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ORIGINAL ARTICLE

Heart Rate Variability Across the Menstrual Cycle in Shift Work Nurses

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Background/Purpose: Reduced heart rate variability (HRV) has been shown to be associated with a risk of cardiovascular disease. The combined influence of shift work and menstrual cycle on HRV in nurses has not been studied. The aim of this study was to examine the effects of the menstrual cycle within shift patterns on HRV in nurses, using a within-subjects design and a multivariable analysis to control covariates.

Methods: Twelve healthy, young, female shift nurses volunteered to have repeat measures of female sex hormones, 24-hour physical activity, and HRV at three points, during their menses, follicular, and luteal phases.

Results: Normal cyclic variations in endogenous sex hormones levels were shown; however, no significant correlations were found between estrogen levels and HRV variables. Results demonstrated that the high frequency (HF) was lower in the follicular phase than in the luteal phases; however, the low frequency (LF) or LF to HF ratio (LF/HF) was significantly higher in the follicular phase than in the luteal phase during sleeping periods after night or day work.

Conclusion: The endogenous sex hormones levels were shown normal cyclic variation. Under the effects of shift work, the diminished parasympathetic activity and the increased sympathetic activity were shown in the follicular phase compared with the luteal phase. This result may serve as a reference to explain why shift workers have high risk of cardiovascular disease.

1. Introduction

Analysis of heart rate variability (HRV) could be a useful tool to assess cardiac autonomic control.[1] Previous studies indicated that HRV seems to be related to sleep and wakefulness.[2] The low frequency (LF) and LF to high frequency (HF) ratio (LF/HF) exhibited 24-hour fluctuations in accordance with different working and sleeping periods.[3] The physical activity was different between working and sleeping time. Thus, HRV variables are also influenced by levels of the physical activity under the influence of the type of shift (day shift or night shift).[3] Therefore, HRV variables should be examined separately according to sleeping and working periods for control of the level of physical activity. Comparisons of HRV variables exhibited different results depending on the type of shifts. Some research has found lower values of LF and LF/HF during night work compared with the morning or evening working periods,[4] whereas other research did not show any significant difference between the levels of HRV variables between day and night shifts.[2,3] The effects of menstrual phases on HRV were not taken into consideration in these studies, yet these could produce the different HRV results observed in shift workers. Consequently, the future studies examining HRV differences comparing the type of shift need to consider the menstrual phase at which HRV recordings were obtained.

The HRV for evaluating cardiac autonomic function is affected by the menstrual cycle.[5] Previous studies have indicated that parasympathetic activity is lower during the luteal phase compared with other phases of the menstrual cycle in healthy women.[6,7] Sympathetic activity is significantly higher in the luteal phase than in the follicular phase.[6,8] However, others have reported the menstrual cycle were not significantly associated with changes in autonomic nervous activity.[9] Hormone levels could be a reason for the discrepancies in studies reporting the differences in HRV across the menstrual cycle. Therefore, the changes of hormone levels across the menstrual cycle merit investigation for female shift nurses.

In women, HRV is related to many factors, including endogenous sex hormones,[9,10] menstrual cycle,[9,11,12] menopause,[10,13] hormone replacement therapy,[14,15] body mass index (BMI),[16,17] and physical

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conditioning.[18,19] In addition, the combined influence of age, BMI, and menstrual cycle has been reported in young women, which indicated that age was an important predictor of HRV, followed by BMI and menstrual cycle.[14] However, the combined influence of shift patterns and other physiological conditions has not been explored in shift workers. This study used a multivariable analysis to control covariates and employed within-subjects design to examine the effects of the menstrual cycle within shift patterns on HRV for shift nurses.

2. Methods

2.1. Study design and sample

This study examined HRV during the three phases of one menstrual cycle using wrist actigraphy in combination with sleep diaries to analyze physical activity. The cyclic variations in female sex hormone levels were also compared in three phases. A convenience sample of 12 shift nurses volunteered to participate in this study. The mean age, the BMI, and the years employed in nursing were 27.1 ± 2.76 years, 23.8 ± 4.13 kg/m^2, and 4.76 ± 1.05 years, respectively. They had a history of regular, predictable menstrual cycles between 28 and 35 days in length within the preceding 6 months. All participants were free of medications and oral contraceptives during the study. Participants had never been pregnant or lactated in their life. After giving informed consent and receiving an orientation about the procedures of this study, participants began the study in the menses (Days 1–2 after menses onset), the follicular phase (7–10 days after menses onset), or the luteal phase (3–7 days before onset of the subsequent menstrual cycle), which occurred during their shift work. Participants were instructed to maintain their shift pattern during each phase of their menstrual cycle.

