Published in final edited form as:

J Psychosom Res. 2008 July ; 65(1): 13–22.

Reduced parasympathetic activity during sleep in the symptomatic phase of severe premenstrual syndrome

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Abstract

Objective—Severe premenstrual syndrome (PMS) is a common, distressing disorder in women that manifests during the premenstrual (late-luteal) phase of the ovulatory menstrual cycle. There is some evidence that altered autonomic function may be an important component of PMS but few studies have used heart rate variability (HRV), as a sensitive marker of autonomic activity, in severe PMS and findings are conflicting.

Methods—We investigated HRV during sleep, a state relatively free of external disruptions, in nine women with severe PMS and twelve controls.

Results—The normal-to-normal (NN) RR-interval was shorter during the sleep period in women with PMS than in controls in both the follicular and late-luteal phases of the menstrual cycle. The standard deviation of all NN intervals (SDNN), a measure of total variability in the inter-beat interval, was lower during the sleep period in the late-luteal phase than in the follicular phase in women with PMS. The square root of the mean of the sum of the squares of differences between adjacent NN intervals (rMSSD), a measure reflecting high frequency activity, showed a similar pattern. High frequency power, a marker of parasympathetic activity, was lower during non-rapid eye movement (non-REM) and REM sleep in the late-luteal phase than in the follicular phase in women with severe PMS. Controls had a shorter NN-interval, but similar HRV measures, in the late-luteal phase compared with the follicular phase.

Conclusion—These results suggest that women with severe PMS have decreased parasympathetic activity during sleep in association with their premenstrual symptoms compared to when they are symptom-free.

Keywords

heart rate variability; menstrual cycle; premenstrual dysphoric disorder; REM sleep

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Introduction

Premenstrual syndrome (PMS) describes a range of emotional, behavioral, and physical symptoms that occur during the luteal phase of the ovulatory menstrual cycle and abate following menstruation (1). Up to 18 % of women have severe PMS and 3–8 % qualify for a diagnosis of premenstrual dysphoric disorder (PMDD) (2). PMDD is classified as a “depressive disorder not otherwise specified” in the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Both severe PMS and PMDD are associated with significant functional impairment and impact quality of life (1), but their etiology remains poorly understood.

To better understand the pathophysiology of severe PMS, studies have investigated indicators of autonomic nervous system function in women with PMS or PMDD, and found signs of altered regulation. Girdler et al. (3) reported that women with PMDD had greater norepinephrine levels than control women both while quietly resting, and when under experimental stress conditions, regardless of menstrual phase, suggesting greater sympathetic nervous system (SNS) activity in the PMDD women. One study (4) reported that women with PMS have a higher resting heart rate than controls in the late-luteal phase, consistent with altered autonomic nervous system function, but others have failed to replicate this effect (5, 6). Measures of skin conductance, used as an index of sympathetic tone, have also produced conflicting results, with some studies reporting greater skin conductance in women with PMS (7), others reporting no difference between women with PMS and controls (8), and yet others reporting higher levels of skin conductance pre-menses than post-menses in women with PMS, an effect opposite to that seen in controls (9).

Analysis of heart rate variability (HRV) provides an alternative and more sensitive noninvasive measure of cardiac autonomic regulation than measures of skin conductance and catecholamine levels. Beat-to-beat variability in the heart’s rhythm is mainly caused by modulation by the autonomic nervous system of the intrinsic cardiac pacemakers (10). HRV analysis, therefore, can provide information on the effective functioning of the heart and on autonomic control through sympathetic and parasympathetic regulation. HRV can be assessed in either the time domain or the spectral domain. Time domain measures, which have been primarily used to assess effective cardiac functioning as reflected in high HRV (11), include the mean NN interval (normal-to-normal RR intervals) as well as statistical measures including the standard deviation of all NN intervals (SDNN), which is a measure of total variability in the inter-beat interval; standard deviation of mean NN intervals (SDANN), a measure of low frequency activity; and square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), a measure of high frequency activity (10). Power spectral density analysis of HRV provides information of how power is distributed as a function of frequency (10) and has primarily been used to assess autonomic control. The two most commonly reported components of the spectrum are high frequency (HF) power, which reflects parasympathetic nervous system (PNS) activity and low frequency (LF) power, which is thought to measure a combination of PNS and SNS activity (10). As such, the LF component is uninterpretable, although most commentators accept that the LF/HF ratio reflects sympathovagal balance (11).

