

OBJECTIVE EVALUATION OF CARDIAC AUTONOMIC ACTIVITY IN DIFFERENT PHASES OF MENSTRUAL CYCLED. Srujana¹, Srinivasarao Chandala²**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: A wide spectrum of biological function is regulated by the cyclic changes in estrogen and progesterone levels during regular menstrual cycle. However limited literature is available concerning the relationship of these hormones and cardiac autonomic activity. In the present study, we hypothesize that there would be heart rate variability during different phases of menstrual cycle, which can be attributed to the effect of ovarian steroids on cardiovascular function in women. The aim of the study is to compare the cardiac autonomic activity in the different phases of menstrual cycle (Menstrual, follicular and luteal phases) using heart rate variability. The objective is to establish a physiological correlation between the cardiac autonomic activity and different phases of menstrual cycle. The study was conducted in 48 regularly menstruating young female, of age group 18-30yrs, in the Upgraded Department of Physiology, Osmania medical college, from December 2011 to August 2013, using LABCHART software provided by ADLABS. The power spectral analysis of HRV was used to calculate low frequency(LF), high frequency (HF) component and their ratio (LF/HF) during menstrual (2±1 days), follicular(11±1 day) and luteal phases (20±1day) from the first day of bleeding. Results showed a significant increase was noted in low frequency component in luteal phase compared to follicular phase (p=0.000), whereas, a tendency for increase in high frequency component was observed in follicular phase (p=0.004). Furthermore, LF/HF was significantly higher in luteal phase than in the follicular phase (p=0.000) indicating an increased sympathetic activity. The conclusion is regulation of autonomic tone is modified during menstrual cycle. The alteration in the balance of ovarian hormones might be responsible for these changes.

KEYWORDS: autonomic activity, HRV, low frequency, high frequency, menstrual cycle.

INTRODUCTION: Menstrual cycle is tightly governed by orchestrated changes in the levels of ovarian estrogen and progesterone, which produce varying responses in diverse tissues and organs.¹ Fluctuating levels of female reproductive hormones bring about various autonomic changes.² with the advent of HRV, a noninvasive measure of cardiac autonomic control had led to increase understanding of changes in autonomic activity.³

Ovarian hormones alterations along the menstrual cycle are associated with corresponding significant changes in multiple neuro-humoral homeostatic mechanisms regulating the cardiovascular system.⁴

The general presence of functional sex steroid hormone receptors in the cardiovascular system is well established and their expression in both heart and blood vessels have been recognized for decades.^{5,6,7,8} Estrogen is also associated with lower levels of endothelin and decreased sensitivity to the vaso-constrictive effects of peptide. The presence of estrogen receptors in the heart, vascular smooth muscle and autonomic brain centers, suggest a possible involvement in the regulation of cardiovascular system. In the follicular phase, estrogen causes an up-regulation in the cardiovascular or myometrial adreno-receptor.

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Testing autonomic function is complicated by the fact that within each part of the output from the autonomic nervous system partial responses occur and any defects whether central or peripheral, may be partially corrected by the other neuronal, chemical or hormonal mechanisms.

The cardiovascular system has proved suitable for analysis of the principles used in testing for autonomic dysfunction and analyzing cardiovascular control is doubly relevant because postural hypotension is one of the commonest symptoms of defective autonomic function.

HEART RATE VARIABILITY: Physiological effects of menstrual cycle on the autonomic function have been extensively examined. Few studies have evaluated neuro-cardiac parameters during the various phases of menstrual cycle; this would be useful and highly relevant for cardiovascular evaluation of women at higher risk to develop heart disease, thus permitting early intervention.⁹

It is questionable whether in general population low HRV is a consequence of a disease or an indicator of an underlying mechanism for future disease. Several studies suggest that there are definite changes in the HRV in the different phases of the menstrual cycle but studies are lacking correlating the cardiac autonomic activity, menstrual cycle and BMI in young females in different phases of menstrual cycle.

The present study aims to describe the HRV and its variation cycle in healthy young women in Time domain and Frequency domain method in different phases of menstrual cycle.

MATERIALS AND METHODS: A total of 48 normotensive, non-pregnant healthy female students studying their MBBS Course in Osmania Medical College, Hyderabad were selected. The subjects are familiarized with the testing equipment and the procedure used in the laboratory and informed written consent was obtained from all participants, and the experiment protocol was approved by Ethics committee of the college.