2.2. Power spectral analysis of HRV

Standard three-channel electrodes were attached to the anterior chest wall of participants and connected to the portable monitor system (E3-8020; Micro-Star International, Taiwan). The electrocardiogram (ECG) waveforms were stored in an integrated circuit card at a sampling frequency of 1000 Hz. Recordings of ECG were visually inspected for ectopic beats and artifacts, after which noise spikes were manually edited. The 24-hours recordings were divided into 24 segments of 1 hour and transferred to a personal computer. Frequency domain analysis of HRV was performed by using standard software package (Athena HRV Analysis software version 1.0; Taiwan) based on the nonparametric Fast Fourier Transformation algorithm. The measurements of HRV followed the standards suggested by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology set in 1996.[20]

Two main spectral components were the LF (0.04–0.14 Hz) and HF (0.15–0.4 Hz) and the ratio of LF to HF was calculated and expressed as LF/HF. Because of large variability between participants, natural logarithmic transformation was performed on these HRV parameters. Power spectral analysis of R-R interval variability has revealed that HF is modulated solely by the parasympathetic nervous system, whereas the LF component is jointly modulated by the sympathetic and parasympathetic nervous systems. Furthermore, the LF/HF is also a useful parameter that reflects cardiac sympathetic modulations or sympathovagal balances.[20]

2.3. Actigraph

To monitor the shift nurses' working periods and sleeping periods, the participants wore a wrist actigraph continuously for 24 hours on the nondominant wrist. Basic Mini-Motionlogger (Ambulatory Monitoring, Inc., Ardsley, NY) contains a piezoelectric accelerometer with a sensitivity 0.01 g or higher. The sampling frequency is 10 Hz, and filters are set to 2–3 Hz. Actigraphs were initialized by ACT Millennium software (Ambulatory Monitoring, Inc., Ardsley, NY, USA) for zero crossing mode to collect data in 1-minute epochs. Actigraph data files were analyzed by Action W-4 version 1.05 software (Ambulatory Monitoring, Inc.). This software identified each epoch as sleep or waking using the mathematical model validated by Cole et al.[21]

2.4. Blood sample assays

Venous blood samples were taken on the second day of each experimental phase. Ten milliliters of blood were collected in tubes and kept on ice. The blood sample was separated by centrifugation at 3000 revolutions per minute for 5 minutes, and the serum was withdrawn and stored until assay. Serum levels of female sex hormones were analyzed by Chemiluminescent Immunoassay using commercial kits from Beckman Access (USA). The female sex hormones included estrogen, prolactin, follicle-stimulating hormone (FSH), luteinizing hormone, and progesterone. Intra- and interrater analysis coefficients of variation were 2.3% and 9.1%, respectively.

2.5. Procedure

A within-subject design was used to minimize individual differences. Each participant was given detailed instructions on the experimental protocol. All participants were requested to refrain from drinking caffeine or alcohol-containing beverages during the study. The participants entered the experiment in the follicular phase and tested at the end of the luteal phase across one menstrual cycle. Each participant underwent 24-hour ECG recordings during the three phases of menstrual cycle. If the participants worked in the day shift, the ECG recordings were started at about 7 PM after finishing day shift work. If the participants worked in an evening shift, the ECG recordings were started at about 2 AM after finishing the evening shift. If the participants worked in the night shift, the ECG recordings were started at about 10 AM after they finished the night shift. At the same time, all participants wore the actigraph on the nondominant wrist for 24 hours during each phase of the menstrual cycle. Participants were instructed to record the time in and out of bed by filling in the sleep log. Any inconsistent data between the sleep log and actigraphy would be excluded.

2.6. Statistical analysis

All statistical analyses were performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Generalized estimating equation (GEE) models were first introduced by Zeger and Liang[22] in 1986. GEEs have become an important strategy in the analysis of correlated data, in which participants are measured at different points in time. In this study, we performed GEE with an identity link and normal distribution to test the primary study hypothesis, that is, to explore the effects of the menstrual cycle within shift pattern on the HRV by controlling the variables of age and BMI. In addition, GEE allows us to test whether there was a pairwise comparison in the menstrual cycle effect using the post hoc procedures of least significance difference (LSD) test. In all analyses, a p value less than 0.05 was considered statistically significant. Finally, we graphed the curves for 24-hours HRVs across all time points.

