



ORIGINAL ARTICLE

Autonomic Modulation in Different Phases of Menstrual Cycle in Younger and Older Indian Women

Bindiya Sathish¹, Ramesh Bhat², Damodara Gowda K M^{1*}

¹K.S. Hegde Medical Academy, Karnataka, India;

²Kasturba Medical College, Bejai, Manipal University, Mangalore, India

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*** Corresponding author:**

K.S. Hegde Medical Academy,
Karnataka, India
Email: medicogen.doc@gmail.com

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ABSTRACT

Background: The menstrual cycle is an integral part of a major portion of a woman's life, associated with significant changes in multiple neuro-humoral homeostatic mechanisms. In the present study, autonomic modulation in different phases of menstrual cycle in young adult and older adult women's was assessed.

Methods: About 90 subjects were recruited and were divided between 2 groups and their HRV was recorded in 3 different phases and compared between young adults and older adult women. The HRV evaluation was done in the frequency domain using the software Version 1.1, AIIMS, New-Delhi. The data was analyzed using students 't' test followed by Mann Whitney-U test and $P < 0.05$ was considered the level of significance.

Result: HRV was analyzed using LF in three phases of menstrual cycle in two sub groups did not show any significant variations. In HF Component in Group-I when compared the menstrual with follicular, luteal phases, the menstrual phase showed significantly higher values. Comparison of LF/HF ratio between menstrual and follicular phase in Group-I showed significantly high variation between menstrual and luteal phases.

Conclusion: We conclude that a slow and steady decline in autonomic modulation with age, may have a close interaction with hormonal activity.

INTRODUCTION

The menstrual cycle is an integral part of a major part of a woman's life. The endocrinal morphology and function undergo characteristic changes in every menstrual cycle. These changes are crucial for perpetuation of the species, and are orchestrated to prepare the endometrium for implantation of conceptus. Lee et.al hypothesized that normal variation in autonomic balance during menstrual cycle, which likely evolved as adaptation for reproduction, may contribute to the catamenial variations in diseases independent of hormonal variations (1). The hormonal changes during different phases of menstrual cycle, as re-

ported earlier, states that the follicle stimulating hormone (FSH) influences the follicular phase. It is also responsible for the production of estradiol and estrogen, which in turn is responsible for stimulating crypts in cervix. As the follicles mature in the follicular phase, they secrete increasing amounts of estradiol, an estrogen. The estrogens initiate the formation of a new layer of endometrium in the uterus. When the egg is nearly matured, the level of estradiol in the body increases enough to trigger a sudden release of luteinizing hormone (LH) from the anterior pituitary gland. Luteinizing hormone helps the maturation of the egg and weakening wall of the follicle in the ova-

ry, causing the fully developed follicle to release its secondary oocyte.

The variation in the levels of FSH and LH also affects the cardiac activity, which can be best evaluated by heart rate variability (HRV). The human heart beat in a healthy individual is neither absolutely regular nor completely random. It varies based on the interplay between many factors including physical and mental stress, exercise, respiration, thermoregulation, blood pressure regulation, rennin angiotensin system, circadian rhythm, and other unknown complex mechanisms (2). This subtle fluctuation in sinus rhythm is known as (HRV). Heart rate variability has proved to be a more sensitive tool for the detection of autonomic balance than mean heart rate (HR). It is seen as reflective and predictive of general health and overall physiological wellness. Heart rate variability is one of the promising markers of autonomic activity. Variations in the heart rate are dependent on the activities of the sinoatrial node, which is the natural pacemaker of the heart innervated by the sympathetic and parasympathetic branches of the autonomic nervous system. The degree of balance between sympathetic and vagal nerve activity determine HRV.

Frequency domain method, which is also known as power spectral density (PSD), provides the basic information on how power as an expression of variance distributes in the function of frequency. Three main spectral components distinguished in a spectrum calculated from short-term recordings of 2 to 5 minutes (3, 4) are very low frequency (VLF), low frequency (LF), and high frequency (HF) components. The distribution of the power and the central frequency of LF and HF are not fixed, and may vary in relation to changes in autonomic modulations of heart period (5). Normally, VLF ranges from <0.04 to 0 Hz, LF ranges from 0.04 to 0.15 Hz with a central frequency of 0.1 Hz, and HF ranges from 0.15 to 0.4 Hz with a central frequency around 0.2 Hz. The distribution of the LF and HF powers and its central frequencies are modulated by fluctuations of the cardiovascular system. The ratio of LF to HF (LF/HF) reflects the modulation of sinus node firing rate, not the average level of parasympathetic or sympathetic tone (4). In a normal person resting in supine position, the amplitude of LF is greater than that of HF. The LF/HF is used as an index of sympatho-vagal balance (6). The Frequency domain parameters can be expressed in: a) absolute values, in which the variability of the spectral analysis is expressed by the total power, and b) normalized units, in which the relative value of each power component is in proportion to the total power minus the VLF component. Although cardiac automaticity is intrinsic to various pacemaker tissues, heart rate and rhythm are largely under the control of the autonomic nervous system (7). The parasympathetic influence on heart rate is mediated via the release of acetylcholine by the vagus nerve. The sympathetic influence on heart rate is mediated by release of epinephrine and nor epinephrine. Activation of β -

adrenergic receptors results in cAMP-mediated phosphorylation of membrane proteins. Under resting conditions, vagal tone prevails (8) and variations in heart period are largely dependent on vagal modulation. Parasympathetic influences exceed sympathetic effects probably through two independent mechanisms including a neither noncholinergically-induced reduction nor epinephrine released in response to sympathetic activity, and a cholinergic attenuation of the response to an adrenergic stimulus.

