EFFECTS OF CAFFEINE ON HEART RATE AND QT VARIABILITY DURING SLEEP

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Administration of caffeine in the evening produces poor sleep. Patients with insomnia have characteristic electrocardiogram (ECG) changes, including increased heart rate (HR), increased sympathetic activity, and decreased parasympathetic activity. Fifteen young adult normal subjects slept in the laboratory for several nights prior to randomization into a caffeine protocol where subjects received caffeine 400 mg 30 min prior to one night of sleep and placebo randomly prior to another night. ECG was sampled at a rate of 500 Hz and recorded onto a PC. Data samples of 256-s periods of the ECG trace were taken from wake (before sleep), stage II, and REM for placebo and caffeine conditions. A peak detection algorithm was used to identify the R-R intervals (in milliseconds) from the ECG. A common QT variability algorithm was used to find the QT interval for each beat using the time-stretch model. The powers for HR and QT series were integrated in the bands of LF (low frequency: 0.04–0.15 Hz) and HF (high frequency: 0.15–0.5 Hz) bands. There was a significant caffeine by sleep stage interaction for LF/HF ratios (F = 4.0; df = 2, 18; P = .04). LF/HF ratios were significantly higher during REM following caffeine administration. There was also a significant caffeine by sleep stage interaction for QTvi (QT variability normalized for mean QT interval divided by HR variability normalized for mean HR; F = 5.6; df = 2, 12; P = .02). QTvi was also significantly higher during REM following caffeine administration. The higher LF/HF ratios and QTvi during REM are most likely due to the sympathetic effects of caffeine. These findings suggest that excessive caffeine intake may result in adverse cardiovascular events in vulnerable subjects. Depression and Anxiety 0:1–6, 2005. © 2005 Wiley-Liss, Inc.

Key words: caffeine; insomnia; heart rate variability; QT variability; cardiac disease; sleep

INTRODUCTION

There is a complex association between anxiety, insomnia, and cardiac sympathetic function and the possible increased incidence of sudden death during sleep. A number of studies have documented the effect of caffeine upon sleep. Studies have typically reported a dose-related reduction in total and stage 4 sleep, and an increase in sleep latency after both oral-administered and intravenously administered (i.v.) caffeine in doses

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ranging from 100 to 400 mg [Karacan et al., 1976; Lin et al., 1997]. Caffeine, when given to normal young adults, has also been reported to produce increased VO₂, increased latencies on sleep latency tests, and changes in mood and personality similar to those seen in patients with chronic insomnia [Bonnet and Arand, 1992]. Patients with insomnia have also been shown to have increased low-frequency (LF: 0.04–0.15 Hz) heart rate (HR) spectral power and decreased high-frequency (HF: 0.15–0.5 Hz) HR spectral power in all stages of sleep [Bonnet and Arand, 1998] compared to normal sleepers, which suggests a relatively higher sympathetic activity in patients with insomnia.

Anxiety is associated with decreased HR variability, most likely due to decreased cardiac vagal function [Yeragani et al., 1993, 1998]. At high doses, caffeine produces dose-related increases in anxiety and cortisol [Nickell and Uhde, 1994/1995; Tancer et al., 1994/1995; Uhde, 1995], and induces escape from dexamethasone suppression [Uhde et al., 1985]. Excessive chronic caffeine consumption mimics generalized anxiety disorder [Uhde, 1988]. Moreover, caffeine has been proposed as an ideal chemical model of panic disorder, a condition associated with decreased HR variability [Cohen et al., 2000; McCarty et al., 2001; Yeragani et al., 1993] and abrupt arousals (i.e., nocturnal panic attacks) in sleep [Mellman and Uhde, 1989; Uhde, 2000]. Several lines of evidence also link anxiety and panic attacks to increased cardiovascular morbidity and mortality [Coryell et al., 1982, 1986; Kawachi et al., 1994; Klein et al., 1995].