As far as we are aware, only two studies have measured HRV in women with PMS or PMDD. Landen *et al.* (12) evaluated HRV in women diagnosed with PMDD and in controls during the follicular and late-luteal phases of the menstrual cycle. Time-domain HRV components were assessed from 24-h electrocardiograph (ECG) recordings and spectral HRV components were determined from 10-min recordings in the supine position when breathing was controlled, followed by 10-min in a standing position. RMSSD, SDNN, and supine HF power were significantly lower in 28 women with PMDD compared with 11 controls in the follicular phase

but no group differences were found in the late-luteal phase (12). Further, there were no differences in HRV between menstrual phases in women with PMDD. Based on these findings, the authors concluded that reduced HRV in patients with PMDD is not related to the occurrence of premenstrual symptoms (12). Matsumoto *et al.* (13) measured spectral-domain components of HRV in women who had low ($n = 11$), moderate ($n = 11$), and high ($n = 8$) scores on a menstrual distress questionnaire. Women who reported high premenstrual distress (although not so severe as to interfere with normal activities) had a higher heart rate and lower HF power during a 20-min period of supine rest in the late-luteal phase than in the early follicular phase. HF power in the late-luteal phase tended to be lower, although not significantly, in the group of women with high premenstrual distress than the other two groups (13). These findings, therefore, suggest that women with moderate symptoms of PMS show altered HRV in association with their symptoms in the late-luteal phase. Given the findings of these two studies (12,13), there is a need to further investigate HRV in women with PMS and PMDD.

Several studies have investigated HRV at different phases of the normal menstrual cycle but results are conflicting. There are reports of increases in the LF/HF ratio, interpreted as indicating increased SNS activity (14–16), increased HF power, interpreted as indicating enhanced PNS activity (17), decreased SDNN and SDANN (12), or no change in time-domain (18) or spectral-domain (19) HRV components during the luteal phase compared with the follicular phase of the menstrual cycle.

None of the studies about HRV in women at different phases of the menstrual cycle or in women with PMS has investigated HRV during the sleep period. Sleep represents a condition relatively free of external disruptive events that can affect measurement of HRV while awake (20), allowing a more accurate measure of basal autonomic activity (21). However, sleep is not a uniform state with regard to cardiovascular activity. NREM sleep is characterized by lower heart rate, and a higher HF power component of HRV compared with wakefulness (22). These changes are reversed during REM sleep; thus heart rate is higher, whereas HF power is lower, compared with NREM sleep (22).

In this study, we investigated HRV based on ECG recordings during a night-time period that comprised mainly sleep in a group of women with severe PMS and in a group of women with minimal premenstrual symptoms (controls). We investigated overall HRV (based on time-domain measures) during the sleep period without consideration for sleep stage effects. Since it is inappropriate to compare time-domain measures obtained from recordings of different durations (10), we analysed the ECG during the first 7-h period after lights-out in all subjects. Time-domain HRV measures provided an overall measure of cardiac functioning. In order to assess autonomic control we analysed frequency domain HRV measures as a function of stable sleep stages (non-REM sleep and REM sleep).

Methods

Subjects

Fourteen women with self-reported severe PMS and 15 women with mild or no symptoms of PMS (control subjects), aged 18 to 40 years, were recruited from the community and consented to participate in our study. The study was approved by the Institutional Review Board of SRI International. All women had a structured clinical interview for DSM-IV to exclude any concurrent major psychiatric diagnosis. Women with severe PMS were still included if they had a past history (> 1 year) of psychiatric illness or alcohol or substance abuse. Women were questioned about their PMS symptoms in a customized module appended to the clinical interview that was based on the DSM-IV criteria for a PMDD diagnosis. Based on the clinical interview, women in the PMS group were given a provisional diagnosis of PMDD, and controls were confirmed as having no or mild PMS. Women were also questioned to ensure that they

had regular sleep-wake schedules, regular menstrual cycles of 24 to 35 days, and good health and had not been taking any chronic medication, including hormonal contraceptives, for the previous 3 months.