Studies also demonstrated that similar to pregnancy, menstrual cycle is also associated with characteristic changes in the cardiovascular system. But, the association of HRV with different phases of menstrual cycle has been documented. Therefore, the present study was undertaken to assess the HRV by frequency domain analysis in different phases of menstrual cycle in young adult and older adult women.

MATERIALS AND METHODS

The present work was carried out at Kasturba Medical College, Bejai, Mangalore after getting the institutional ethical clearance. After obtaining informed consents 45 female medical undergraduate students, who were below 25 years of age (Group I) and 45 women, who were above 25 years of age (Group II) were recruited for the study. The average age of group I and group II was 22 ± 2 years and 40 ± 5 years respectively. Minimal sample size was used as per the directions of a statistician to get the statistically valid results.

The individuals in Group I and Group II were non pregnant, non breastfeeding ladies with normal menstrual cycle. Females who could follow instructions, had regular menstrual cycles, were healthy, and were doing their routine work by themselves were included in the study. The females, who had undergone hormone replacement therapy, had menstrual dysfunction and past history of medical illness were excluded from the study.

A detailed clinical history of each subject was taken. Relevant past history of any hormone treatment, family history of diabetes, transplantation therapy and radiotherapy, and any personal history including smoking, alcoholism and occupation were also taken. General physical examination as well as a complete systemic examination was done. The effects of menstrual cycle on the HRV in 3 different phases was investigated, and compared between young adults and older adult women. The HRV evaluation was done in the frequency domain in accordance to the task force (9).

A high quality ECG recording was taken from each participant under standardized condition to minimize artifacts. The ECG signals were first analogally recorded, and then were digitally converted. Analysis of the signals in the frequency domain was done using All India Institute of Medical Sciences software, ver-

sion 1.1. The software was procured from All India Institute of Medical Sciences, New-Delhi. To minimize artifacts, the software records a high quality ECG under standardized condition. In this software analysis of both time and frequency domains were done. Recording was done in mornings after breakfast between 10:00 to 11:00 AM in a cool room with a temperature of 20 to 28 °C. The subjects were requested to attend the study in a relaxed condition and quiet mood. The room was darkened and without acoustic disturbance. The subjects were instructed to be relaxed and breathe spontaneously at their own rate. The procedure was explained to the subject. After a resting period, the subjects' ECGs were recorded for five minutes in the supine position during normal breathing. The ECG recordings were taken in both groups during the three phases of menstrual cycle namely, menstrual phase (M); day 1 to day 5 of bleeding (mean: 5 ± 2 days), follicular phase (F); day 6 to day 14 of menstrual cycle (mean: 7 ± 2

days), and luteal phase (L); day 15 to day 28 (mean: 14 ± 2 days).

The data obtained was analyzed for statistical significance using students t- test followed by Bonferroni test using Graph pad Prism software. A P value of < 0.05 was considered statistically significant.

RESULTS

Low Frequency Component Analysis (LF)

Heart rate variability analyzed using low frequency domain analysis (sympathetic activity) in three phases of menstrual cycle in the two groups is shown in table-1. There was no significant difference in LF component of HRV of groups I and II in menstrual ($p = 0.681$), follicular ($p = 0.971$) or luteal phases ($p = 0.971$).

Table 1: LF and HF Component of HRV in different phases of menstrual cycle in Group- I and Group- II

Phase	LF Component of HRV in Hz (Mean \pm S.D)		HF Component of HRV in Hz (Mean \pm S.D)	
	Group I (n=45)	Group II (n=45)	Group I (n=45)	Group II (n=45)
Menstrual	41.4 ± 19.46	44.02 ± 17.04	61.18 ± 14.94 †**	54.61 ± 16.17
Follicular	47.04 ± 17.58	47.28 ± 20.74	52.95 ± 17.58 **	52.72 ± 20.74
Luteal	62.85 ± 16.35 **	59.91 ± 23.3	38.41 ± 14.43	48.23 ± 24.83

$p < 0.05$ was considered the level of significance. ** $p < 0.001$, Menstrual Vs Luteal Phase, † = $p < 0.05$ Menstrual Vs Follicular,

High Frequency Component Analysis (HF)

In HF Component of frequency domain analysis in Group-I, comparison between menstrual & follicular phase and menstrual & Luteal phases, the menstrual phase showed significantly higher values ($p < 0.032$ and $p < 0.018$ respectively) whereas follicular and Luteal phases have exhibited very high significant difference ($p < 0.001$, Table-1). The data obtained in the menstrual phase, follicular phase and Luteal phase when compared for the statistical between Group-I & II was, $p = 0.223$, $p = 0.971$ and $p = 0.151$ respectively.