Table 1 Basic characteristics and comparisons of female sex hormones in the three phases of the menstrual cycle ($n = 12$)

Effect	Menses, mean (SE)	Follicular phase, mean (SE)	Luteal phase, mean (SE)	p
Estrogen	49.08 (8.38)	120.33 (41.17)*	103.42 (15.30)	<0.05
Prolactin	16.76 (2.41)	17.82 (1.85)	22.91 (2.36)	0.208
FSH	7.04 (0.43)	7.48 (0.51)	4.73 (0.57)*,†	<0.001
LH	3.02 (0.46)	9.40 (2.07)*	3.42 (0.43)†	<0.05
Progesterone	0.89 (0.24)	1.34 (0.53)	6.81 (2.22)*,†	<0.05

* Reference group: menses; † Reference group: follicular phase.
FSH = follicular stimulating hormone; LH = luteinizing hormone; SE = standard error.

3. Results

Compared with the menses, estrogen, and progesterone were significantly higher in the luteal phases; however, the FSH was significantly lower in the luteal phase (Table 1). The effects of the menstrual cycle within shift pattern on various HRV parameters are given in Tables 2 and 3 by controlling the variables of age and BMI. During working periods (Table 2), a significant increase was found in the HF during the luteal phase compared with the follicular phase. Furthermore, a significant increase was noted in the LF/HF of the follicular phase compared with the menses during the day shift, whereas a tendency for decreased LF/HF was observed in the night shift. While sleeping (Table 3), The LF and LF/HF were significantly lower in the luteal phase than in other phases of the menstrual cycle after night work or day work. In addition, a significant increase was found in the HF during the luteal phase compared with the follicular phase. In Figure 1, LF and LF/HF ratio were higher during working time and lower when participants were sleeping. Conversely, HF was lower when working activities had been performed at three shifts compared with the sleeping periods.

4. Discussion

The follicular phase was associated with a greater increase in the LF and LF/HF component during sleeping periods after day or night shift. Furthermore, the HF component was significantly lower in the follicular phase than in the luteal phase. This study demonstrates that sympathetic activity was diminished in the luteal phase; however, the vagal activity was significantly increased at this time. Our data provide that the effects of menstrual cycle on HRV under the shift work system were not consistent with previous studies, which indicated that the sympathetic activity was increased in the follicular phase. This study support that significant differences were found between phases of the menstrual cycle after day or night work. This result may serve as a reference to explain why shift worker had higher risk of cardiovascular disease.

The increased sympathetic activity and lower vagal activity were found in the follicular phase, which was not consistent with previous studies.[6–8] This study did not support the idea that the increased parasympathetic activity at follicular phase is because of the increased endogenous estrogen levels, whereas the greater sympathetic activity during the luteal phase is related to greater endogenous progesterone levels.[6–8] In this study, the estrogen levels in the follicular phase and progesterone levels in the luteal phase were significantly higher compared to the menses of the menstrual cycle. However, the FSH was significantly lower in the luteal phase compared with the follicular phase and menses. These results showing hormone levels were in agreement with those from a previous study,[9] which indicated that menstrual phases could be pinpointed accurately. The sex hormone levels in each phase of the menstrual cycle were also similar to those found in another study of healthy young women.[9] It was consequently inferred that the sex hormone levels presented were not affected by shift work in this study. Therefore, we concluded that the fluctuations of HRV during menstrual cycle may have interaction with shift pattern not with endogenous sex hormone levels in nurses.

Another possible explanation is that under the effects of shift work, parasympathetic activity decreased during the menses or follicular phases of menstrual cycle. Saleh et al[23] in 2001 demonstrated that estrogen has a neuroprotective effect and can prevent stroke-induced autonomic dysfunction. According to our analysis of estrogen levels, the estrogen level peaked at the follicular phase, a finding similar to other studies.[9] However, in our study, the decreased parasympathetic activity was shown during the follicular phase, which may indicate that the estrogen did not produce marked cardioprotective effects on the autonomic function. This may explain why shift workers have high risk of cardiovascular disease. However, mechanisms to explain these findings need further research to be proven.