All women completed the Penn Daily Symptom Rating (DSR, (23)), which is a validated diagnostic tool for PMS, over at least 2 menstrual cycles. The DSR lists 17 common PMS symptoms, including the 11 symptoms listed in the DSM IV as criteria for a PMDD diagnosis: depression; anxiety; mood swings; irritability; decreased interest; difficulty concentrating; fatigue; food cravings; hypersomnia or insomnia; feeling overwhelmed; physical symptoms such as breast tenderness or headaches. Subjects rate each item on a 5-point scale (0=none to 4=extreme). Follicular phase scores are calculated by adding the ratings of cycle days 5 through 10 (where day 1 is the first day of bleeding). Pre-menstrual (late luteal phase) scores are calculated by adding the ratings of the 6 days before menses. To qualify for severe PMS, women need to score 80 or greater on the DSR in their late luteal phase and show an increase of at least 50% from the follicular phase score for both screening months. To meet DSM-IV criteria for PMDD, women have to rate at least five PMDD symptoms as severe (3 or 4), with at least one symptom being mood-related, on at least two premenstrual days, with the same symptoms being rated as absent or minimal (0 or 1) post menstrually. All the women reported either severe mood swings or depressed mood, and seven women also reported severe irritability, during the late luteal phase. Of the initial sample, 5 women were confirmed as having PMDD and 4 women received a diagnosis of severe PMS, according to DSR criteria, and were included in the study. Women in the PMS group scored 38 ± 39 and 152 ± 70 on the DSR in the follicular and late luteal phase, respectively.

Based on their DSR scores, all the control subjects were confirmed as having no or mild PMS. Two of the control subjects dropped out before the study was completed, and one control subject was excluded because her menstrual cycle became irregular during the study. The remaining controls scored 15 ± 20 and 17 ± 21 on the DSR in the follicular and late luteal phase, respectively. Nine women with severe PMS (Age: 28 ± 6 y; mass: 65.6 ± 10.1 Kg; Height: 1.7 ± 0.05 m) and 12 control subjects (Age: 31 ± 5 y; mass: 61.7 ± 8.2 Kg; Height: 1.7 ± 0.08 m) were included in the final analysis. The groups did not differ with regard to age ($t(19) = 1.4$, $p = 0.2$), mass ($t(19) = -1$, $p = 0.3$), or height ($t(19) = -0.1$, $p = 0.9$).

Study Procedures

Following the screening period, subjects were scheduled for a full night of clinical polysomnography in the controlled environment of our laboratory to confirm absence of any sleep disorder and to allow subjects to adapt to the laboratory. The women returned to the laboratory for recordings on 2 occasions during their menstrual cycle: once during the mid-follicular phase (6–12 days after the onset of menstrual flow) and once during the late luteal phase (9–13 days after the luteinizing hormone surge). Women entered the study at different phases of the menstrual cycle; 5 women with PMS and 8 control subjects had their follicular phase recording first. On study days, the women were requested to refrain from drinking caffeinated beverages after 15:00, not to drink any alcoholic beverages, and not to take naps. Women were screened for presence of alcohol with a breathalyzer on arrival at the sleep laboratory; all participants registered 0 on the breathalyzer. Lights-out and lights-on times were based on the customary schedules for each individual.

Blood samples were taken from each woman on study days; all women were confirmed as having ovulatory menstrual cycles based on a post-ovulatory rise in progesterone (See (24) for details).

Data acquisition and analysis

Electrocardiographic (ECG), electroencephalographic (EEG), electrooculographic, electromyographic recordings were made using E-series amplifiers and Profusion software (Compumedics, Abbotsford, Victoria, Australia) linked to appropriate transducers. For each subject, thirty-second epochs of the polysomnogram were scored according to standard criteria (25) to determine sleep stages. Results from this analysis have been reported elsewhere (24). The ECG was recorded through Meditrace Ag/AgCl spot electrodes placed on the subject's lower left rib cage and on the right clavicle notch. The ECG signal was digitized at a sampling rate of 512 Hz.

Heart rate variability analyses

The ECG across the first seven hours after lights-out was subjected to analyses of HRV according to the guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (10). The analyses were conducted using software developed at the University of Melbourne (22). During initial analyses of the ECG, R waves were detected using an automated algorithm, allowing inter-beat interval to be calculated by the program. The detection of R waves was visually checked and edited where the automatic detection was incorrect.