Taken together, these observations underscore the importance of studying caffeine’s effects on cardiovascular function in sleep, which may have particular relevance to patients with selective anxiety disorders.

LF power (0.04–0.15 Hz) is related to baroreceptor sensitivity mediated by vagal as well as sympathetic systems, whereas the HF power is influenced by respiratory sinus arrhythmia [RSA; Akselrod et al., 1981; Pomeranz et al., 1985]. A substantial number of studies have shown that decreased HR variability, most likely due to decreased cardiac vagal function and/or an increase in relative cardiac sympathetic activity, which may be observed in an increase in the LF/HF ratios of HR variability, is associated with increased risk for cardiac mortality in patients with cardiac disease, as well as normal controls [Bigger et al., 1992; Kleiger et al., 1987; Molgaard et al., 1991].

A recent measure, beat-to-beat QT interval variability, appears to be a better indicator of cardiac sympathetic function [Dinca-Panaiteescu et al., 1999; Negoeescu et al., 1997; Pohl et al., 2003; Yeragani et al., 2000a]. QT interval on the surface electrocardiogram (ECG) reflects time for repolarization, and several studies have shown a relationship between prolonged QTc (QT interval corrected for the mean R-R [inter-beat] interval) and life-threatening arrhythmias [Jervell and Lang-Nelson, 1957; Schwartz and Wolf, 1978]. Recent literature also implicated abnormal repolarization in serious ventricular arrhythmias [Binah and Rosen, 1992; Tomaselli et al., 1994]. We have recently found that patients with panic disorder and depression have higher QTvi [a log value of QT variance corrected for mean QT interval divided by the HR variance corrected for mean HR; Yeragani et al., 2000b], which is reportedly associated with symptomatic patients with cardiomyopathy and also sudden cardiac death [Atiga et al., 1998, 2000; Berger et al., 1997].

In this study, we sought to examine spectral powers of beat-to-beat HR and QT intervals after the administration of caffeine to normal young adults during sleep, with the hypothesis that caffeine would produce changes similar to those seen in patients with insomnia, reflecting an increased cardiac sympathetic function associated with increased HR LF/HF ratios and increased QTvi.

**METHODS**

**SUBJECTS**

This study was approved by the Institutional Review Board at the Wright State University School of Medicine, Dayton, Ohio. Subjects were healthy 18- to 39-year-old males and females. Potential subjects were solicited from research referrals and from advertisements in the local newspapers for participants in sleep research. Individuals considered further completed a screening questionnaire that indicated that they had normal sleep with rare daytime naps and no current history of night work. Selected subjects did not consume excessive caffeine (more than 250 mg of caffeine per day) and had not used psychoactive medications within the previous year. Potential subjects who had histories strongly suggestive of circadian desynchrony (e.g., shift workers), sleep apnea, or periodic leg movements were excluded. We selected subjects who were moderate caffeine users. Our definition of “moderate” was anything less than 250 mg per day based on a questionnaire response from subjects asking for caffeinated coffee, tea, and soft drink consumption on an average day. This definition of “moderate” was based up on data from Greden and Walters [1992], who indicated that 80% of adults in the United States use caffeine daily, and that their per capita intake of caffeine has been estimated at more than 200 mg. Subjects meeting these criteria were invited to participate in the study after completing an informed consent, and practice on computer tests and questionnaires to be used in the study.

**DESIGN**

After completing the consent form, subjects were scheduled for an adaptation night followed by two consecutive nights on the following days. On the adaptation night, a standard clinical polysomnogram, including two eye channels, central and occipital EEG channels, chin and leg EMG channels, ECG, airflow, chest movements (two channels), and oxyhemoglobin saturation (SaO₂) were performed [Bornstein, 1982].
Subjects with an apnea/hypopnea index greater than 10 or a periodic leg movement arousal index greater than 10 were disqualified. On one of the two laboratory nights, subjects received a placebo (sugar pill) 30 min prior to going to bed. On the other night (counter-balanced across subjects), subjects received caffeine, 400 mg, 30 min prior to going to bed.

