998; Togo and Yamamoto, 2001), and might be the result of either cortically or subcortically acting stimuli. An important next step is to determine if bouts of tachycardia correlate with clinical complaints of fatigue or sleepiness.

Our study has several limitations. First, our sample size is small and limited to young healthy men. Thus the work needs to be extended to a larger number of healthy male and female subjects of different ages as well as to patients with complaints of unrefreshing sleep. Next regards our use of the P4–A2 lead for collection of EEG data. Using a more frontal electrode placement might provide even better detection of both cortical and subcortical arousal in future studies. Finally, we do not know the mechanism for the bouts of tachycardia-bradycardia we identified. Knowing the underlying cause of these bouts might lead to more specific autonomic measures to study. Despite these limitations, however, the data presented here do suggest that assessment of HR changes during sleep might be a useful tool in assessing arousals during sleep.

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Fig. 1. Ensemble-averaged RR interval variations before and after the onset of each bout of cortical arousal for each subject (dotted line) and for the group as an average (solid line). Individual subject data were adjusted to fit within the graphical frame. Grouped data are presented as means $\pm$ SE. Comparisons were made from baseline RR value (indicated by short up-going arrow). * indicates $P < 0.05$.

Fig. 2.
Distribution of the relation between onset of cortical arousals and the onset of every bout of tachycardia-bradycardia as indicated by the arrow for all subjects.

Fig. 3.

Ensemble-averaged RR intervals depicting algorithm-identified, 30 beat bouts of tachycardia-bradycardia (epochs begin and end with vertical dashed lines) with (solid line) and without (dashed line) cortical arousals as determined by visual scoring. Values are means $\pm$ SE. We determined change in RR interval from baseline, the beat occurring at time 0. * indicates $P < 0.05$ from baseline within a group; † indicates $P < 0.05$ difference between groups.

Fig. 4.

EEG power at different frequencies (see box for legend) before and during ensemble-averaged bouts of tachycardia-bradycardia followed by cortical arousals. The vertical arrow indicates the start of these bouts. Grouped RR interval data are also depicted (circles connected by dashed line). Asterisks depict significant change at $P < 0.05$ from baseline values (i.e., at time 0). Note delta and theta activity increase followed soon thereafter by an increase in alpha activity.

Fig. 5. EEG power at different frequencies (see box for legend) before and during ensemble-averaged bouts of tachycardia-bradycardia unaccompanied by cortical arousals. The vertical arrows indicate the start of these bouts. Grouped RR interval data are also depicted (circles connected by dashed line). Panel A depicts EEG power during sleep stages I/II; Panel B during sleep stages III/IV; and Panel C during rapid eye movement (REM) sleep. Asterisks depict significant change ($P < 0.05$) in power from baseline value (i.e., at time 0). Note that the only component of EEG power that increases is delta, and it increases after the onset of the bout of tachycardia-bradycardia. This increase is not seen during REM sleep (panel C).

Table 1

Polygraphic characteristics of subjects

Total sleep time (min)	400 ± 19
Sleep efficiency (%)	94.0 ± 3.6
Latency (min) to:	
stage II	8 ± 6
stages III/IV	21 ± 13
stage REM	92 ± 34
Total duration (min) of:	
stages I/II	222 ± 33
stages III/IV	95 ± 9
stage REM	83 ± 22

Sleep efficiency is the percentage of time asleep relative to the time spent in bed. REM, rapid eye movement.

Table 2

Identified heart rate changes during different sleep stages

		Total	stages I/II	stages III/IV	stage REM
with cortical arousal	# of events / hour / subject distribution (%)	9.0 ± 3.8	12.8 ± 6.4	3.2 ± 2.1	6.9 ± 4.0 *
without cortical arousal	# of events / hour / subject distribution (%)	10.2 ± 6.6	75.2 ± 12.0 * 8.4 ± 6.6 47.5 ± 22.8	8.9 ± 6.4 5.8 ± 6.0 11.8 ± 8.9	16.0 ± 7.2 * 19.0 ± 11.5 40.6 ± 25.1

Values are means ± SD.

* Significantly (P < 0.05, paired t-test) different from without cortical arousal.