Two forms of HRV analysis were employed in order to assess two different aspects of the data. First, time domain analysis was used to assess overall HRV. In these analyses periods of sleep disturbance, such as micro arousals and body movements were retained in the data. Second, spectral analyses were conducted in order to assess cardiac autonomic control. As HRV resulting from sleep disturbance masks autonomic control effects, periods of stable sleep were selected for these analyses and results were reported as a function of REM sleep and non-REM sleep.

For time domain analyses, NN (normal-to-normal RR interval) and the following HRV time domain variables were calculated as hourly values and as averages of the first 7-h sleep period: standard deviation of all RR intervals (SDNN); standard deviation of mean NN intervals for all 5-min epochs (SDANN), and square root of the mean of the sum of the squares of differences between adjacent NN intervals (rMSSD).

Power spectrum analysis of HRV was conducted to determine activity in the high frequency (HF) and low frequency (LF) bands according to published guidelines (10) and following procedures used in a previous study (22). Periods of stable sleep were analysed in 2 minute epochs (see below for criteria used to identify epochs). An epoch length of 2 min was selected because it is within the recommended range for the LF component (10), and because intervals meeting the criteria set out below become increasingly rare as epoch length increases. The inter-beat interval time series for each 2-minute data epoch selected for analysis was first re-sampled at a frequency of 4 Hz. The time series was then de-trended using a third order polynomial with a 20 second (81 point) window. The effect of this size window was to filter the DC component, but leave intact LF activity. Power spectrum analysis was then applied to the time series. The program calculated the power spectrum density estimate for frequency bins that were then combined to form frequency bands 0.02 Hz wide. Thus, the total power spectrum ranged from 0 to 0.5 Hz in 0.02 Hz bands. To identify the LF component the algorithm searched for the greatest value in the frequency bands from 0.03 to 0.15 Hz. The width of the LF component was defined by the first frequency bands either side of the peak to fall to 50% of the peak value. The area between and including these frequency bands was then integrated. The same procedure was used to identify the HF component, with the exception that the peak value was identified between 0.15 and 0.40 Hz. Power within the LF and HF bands was

quantified by the absolute integrated power in arbitrary units. Peak frequency of the high frequency band (HF_{fr}), which is a measure of respiratory rate (22), was also calculated.

Two minute epochs were identified and selected over the first 7-h after lights-out according to the following rules:

1. The 2 min before the epoch and the epoch itself had to be: free of body movements; indications of arousal, such as abrupt changes in EEG frequency, bursts of electromyographic activity, or eye movements; and other artefacts.
2. There could not be a stage change during the 4 min, other than between stages 3 and 4.
3. Once an epoch was identified, another epoch could not be identified for a further 5 min, unless there was a change of sleep stage.
4. Epochs were not identified during periods of wakefulness within the sleep period or during stage 1 sleep.

In summary, each 2-min epoch provided an estimate of absolute power for LF and HF components. Importantly, the estimated power was restricted to a narrow band surrounding the component itself, as defined by the peak frequency. In addition, the ratio of LF to HF power (LF/HF) was calculated. From an interpretative perspective the HF component provided an estimate of vagal activity, while the LF/HF ratio estimated sympathovagal balance. Finally, average inter-beat interval was calculated for each 2 minute epoch. The resulting 2 minute values were then sorted according to stage of sleep (Non-REM sleep and REM sleep).

Statistical Analysis

Averages over the 7-h period after lights-out for NN-interval, and HRV time domain variables were analyzed with repeated-measures two-way analyses of variance (ANOVA) at the 0.05 alpha level with “menstrual phase” as the within factor and “subject group” as the between factor. To determine the effect of time-of-night, a repeated-measures ANOVA was run on the hourly averages for heart rate, NN-interval and time-domain HRV variables with “menstrual phase” and “time” as within factors and “subject group” as a between groups factor. When Mauchly’s test of sphericity showed significance, probability values were adjusted using the Greenhouse-Geisser correction but original degrees of freedom are reported. HRV variables in the spectral domain were analyzed as a function of Non-REM and REM sleep. Since absolute LF and HF power variables were skewed, data were log-transformed before analysis with repeated-measures two-way ANOVA, with “menstrual phase” and “sleep stage” as the within factors and “subject group” as the between factor. Where significant interactions were found, paired t-tests were conducted within subject groups to establish simple effects. Values are reported as mean $\pm$ SD unless otherwise indicated.