All subjects were assigned their own room for the course of the study. Each room contained a standard hospital bed and furniture, including a desk with an Apple IIGS computer. Subjects participated in the study in groups of one to two individuals. Subjects completed tests and questionnaires at their individual computer workstation in their room under technician observation via video monitors. Meals and breaks were scheduled in another area of the laboratory, which was also within technician observation. Subjects performed computer tests, completed a Minnesota Multiphasic Personality Inventory (MMPI) and a sleep history, and were fed the same menu of food prepared at the laboratory during the day. Caffeinated beverages were not available. Subjects usually did not leave the laboratory during the day and did not engage in vigorous activity. Subjects were allowed to leave the laboratory after the entire sleep test was completed.

All times cited in this article were specified for a subject who normally went to bed at 2300 and arose at 0700. For subjects who normally went to bed somewhat later (or earlier), bedtime and wake-up time were adjusted to approximate normal weekday times. Testing and sleep latency tests were correspondingly moved to maintain similar circadian timing for all subjects on all nights.

During each day, all subjects remained at the laboratory. Immediately after awakening each morning, subjects had a 20-min waking metabolic observation that was also used to collect HR data. Starting 2 hr after awakening, subjects had four research sleep tests at 2-hr intervals. Following each sleep test, subjects had a 20-min waking metabolic observation that was also used to collect HR data. Between sleep test observations, subjects performed psychomotor performance tests and mood evaluations.

Sleep recordings (LE-A2, RE-A2, C3-A2, OZ-A1, V5-right clavicle, and time code) were made during nocturnal sleep periods, sleep latency evaluations, and waking metabolic observations. All sleep and nap recordings were scored in 30-s epochs using the Rechtschaffen and Kales [1968] criteria.

ECG data collection: Throughout each night and the 20-min daytime sessions, ECG data were recorded through a Grass Braintree system running Gamma software (version 4) at a sampling rate of 500 samples/s. After collection, the ECG and time data were visualized and checked for artifacts with the Gamma software. Further details of ECG data collection and analysis procedures are published elsewhere [Bonnet and Arand, 1998].

We took 256 s of data from wake stage before sleep, stage II of NREM (nonrapid eye movement), and REM periods for placebo as well as caffeine conditions. We used a peak detection algorithm to identify the R-R intervals (in milliseconds) from the ECG.

**QT VARIABILITY**

All these analyses were conducted on 256-s segments of data sampled at 500 Hz. This QT variability algorithm has been described by Berger et al. in detail and has been used by his and our groups in previous studies [Atiga et al., 1998, 2000; Berger et al., 1997; Yeragani et al., 2000a–d]. This was performed on a PC using Solaris Desktop Unix software (Sunsoft, Mountain View, CA), which uses a graphical interface of digitized ECG where the time of the “R” wave is obtained using a peak detection algorithm. Then the operator provides the program with the beginning and the end of the QT wave template. This algorithm finds the QT interval for each beat using the time-stretch model. If the operator chooses a longer QT template, all the QT intervals will be biased accordingly. This algorithm’s purpose is mainly to study QT variability and not the mean QT.

The HR (beats per minute: bpm) time series were sampled at 4 Hz using the technique of Berger et al. [1986]. This technique also works as an antialiasing filter. It behaves as a low-pass filter, passing very little power beyond the Nyquist rate. It preserves all the frequencies up to one fourth of the sampling rate. It does not affect the information up to 1 Hz as we sample the signal at 4 Hz. We used HR time series free of ventricular premature beats and noise. We then detrended the data by using the best-fit line prior to the computation of spectral analyses.

**SPECTRAL ANALYSIS**

HR time series (256 s of data at 4 Hz = 1,024 points, during each wake and each sleep stage) were subjected to spectral analyses, and the power spectrum was computed with the Blackman–Tukey method [Berger et al., 1989]. The powers were integrated in the bands of LF and HF regions.