Women aged between 18 -30 years, eumenorrheic i.e. Normal regular menstrual cycles of 26-32 days and normotensive (<140/90) were included in the present study.

Women with pregnancy, h/o irregular cycles, h/o menorrhagia, h/o hypertension, h/o any medication during study (including oral contraceptive pills), h/o smoking /alcohol intake, lactating women, and with h/o CVS, pulmonary, neurological or endocrine diseases were excluded from the present study.

STATISTICAL ANALYSIS: The statistical analysis was done using repeated measure ANOVA (Analysis Of Variance) technique. 'P' value is <0.05, is considered significant.

LOW FREQUENCY TO HIGH FREQUENCY RATIO (LF/HF):

	Mean	Std. Deviation	N
LF/HF in menstrual phase	.74083	.253356	48
LF/HF in follicular phase	.99342	.385644	48
LF/HF in luteal phase	2.19104	.756831	48

Fig. 1: Descriptive Statistics

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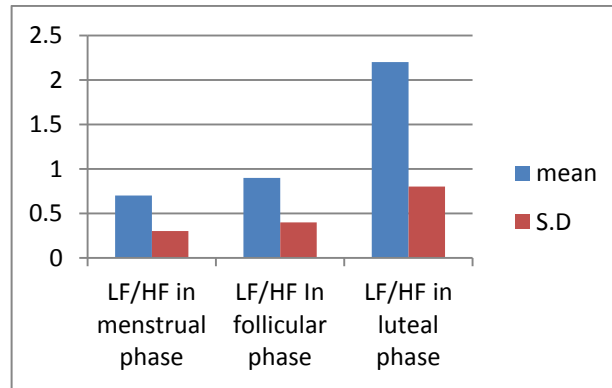


Fig. 2

Measure: LF HF ratio

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	Df	Sig.	Epsilon ^a		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
Phase	.691	17.021	2	.000	.764	.784	.500

Fig. 3: Mauchly's Test of Sphericity

Measure: LF HF ratio

Source		Type III Sum of Squares	Df	Mean Square	F	Sig.	Partial Eta Squared
Phase	Sphericity Assumed	57.619	2	28.810	112.244	.000	.705
	Greenhouse-Geisser	57.619	1.528	37.720	112.244	.000	.705
	Huynh-Feldt	57.619	1.568	36.736	112.244	.000	.705
	Lower-bound	57.619	1.000	57.619	112.244	.000	.705
Error (Phase)	Sphericity Assumed	24.127	94	.257			
	Greenhouse-Geisser	24.127	71.795	.336			
	Huynh-Feldt	24.127	73.719	.327			
	-Lower-bound	24.127	47.000	.513			

Fig. 4: Tests of Within-Subjects Effects

Measure: LF HF ratio

Phase	Mean	Std. Error	95% Confidence Interval	
1	.741	.037	.667	.814
2	.993	.056	.881	1.105
3	2.191	.109	1.971	2.411

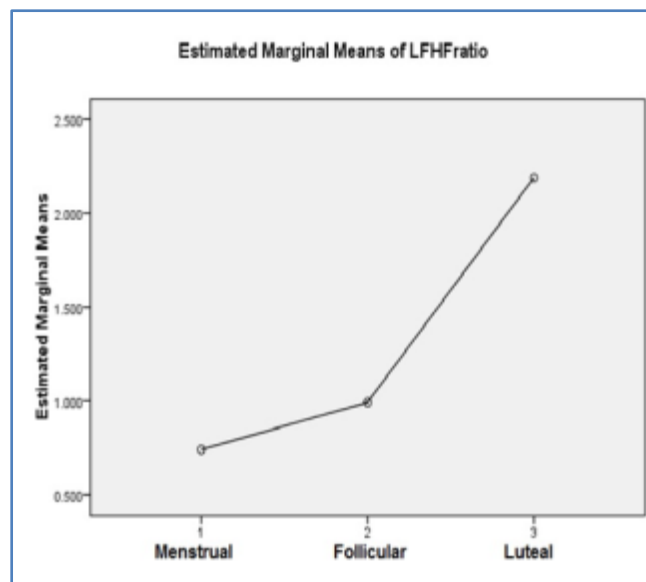
Fig. 5: Estimates

Measure: LF HF ratio

S (I) Phase	(J) Phase	Mean Difference (I-J)	Std. Error	P value Sig.	95% Confidence Interval for Difference ^a	
					Lower Bound	Upper Bound
1	2	-.253*	.069	.000	-.424	-.081
	3	-1.450*	.116		-1.738	-1.163
2	1	.253*	.069	.000	.081	.424
	3	-1.198*	.118		-1.491	-.905
3	1	1.450*	.116	.08	1.163	1.738
	2	1.198*	.118		.905	1.491