Results

Cardiac Activity over the Sleep Period – Time Domain Analyses

Averages for NN-interval and time domain HRV variables in the women with PMS and controls are shown in Table 1. Women with severe PMS had a significantly shorter mean NN-interval than controls regardless of menstrual phase (Table 1). There was also a significant phase effect for the 7-h average of NN-interval: both groups of women had shorter NN-intervals during the late-luteal phase than the follicular phase.

There were no significant group differences in any of the HRV measures in the time domain. However, there were significant phase and phase $\times$ group interaction effects for SDNN and

rMSSD. As shown in Table 1 and Figure 1, women with severe PMS had a significantly lower SDNN (paired t-test, $p = 0.01$) and rMSSD (paired t-test, $p = 0.02$) in the late-luteal phase than the follicular phase whereas these variables were similar in both menstrual phases for controls. There were no significant main or interaction effects for SDANN.

Figure 1 shows hourly averages across the night for NN-interval, SDNN, SDANN, and rMSSD. There were significant time effects for NN-interval ($F_{6,14} = 11.9$, $p = 0.006$) and SDNN ($F_{6,14} = 4.1$, $p = 0.01$). Both groups of women showed an increase in NN-interval and an increase in SDNN across the night (Figure 1). There were no significant interaction effects between time and menstrual phase or group.

Cardiac Autonomic Control – Spectral Domain

HRV indices in the frequency domain for Non-REM and REM sleep are shown in Table 2. Total power did not vary significantly either according to group, menstrual phase, or sleep stage. There was a significant group effect for HFfr, which was lower in women with PMS than controls, during both phases of the menstrual cycle (Table 2). Because of the known impact of respiration on HRV, with HF power being inversely related to respiratory rate (26), it is likely that the women with PMS in our study have inflated values for HF power in both menstrual phases. As shown in Table 2, HF power appeared higher in the women with PMS, especially in the follicular phase, although the group effect did not approach significance.

To account for the different respiratory rates between study groups, late-luteal phase values of HF power are expressed relative to follicular phase values in Figure 2. There were significant phase and phase $\times$ group interaction effects for HF power owing to a significantly lower HF power during non-REM and REM sleep in the late-luteal phase than the follicular phase in the women with PMS (paired t-tests, $p < 0.05$) but not in controls. Indeed, women with PMS in the late-luteal phase had, on average, only 63 % of their HF power in the follicular phase during NREM sleep (Figure 2). The ratio of LF/HF did not vary significantly according to menstrual phase in either group (Table 2).

Sleep stage influenced HRV variables. HF power was significantly higher and the LF/HF ratio was significantly lower in Non-REM sleep than REM sleep (Table 2). There were no significant group $\times$ stage, phase $\times$ stage, or group $\times$ phase $\times$ stage interaction effects for any of the variables (ANOVA, $P > 0.1$).

Discussion

In our study, when assessed by time domain analyses over the sleep period, women with severe PMS had lower heart rate variability (SDNN) and a lower high frequency sensitive component (rMSSD), when they were symptomatic in the late luteal phase compared to the symptom-free follicular phase. Our analysis of spectral power of the ECG during undisturbed Non-REM and REM sleep revealed that women with PMS also had lower HF power in the late-luteal phase compared with the follicular phase. This significant reduction in HF power suggests that women with severe PMS have reduced parasympathetic activity during sleep when they are symptomatic in the late-luteal phase of the menstrual cycle. A group of women without significant premenstrual symptoms (controls) showed no significant change in HRV between the two menstrual phases. Our results, therefore, indicate that reduced HRV during sleep is linked to PMS symptom expression and cannot be attributed to variation associated with the normal menstrual cycle.

Polysomnographic measures of sleep continuity (sleep onset, total sleep time, sleep efficiency), and percentages of slow wave sleep and REM sleep during the night were similar in both groups of women, as previously published (24). Also, both groups of women showed an increase in