The results in Table 3 show that decreased sympathetic activity was found during the luteal phase compared with other phases of the menstrual cycle regardless of day or night work. These results differ from those of previous studies, which have reported higher sympathetic activity during the luteal phase compared with other phases of the menstrual cycle.[6–8] Our analysis showed the progesterone level peak at the luteal phase, which is similar to findings from other studies.[9] We assumed that the effects of sympathetic activity attributed to progesterone levels would be similar. This led us to infer that progesterone may have similar effects on HRV, that is, greater sympathetic activity would be found in the luteal phase. However, our study shows sympathetic activity was lower in the luteal phase than in other phases of the menstrual

Table 2 Results of GEE analysis examining HRV changes in the three phases of the menstrual cycle during working periods

Variable	Day shift, mean (SE)	p	Evening shift, mean (SE)	p	Night shift, mean (SE)	p
HF						
Menses	4.47 (0.17)	<0.05	5.21 (0.23)	0.559	5.10 (0.27)	0.922
Follicular phase	4.20 (0.14)		5.04 (0.22)		4.94 (0.16)	
Luteal phase	4.73 (0.11)*		5.16 (0.29)		4.95 (0.17)	
LF						
Menses	6.23 (0.23)	0.234	6.30 (0.21)	0.243	6.63 (0.31)	0.132
Follicular phase	6.09 (0.05)		6.40 (0.14)		6.46 (0.27)	
Luteal phase	6.18 (0.21)		6.64 (0.17)		5.03 (0.54)	
LF/HF						
Menses	1.76 (0.06)	<0.001	1.14 (0.20)	0.235	1.54 (0.14)	<0.001
Follicular phase	1.89 (0.10)†		1.34 (0.21)		1.51 (0.39)	
Luteal phase	1.45 (0.16)		1.67 (0.18)		0.18 (0.67)†	

* Reference group: follicular phase; † Reference group: menses.
LF = low frequency; HF = high frequency; HRV = heart rate variability; GEE = generalized estimating equation; SE = standard error.

Table 3 Results of GEE analysis examining HRV changes in the three phases of the menstrual cycle during sleeping periods

Variable	Day shift, mean (SE)	*p*	Evening Shift, mean (SE)	*p*	Night shift, mean (SE)	*p*
HF						
Menses	5.76 (0.47)	<0.001	5.57 (0.41)	0.975	5.86 (0.29)	0.147
Follicular phase	5.40 (0.17)		5.82 (0.26)		5.95 (0.27)	
Luteal phase	5.64 (0.20)*		5.78 (0.18)		5.52 (0.10)	
LF						
Menses	5.92 (0.08)	0.856	6.56 (0.15)	<0.001	6.21 (0.20)	<0.001
Follicular phase	5.94 (0.32)		6.21 (0.14)		6.63 (0.18)	
Luteal phase	5.76 (0.31)		5.83 (0.37)†		5.82 (0.07)*	
LF/HF						
Menses	0.87 (0.22)	<0.001	0.68 (0.26)	0.489	0.35 (0.10)	<0.001
Follicular phase	0.83 (0.35)		0.39 (0.25)		0.68 (0.08)	
Luteal phase	0.06 (0.48)*,†		0.02 (0.35)		0.30 (0.03)*	

* Reference group: follicular phase; † Reference group: menses.
LF = low frequency; HF = high frequency; HRV = heart rate variability; GEE = generalized estimating equation; SE = standard error.

cycle. Consequently, we think this possible alteration of sympathetic activity was not shown under the effects of progesterone for shift work nurses, thereby indirectly inducing higher sympathetic activity during follicular phase.

Our findings indicated that the circadian rhythm pattern of HRV had higher HF values and lower LF/HF values during sleeping periods than during working periods, which were independent of the day-night cycle, regardless of menstrual cycle. This study shows