Fig. 6: Pairwise Comparisons

Based on estimated marginal means

**RESULTS:**

HRV ANALYSED USING TIME DOMAIN METHODS: HRV in menstrual phase was 15.59 ± 4.93 , in follicular phase was 20.68 ± 7.96 and during luteal phase was 17.13 ± 4.24 . Though the follicular phase value is greater than the other two phases, it was not statistically significant, when compared to other two phases. There was no significant difference in HRV in menstrual phase and luteal phase also.

HRV ANALYSED USING FREQUENCY DOMAIN METHODS: The low frequency component in menstrual phase was 43.57 ± 11.4 , follicular phase was 51.08 ± 11.3 and luteal phase was 85.04 ± 30.2 . In luteal phase, LF was significantly higher ($p = 0.000$) compared to follicular and menstrual phase ($p = 0.008$), but between menstrual and follicular phase there was no significant difference. The high frequency (HF) component in menstrual phase was 58.92 ± 9.49 , in follicular phase it was 55.53 ± 11.5 and in luteal phase, it was 39.83 ± 8.1 . Follicular phase has significantly higher HF than luteal phase ($p = 0.0001$). Analytically menstrual phase HF was greater ($p = 0.0001$) than luteal phase and slightly

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higher than follicular phase which was not significantly evident. The LF/HF ratio in menstrual phase was 0.74 ± 0.2 , follicular phase was 0.99 ± 0.3 , and luteal phase was 2.19 ± 0.75 . It was significantly greater ($p = 0.000$) in luteal phase compared to follicular phase and very significantly higher ($p = 0.000$) compared to menstrual phase. The LF/HF ratio is greater in follicular phase compared to menstrual phase though not significantly inferred.

DISCUSSION: Analysis of HRV during the luteal phase of the menstrual cycle, showed a statistically significant increase in the LF/HF ratio. Previous studies have reported increased vagal activity as suggested by and LF/HF ratio, during the follicular phase (days 3–11) compared with other phases of the menstrual cycle. This was supported by the findings of Sato et al,¹⁰ 1995 and Saeki et al,¹¹ 1997. Significantly greater vagal activity in the follicular phase (Sato et al;¹⁰ Saeki et al.¹¹) and greater sympathetic activity during the luteal phase (Guasti et al.¹² 1999; Yildirim et al.¹³ 2002) compared with other phases of the menstrual cycle have been reported.

In the current study, we examined HRV only at times of low and high sex hormone levels during the menstrual cycle as it was anticipated that during these times the possible interaction between the levels of endogenous female sex hormones and HRV would be more apparent. Collectively, the results of the current and previous studies indicate that vagal activity may be greater during the early follicular phase of the menstrual cycle and subsequently lower at other phases of the menstrual cycle, possibly due to the influences of increasing levels of FSH and LH (ovulation) and progesterone (Ovulation and luteal phases).

In the current study, significant correlations between estrogen levels and all absolute measures of HRV at ovulation were demonstrated reflecting a positive relationship between estrogen and vagal activity as only the parasympathetic nervous system regulates HR control at all frequencies (Akselrod et al.¹⁴ 1985).

This significant relationship between estrogen levels and HRV in the current study, and reports of estrogen-induced enhancement of vagal activity (Saleh & Connell et al¹⁵, 2000) and reduction of sympathetic activity (Ettinger et al.¹⁶ 1998; Mercurio et al.¹⁷ 2000) suggest that vagal dominance during the early follicular phase of the menstrual cycle may result from increasing levels of endogenous estrogen. Subsequent increases in endogenous levels of FSH, LH and progesterone may then inhibit the influence of estrogen on cardiac autonomic control as demonstrated by the similar HRV during the ovulation and luteal phases in the current and previous studies (Kondo et al¹⁸. 1989; Saeki et al.¹¹ 1997).