wakefulness and a marginal increase in the arousal index during sleep in the late-luteal phase compared with the follicular phase (24). Thus, disturbances in sleep during the late-luteal phase were apparent in all women regardless of whether or not they suffered from severe PMS. Yet, only the women with PMS in our study showed a menstrual phase-related change in HRV during the sleep period. It, therefore, is unlikely that reduced HRV during the sleep period is secondary to disturbed sleep in women with PMS. Further, we analysed spectral measures of HRV within epochs of undisturbed non-REM and REM sleep that were preceded by at least 2-min of undisturbed sleep. In this way, we controlled for the effect that arousals and intervening wakefulness may have on HRV measures (27). Reduced parasympathetic modulation during sleep, as found in the women with PMS when symptomatic, may impact the restorative properties of sleep (28). Consequently, the perception of sleep quality may be affected; women with PMS report a poorer sleep quality, although polysomnographic-defined sleep efficiency is unchanged, when they are symptomatic in the late-luteal phase compared with the follicular phase (24). Similarly, patients with irritable bowel syndrome, who report a poorer sleep quality in the absence of objective sleep disturbances (29), have altered sympathovagal balance during REM sleep (21).

To our knowledge, this study is the first to investigate HRV during the sleep period in women with severe PMS and few studies have investigated heart rate variability at all in women with PMS or PMDD with which to compare our results. Similar to our findings, Matsumoto *et al.* (13) found that heart rate was increased and HF power was decreased during the late-luteal phase compared with the follicular phase in women who scored high on a premenstrual distress questionnaire. HF power did not vary between menstrual phases in women who had a low score on the questionnaire (13). In contrast to our findings, another study found no change in HRV between the follicular and luteal phases in women diagnosed with PMDD. However, women with PMDD had a lower rMSSD and HF power in the follicular phase compared with controls (12), which we did not find. The only significant group difference we found was a shorter NN-interval in women with PMS.

Differences in methodology may explain the different results between Landen *et al.* (12) and our study. First, in our study, four women did not qualify for a diagnosis of PMDD, based on prospective ratings, whereas all the women included in the study by Landen *et al.* (12) met DSM-IV criteria for a PMDD diagnosis. Possibly, severity and type of premenstrual symptoms may influence heart rate variability measures. Second, the time frame of the analysis of the ECG differed between studies; we investigated time domain HRV variables during a 7-h period that comprised mainly sleep and we investigated frequency domain variables as a function of Non-REM and REM sleep. Landen *et al.* (12) used 24-h ECG recordings for their time domain HRV measures, and 10-min ECG recordings when subjects were awake for frequency domain HRV measures. Total variance of HRV depends on the length of the recording period (10) and there are differences in HRV measures between waking and sleeping hours (30) and according to sleep stages (22). By using a 24-h recording period that combined wake and sleep periods, menstrual phase differences in time-domain HRV variables in the women with PMDD may have been masked in the study by Landen *et al.* (12). An intriguing possibility that deserves further study is that women with severe PMS or PMDD may show different alterations in autonomic functioning depending on whether they are asleep or awake.

Anxiety and depressive disorders have also been linked with autonomic dysfunction as assessed by measures of HRV. Patients with panic disorder have lower SDNN (31) and HF power (32) as well as a higher LF/HF ratio than controls (32). Many studies have reported that depression is associated with a lower resting HRV (See (33) for review) but it is unclear whether disruption in autonomic nervous system function is a trait or state marker for depression (34). There are many similarities between severe PMS/PMDD and depressive and anxiety disorders, including symptom overlap and the effectiveness of selective serotonin reuptake inhibitors as

treatment options (35). There is also a high degree of comorbidity between severe PMS/PMDD and depression and anxiety (36). Our finding of reduced HRV in women with severe PMS in association with their symptoms provides further evidence that severe PMS/PMDD, depression, and anxiety disorders may share common underlying pathophysiological disturbances. PMS is a unique disorder because the symptoms have a cyclic pattern in association with the menstrual cycle. Our findings suggest that reduced HRV during sleep, and specifically reduced parasympathetic activity, is state specific – occurring only in association with premenstrual symptom expression in the late-luteal phase.

Although the women with severe PMS had reduced HF power during sleep in the late-luteal phase, relative to the follicular phase, they still showed the expected higher HF power and lower LF/HF ratio during non-REM sleep compared with REM sleep (22). Controls also showed the expected changes in HRV as a function of sleep stage. Indeed, autonomic control is altered during sleep compared with wake, with non-REM sleep being characterised by elevated parasympathetic nervous system activity and reduced sympathovagal balance whereas during REM sleep these changes are reversed (22). In addition, we found an increase in NN-interval across the 7-h recording period, which may reflect circadian influences on heart rate (30,37).