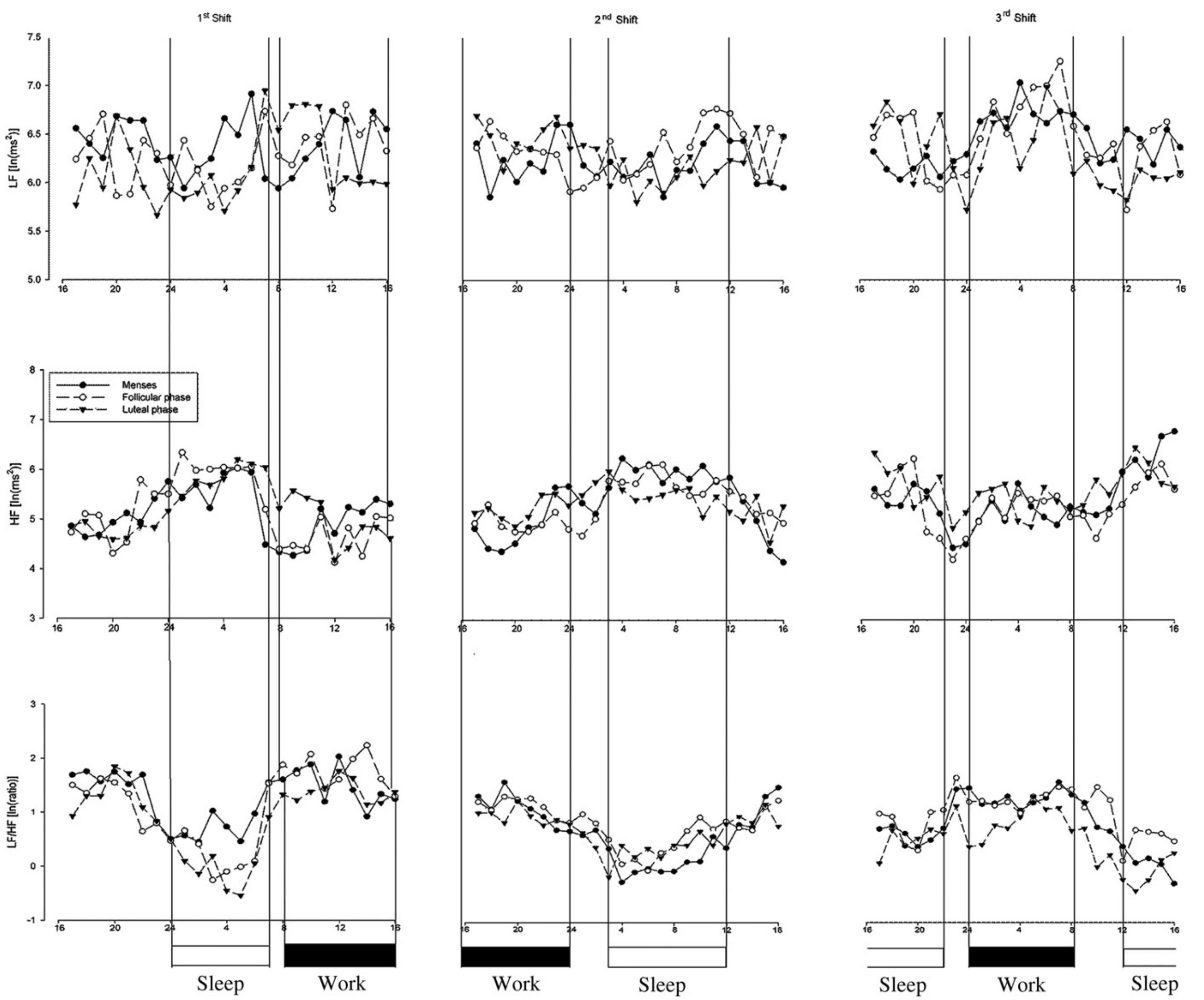

Figure 1 The 24-hour variations of spectral indexes of cardiac autonomic modulation were shown during three shifts. First shift means day shift, second means evening shift, and third shift means night shift.

that the circadian rhythm pattern of HRV had lower LF/HF values during night work (Figure 1), in line with previous studies.[4] Therefore, sleeping and working periods which have different physical activity was clearly a factor inducing changes in autonomic nervous activities in shift nurses, after taking into consideration menstrual cycle, BMI, and age factors. Therefore, consideration of HRV should be given to evaluate physical activity among shift nurses.

The study included a small sample of nurses and had, as a result very low power, particularly in terms of finding differences between various menstrual cycles. The other limitation was the lack of a control group; however, we demonstrated the effects of menstrual cycle within shift pattern on HRV according to sleeping and working time. This study provided only a brief picture of the HRV of rotating three-shift nurses who work on day, evening, and night shifts followed by 2 days off. The effects of menstrual cycles on HRV for nurses, who work on permanent night shifts and regular morning shifts, would warrant future study.

5. Conclusions

This study indicated that for shift nurses, normal cyclic variations in endogenous sex hormones levels were shown. In addition, the decreased parasympathetic activity and the predominant sympathetic activity were found in the follicular phase compared with the luteal phase. This result may indicate that the estrogen did not produce marked cardioprotective effects on the autonomic function. This study would seem important to explain why shift workers are high-risk groups for cardiovascular disease. Future investigations focusing on the effects of shift work on HRV should consider the differences during menstrual cycle for female nurses. Further studies examining the HRV in shift nurses considering the factors of physical activity are also necessary for the clinical studies.

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