**STATISTICAL ANALYSIS**

We used BMDP statistical package (Berkeley, CA) to perform all the analyses. First, we used repeated measures analysis of variance (ANOVA) to compare placebo and caffeine conditions for wake, stage II NREM, and REM periods (two levels of repeated measures) followed by post hoc t tests for significant effects on ANOVA to identify differences, especially between REM and other stages. We used a probability value of .05 for significance to avoid type II error, because there were only a few subjects and this was mainly a preliminary study.
II NREM, second stage of NREM sleep.

Caffeine condition (Table 3). Values of QTvi during placebo and caffeine sessions

Table 1 shows the mean ± SD for HR and QT mean and variability measures. There were no significant differences on ANOVA. Table 2 shows the results of comparisons for LF/HF ratios. Drug versus sleep stage interaction was significant (F = 4; df = 2.18; P = .04). LF/HF ratios were significantly higher during the REM stage, during the caffeine condition (Table 2). Table 3 shows the results of comparisons for QTvi. Drug versus sleep stage interaction was significant (F = 5.6; df = 2.12; P = .02). QTvi was significantly higher during the REM stage, during the caffeine condition (Table 3).

RESULTS

The main findings of this study are the significant increases in LF/HF ratios after caffeine administration and QTvi during REM sleep. This can be explained on the basis that the relative increase in sympathetic activity during REM sleep has made the subjects more sensitive to the sympathomimetic effects of caffeine. It is possible that significant differences were not found in the wake measure because the time placement of that measure was about 30 min after caffeine administration (pill form) and perhaps before significant drug became available. However, stage II of NREM and REM observations were chosen to occur at similar times during the second half of the night, so lack of significant findings during stage II NREM sleep cannot be explained by caffeine time course. To our knowledge, this is the first study to show significant

II NREM, stage II of NREM sleep.
increases in QT\text{Vi} during REM sleep in normal subjects after the intake of caffeine.

The short-term consumption of caffeine can result in increased urination, gastrointestinal distress, tremors, decreased sleep, and anxiety in certain individuals. At the cellular level, caffeine is a competitive antagonist of adenosine receptors, causing increased lipolysis, and facilitates central nervous system transmission [Tarnapolsky, 1994]. However, the relationship between adenosine receptors, caffeine, and cardiac function is unclear.

Caffeine intake results in an increase in HR and HR variability, especially the LF power during rest and also during aerobic exercise [Kolodiichuk and Arushanian, 1991; Nishijima et al., 2002]. It should be noted that if the increase in HR variability is predominantly from the contribution of LF power, it may reflect in higher LF/HF ratios, and this could be detrimental to patients at risk for cardiovascular disease. Lane et al. [2002] have shown that caffeine may exaggerate sympathetic adrenal medullary responses to the stressful events of normal daily life, suggesting that excessive caffeine intake may have detrimental effects in patients with cardiac illness.

Generally, sleep is considered to be a condition associated with a relatively high vagal activity. However, this increase in vagal activity may be blunted in patients with coronary artery disease [Huikuri et al., 1991; Nishijima et al., 2002]. Vanoli et al. [1996] have shown that myocardial infarction is associated with increased LF/HF ratios during NREM as well as REM sleep, suggesting a sympathetic predominance during sleep. Our findings in this study of significant increases in LF/HF ratios of HR variability, as well as QT\text{Vi}, suggesting sympathetic predominance, have implications for excessive intake of caffeine and the nocturnal occurrence of sudden death. Further studies are needed to study the effects of caffeine on QT\text{Vi} during sleep in patients with coronary artery disease.

We should also comment on the acute versus chronic intake of caffeine, especially of more than 400 mg. If this is an acute intake, it can lead to a significant increase in cardiac sympathetic activity and can be detrimental, especially in patients with other cardiac risk factors.

REFERENCES