Table 2: LF/HF ratios in different phases of menstrual cycle in Group- I and Group- II

Phase	LF/HF Ratio in Hz (Mean \pm S.D)	
	Group I (n=45)	Group II (n=45)
Menstrual	0.777 ± 0.668	0.96 ± 0.629
Follicular	1.09 ± 0.657 *	1.748 ± 2.746
Luteal	1.94 ± 1.069 **	2.02 ± 3.37

* = $p < 0.05$ Menstrual Vs Follicular phase, ** = $p < 0.01$ Menstrual Vs Luteal Phase., The LF/HF ratio of HRV in Menstrual, Follicular and Luteal phase didn't show any significant difference when compared between subjects of Group I and Group II.

LF/ HF (sympatho-vagal balance) Ratio:

Comparison of LF/HF ratio between menstrual and follicular phase of menstrual cycle in group1 showed significance with $p < 0.044$, between menstrual and

Luteal phases was highly significant ($p < 0.009$), between follicular and Luteal phases showed very high significant difference ($p < 0.001$) (Table-2). In the menstrual phase, the p value when compared between Group- I & II was, $p = 0.418$, in the follicular phase $p = 0.308$ and in the Luteal phase $p = 0.918$ respectively. The results obtained in our study was in line with the results obtained by Kobayashi et.al, 1999 (10), Chapman et.al. (11), Huikuri et.al. (12) and Tkachenko N M et.al. (13).

DISCUSSION

In the female reproductive physiology, the maturation of the female gamete, the egg occurs in the ovary. Its release from the ovary- ovulation is cyclical. These cycles in humans is called menstrual cycle (14). In terms of ovarian functions the menstrual cycle is divided into 2 phases approximately equal in length and separated by ovulation. During follicular phase, a single mature follicle and secondary oocyte develop and the Luteal phase, beginning after ovulation and lasting until the involution of the corpus luteum. This is followed by menstruation which is the most obvious event of a menstrual cycle. The hormonal interaction between the ovaries, hypothalamus and anterior pituitary gland produce the cyclical changes in the ovary. The menstrual cycle is characterized by phases with the cyclical changes of female hormones. There is an increase in estrogens. They are mainly produced by the granulosa cells of

the ovarian follicles, the corpus luteum and the placenta in pregnancy (15).

In this study the HRV did not vary much in the time domain analysis in different phases of menstrual cycle in both the groups except for the Luteal phase here as Group-II (adult women) showed significantly high ($p < 0.05$) value. This apart, the HRV reflects the overall neurohumoral shifts which nullified each other and have no appreciable variations.

When the LF component was compared between Group-I and Group-II in different phases they showed difference but they were not significant. This shows that sympathetic activity is not affected in all the three phases in both the groups and this does not alter the ANS. This indicates that the low frequency (LF) component is jointly modulated by the sympathetic and parasympathetic nervous systems.

On the other hand, high frequency (HF) component is present at the respiratory frequency, modulated solely by parasympathetic nervous system. In this study when HF component was compared between Groups-I and Group-II does not exhibit any significant difference. The LF/HF ratio also did not show significant difference. This shows that parasympathetic activity is not affected in all the three phases in both the groups and does not alter the Autonomic Nervous System (ANS) as reported by Guasti et.al, (16) when compared the HRV of follicular with luteal phase. In the frequency domain the LF was significantly increased, HF was increased. Consequently, the LF/HF ratio was increased in the luteal phase when compared to that of follicular phase. There was no significant difference in Group-II. There was a significant increase of HF in the follicular phase as compared to menstrual phase. There was significant increase of HF in Luteal phase also as compared to menstrual phase. The LF/HF ratio was highly significant in luteal phase as compared to menstrual phase.

The LF/HF ratio was also significant in follicular phase as compared to menstrual phase. A high concentration of progesterone, estrogen and or other hormones may influence ANS during Luteal phase. In this study, it was seen that HRV was significant in the luteal phase when Group-I and Group-II were compared, than the other two phases. The LF and HF were compared in Group-I and it was seen that LF and HF in Luteal phase was significant, whereas in the older group no significance was seen. This shows hormonal fluctuation on the ANS is evident in the younger age group and as the age advances it is stabilized. This result is in agreement with others findings; where it was reported that normal ageing is associated with a constant decline of cardio vagal modulation, due to significant increase of parasympathetic activity which results in a decrease in HRV as the age advances in healthy adults (17-19).

CONCLUSION

The LF value shows more during Luteal phase indicating increased sympathetic activity. This autonomic modulation is more evident in younger age group. The HF component is significantly more in the menstrual phase only in younger age. The HF component is not significantly varied in elderly age group. Thus, loss of physiologic complexity in cardiac interbeat interval variability in sinus rhythm may have a value in identifying syncope patients at risk of sudden death, determining the seriousness of intermittent cardiac arrhythmias and assessing the severity of congestive heart failure.

Conflict of interest: No conflict of interest

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