Previous reports of greater sympathetic activity during peak progesterone levels of the luteal phase (Sato et al,¹⁰ 1995; Guasti et al,¹² 1999; Yildirim et al,¹³ 2002) and increased HR and lower HRV in post-menopausal women following combined estrogen/ progesterone hormone replacement therapy (HRT) (Christ et al,¹⁹ 2002) provide further support of the proposed vagal inhibitory nature of progesterone.

Different investigators have suggested some mechanisms responsible for decreased parasympathetic activity in late luteal phase of menstrual cycle. In follicular phase, the enhanced parasympathetic activity may be due to increased oestrogen level (Sato et al.¹⁰ 1995; Guasti et al.¹² 1999; Yildirim et al.¹³ 2002). In follicular phase, oestrogen increases density as well as the function of presynaptic α_2 adreno-receptors thereby resulting in significant decrease in nor-epinephrine induced responses.¹⁵ Oestrogen stimulates the opening of calcium activated potassium channels by nitric oxide.¹⁹ Estrogens also stimulates opening of calcium activated potassium channels by cyclic

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Guanosine mono-phosphate dependent pathway.²⁰ Thus oestrogen relaxes vascular smooth muscle and promoting vasodilatation. Again, estradiol might be associated with increase in acetylcholine concentration.²¹ These findings suggested that, oestrogen has facilitating effect on cardio-vagal function.

On the contrary, decreased parasympathetic activity in late luteal phase might be due to increased level of progesterone during this phase. It has been suggested that, progesterone inhibits the influence of oestrogen on cardio-vagal activity.¹⁸ Again, Progesterone may increase cardiac excitability by its opposing effects on estrogen.²¹ It has also been reported that estradiol increases the number and sensitivity of progesterone receptors, thereby increasing the action of progesterone hormone during luteal phase. Also, progesterone exerts inhibitory effect on the cardio-vagal baro-reflex responses.²²

In the present study, fluctuation of estrogen and progesterone levels may be responsible for the changes in parasympathetic activity in follicular and late luteal phases of menstrual cycle.

However, increased parasympathetic activity during follicular phase might be due to the influence of estrogenic effect and decreased parasympathetic activities in late luteal phase may be due to increased level of progesterone.

Many studies suggested a correlation between oestrogen levels during follicular phase with increased parasympathetic activity. However, study conducted by Min- Hey²³ showed a significant decrease in parasympathetic activity and an increase in sympathetic activity in follicular phase. Princi et al²⁴ reported an increased HF and decreased LF in luteal phase than in follicular phase. Further the studies conducted by Andrew et al,²⁵ and spielman et al²⁶ reported no significant LF, HF, LF/HF changes with different phases of menstrual cycle.

Though few studies contradict to the results of present study, majority of them in which the study group were more, supported the results found in the present study. The possible existence and extent of the inhibitory influences of FSH and LH on cardiac autonomic control is presently unknown. Further studies are needed to explore the possible vagal inhibitory actions of FSH and LH and whether there is a period during the menstrual cycle of reduced cardio protection and increased risk of cardiac arrhythmias/events.

CONCLUSION: This study explores the complex relationship between female reproductive hormones and the cardiac autonomic activity, during different phases of menstrual cycle. Ovarian hormone variations along the menstrual cycle are associated with corresponding significant changes in multiple neuro-humoral homeostatic mechanisms regulating the cardiovascular system.

So, from the above study, we conclude that:

1. Power spectral analysis of HRV has more sensitivity in assessing the slight fluctuation of autonomic activities during menstrual cycle. This method has proved to be of great clinical usefulness in studying several pathological conditions due to the hormonal imbalance in women.
2. Luteal phase of MC was associated with a significant increase in the LF component and a significant decrease in the HF component, resulting in a high LF/HF ratio. Our findings were in agreement with earlier work who observed that sympathetic nervous activities are predominant in the luteal phase as compared with follicular phase.

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3. This high LF/HF ratio during luteal phase is attributed to the predominant sympathetic activity of progesterone.
4. Follicular phase of MC was associated with significant increase in HF component and decrease in LF. This may be attributed to increased estrogen levels during follicular phase, affecting the vagal activity of heart.
5. LF/HF ratio is the most sensitive indicator of sympatho-vagal balance. Our results clearly demonstrated a significant difference in the autonomic nervous activity in the luteal phase of the menstrual cycle in young females.

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