Our findings in the control group that menstrual phase did not influence HRV during sleep support those of some previous studies that have investigated resting HRV in young women when awake (13,19). Others, however, have reported an increase in the LF/HF ratio in the luteal phase (14–16), which we did not find. Conflicting results between studies that have investigated HRV at different phases of the menstrual cycle may be due to different methodologies, small sample sizes, varying sampling times during the menstrual cycle, and lack of control for the presence of premenstrual symptoms in subjects. Our findings show that, in the absence of significant premenstrual symptoms, HRV during sleep does not differ in the late-luteal phase compared with the follicular phase. However, we did find that the NN-interval was significantly shorter in the late-luteal phase than in the follicular phase in controls and in women with PMS. Similar to our findings, Driver *et al.* (38) reported that women without menstrual-associated complaints had a significantly faster heart rate, which was associated with increased body temperature, during the sleep period in the luteal phase compared with the follicular phase.

There are limitations to our study that need to be considered. First, our study groups are small and the between-subject variability was high particularly in spectral HRV measures, which may have impacted our ability to detect group differences. Further, not all the women in our PMS group met criteria for a PMDD diagnosis making it difficult to compare our results with those of other studies. However, all the women rated their symptoms on a daily basis and were confirmed as having premenstrual symptoms that were distressing to them, thus having what could be termed ‘clinically-significant PMS’ (1). Future studies of larger numbers of women are needed to further investigate possible differences in HRV between women with and without severe PMS as well as in those women meeting the DSM-IV criteria for PMDD. These limitations, however, do not negate our findings of a significant difference in HRV within the group of women with severe PMS when they were symptomatic in the late-luteal phase compared with the follicular phase.

Although HF power is accepted as a measure of PNS activity (10), variations in respiratory activity can modulate this component (22,26). We therefore analysed the frequency of the peak of the HF component (HFfr) as a measure of respiratory rate. We found that HFfr was lower, indicating a slower respiratory rate, during non-REM and REM sleep in women with PMS than controls, in both menstrual phases. A slower respiratory rate would give a slightly higher HF component (as an artifact) and could account for the non-significant tendency for a higher

HF component in the women with PMS compared with controls. Investigators of HRV in subjects who are awake have attempted to minimize the influence of respiratory rate by controlling breathing rates, but controlled breathing can also impact HRV measures (39), and obviously cannot be done during sleep. We did not find any difference in HFfr between menstrual phases in either study group. Therefore, our finding of a menstrual phase effect on HF power in women with PMS is unlikely to be an artefact of a change in respiratory rate.

In conclusion, we have found that HRV, and more specifically HF power reflecting parasympathetic nervous system activity, is lower during sleep in women with PMS in association with their symptoms.

Acknowledgements

Dr Baker was supported by a developmental grant from SRI International and NIH grant 1R21HL088088-01. We thank all research staff for their invaluable technical support, and are especially grateful for the assistance of Alison Hughes with data analysis. We also thank all volunteers for their dedicated participation.

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Figure 1.

Mean ($\pm$ SEM) NN-interval and time domain indices of heart rate variability across the first seven hours after lights-out in 9 women with severe PMS and in 12 controls during the follicular and late luteal phases of the menstrual cycle.

Figure 2.

High frequency power component of heart rate variability during non-REM and REM sleep in the late-luteal phase, expressed as a percentage ($\pm$ SEM) of follicular phase values, for 9 women with severe premenstrual syndrome (PMS) and 12 control subjects. * indicates significant difference from follicular phase ($P < 0.05$).

Table 1

Average ($\pm$ SD) NN-interval and heart rate variability measures in the time domain for the first 7 hours after lights-out in 12 controls and 9 women with severe PMS.

Variable	Controls		PMS		ANOVA
	Follicular	Menstrual Phase Late luteal	Follicular	Menstrual Phase Late luteal	
NN-interval (ms)	1034.2 $\pm$ 137.2	996.3 $\pm$ 124.4 ^a	943.4 $\pm$ 162.5 ^b	841.1 $\pm$ 115.1 ^{ab}	Group effect: $F_{1,19} = 4.8$, $p = 0.04$ Phase effect: $F_{1,19} = 12.2$, $p = 0.002$ Interaction: $F_{1,19} = 2.6$, ns
SDNN (ms)	108.9 $\pm$ 49.5	107.3 $\pm$ 34.3	121.3 $\pm$ 37.3	92.5 $\pm$ 23.9 ^a	Group effect: $F_{1,19} = 0.006$, ns Phase effect: $F_{1,19} = 5.7$, $p = 0.03$ Interaction: $F_{1,19} = 4.5$, $p = 0.05$
SDANN (ms)	54.5 $\pm$ 24.3	56.4 $\pm$ 17.3	59.8 $\pm$ 17.8	53.4 $\pm$ 13.4	Group effect: $F_{1,19} = 0.03$, ns Phase effect: $F_{1,19} = 0.24$, ns Interaction: $F_{1,19} = 0.8$, ns
rMSSD (ms)	82.6 $\pm$ 61.8	82.8 $\pm$ 51.1	101.2 $\pm$ 55.2	63.1 $\pm$ 21.7 ^a	Group effect: $F_{1,19} = 0.001$, ns Phase effect: $F_{1,19} = 7.5$, $p = 0.01$ Interaction: $F_{1,19} = 7.6$, $p = 0.01$

^a significantly different from follicular phase (t-test, $P < 0.05$)

^b significantly different from controls
ns, not significant.

Table 2

Average ($\pm$ SD) heart rate variability parameters in the frequency domain for Non-REM and REM sleep in 12 controls and 9 women with severe PMS.

Variable	Sleep Stage	Controls		PMS		ANOVA
		Follicular	Menstrual Phase Late luteal	Follicular	Menstrual Phase Late luteal	
Total power (arbitrary units) *	Non-NREM REM	6.3 $\pm$ 1.1 6.5 $\pm$ 1.3	6.2 $\pm$ 0.8 6.6 $\pm$ 0.8	6.9 $\pm$ 1.3 6.9 $\pm$ 1.5	6.3 $\pm$ 1.2 6.1 $\pm$ 1.4	Group effect: $F_{1,19} = 0.1$, ns Phase effect: $F_{1,19} = 3.6$, ns Group $\times$ Phase: $F_{1,19} = 3.6$, ns Sleep stage: $F_{1,19} = 0.3$, ns
HF peak frequency (Hz)	Non-REM REM	0.27 $\pm$ 0.03 0.26 $\pm$ 0.03	0.28 $\pm$ 0.04 0.27 $\pm$ 0.04	0.23 $\pm$ 0.03 ^b 0.23 $\pm$ 0.02 ^b	0.24 $\pm$ 0.03 ^b 0.23 $\pm$ 0.03 ^b	Group effect: $F_{1,19} = 8.4$, $p = 0.01$ Phase effect: $F_{1,19} = 2.8$, ns Group $\times$ Phase: $F_{1,19} = 0.1$, ns Sleep stage: $F_{1,19} = 2.0$, ns
HF power (arbitrary units) *	Non-REM REM	4.6 $\pm$ 1.3 4.2 $\pm$ 1.4 ^c	4.7 $\pm$ 1.1 4.3 $\pm$ 1.3 ^c	5.5 $\pm$ 1.6 4.9 $\pm$ 2.1 ^c	4.8 $\pm$ 1.3 ^a 4.0 $\pm$ 1.3 ^{ac}	Group effect: $F_{1,19} = 0.4$, ns Phase effect: $F_{1,19} = 5.7$, $p = 0.03$ Group $\times$ Phase: $F_{1,19} = 10.2$, $p = 0.005$ Sleep stage: $F_{1,19} = 17.5$, $p = 0.001$
LF/HF ratio	Non-REM REM	1.2 $\pm$ 1.3 2.2 $\pm$ 1.6 ^c	1.1 $\pm$ 1.0 2.6 $\pm$ 2.1 ^c	0.6 $\pm$ 0.6 2.0 $\pm$ 2.5 ^c	0.9 $\pm$ 0.7 2.2 $\pm$ 1.5 ^c	Group effect: $F_{1,19} = 0.5$, ns Phase effect: $F_{1,19} = 0.8$, ns Group $\times$ Phase: $F_{1,19} = 0.01$, ns Sleep stage: $F_{1,19} = 40.5$, $p < 0.001$

HF = high frequency (0.15 – 0.40 Hz)

^a significantly different from follicular phase (t-test, $P < 0.05$)

^b significantly different from controls

^c significantly different from NREM sleep

ns, not significant

* expressed as natural logarithm of values.