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Original Article

Assessment of Cardiovascular Autonomic Functions and Baroreceptor Reactivity in Women with Premenstrual Syndrome

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Abstract

Objectives: The study was conducted to assess the autonomic status of women with mild PMS using short-term heart rate variability (HRV) analysis and conventional autonomic function tests (CAFT).

Methods: Sixty females in the age group 17-25 years with mild premenstrual syndrome were identified using a self-report questionnaire, the shortened premenstrual assessment form. HRV and CAFTs were recorded 1-5 days prior and 8-10 days after menstruation.

Results: The subjects showed a significant increase in HR and SBP in luteal phase. In HRV, an increase in mean HR and LF-HF ratio were seen in the luteal phase whereas an increase in the NN50, RMSSD and

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pNN50, HF, HF(nu) and TP were seen in the follicular phase. In CAFT, no change in HRB, 30:15 and E/I ratios but increase in ?DBP(ihg) in the luteal phase was seen.

Conclusion: The increase in HR and SBP in the luteal phase could be because increased water and salt retention due to the ovarian steroids. A decrease in HRV, increase in ?DBPihg with no change in 30:15 ratio in the luteal phase could be attributed to delayed withdrawal of ovarian hormones in the luteal phase.

Key words: Premenstrual syndrome, HRV, Autonomic function test, Ovarian steroids.

Introduction

Menstrual cycle is commonly divided into two phases: the follicular phase and the luteal phase (1). Premenstrual syndrome (PMS) refers to somatic and psychological symptoms that occur in relation to the luteal phase of menstrual cycle. Any symptom or cluster of symptoms qualify as PMS if they occur during luteal phase of menstrual cycle, are alleviated shortly following menses and are not merely exacerbation of other underlying condition (2). It has been reported that upto 85-90% of menstruating women report having one or more premenstrual symptoms and 2 to 10% report disabling and incapacitating symptoms described as premenstrual dysphoric disorder (3). In a study in Saudi Arabia, out of 464 female students study participants 448 (96.6%) females had at least one premenstrual symptom (4).

One of the scales used for assessing premenstrual syndrome is Shortened Premenstrual assessment form (SPAF) having 10 questions. SPAF is reliable and valid instrument to assess distinct and relatively stable set of premenstrual symptoms incidence and severity (5). The autonomic nervous system (ANS) is responsible for maintenance of milieu interior via sympathetic and parasympathetic system. Evaluation of cardiovascular autonomic functions is the corner stone in research and investigation of autonomic functions (6, 7). Evaluation of changes in heart rate (30/15 ratio) is performed during the initial phase of adaptation to orthostasis and the ratio is calculated as a quotient of the maximal (around 30th heart beat) to minimal (near 15th heart beat) RR interval in this period (8).

Autonomic nervous system functioning is influenced by sex steroids, estrogen and progesterone (9). There are contradicting reports about the autonomic status of women in their luteal phase when compared to their postmenstrual period (9, 10, 11). Only in very few articles have they classified women according to their premenstrual syndrome severity but none were from India. The main objective of our study was to assess the cardiovascular autonomic status and baroreceptor reactivity in women having PMS with mild symptoms.

Methods

The study was conducted in Department of Physiology in collaboration with Department of Obstetrics and Gynecology, JIPMER, Pondicherry, India. Institute ethics committee approval was obtained before starting the recruitment of participants. Sixty females between 17 and 25 yrs of age, having menstrual cycle of 28±5 days for the last six months were included in the study. Shortened premenstrual assessment form (SPAF) was used to evaluate and classify women based on severity of their premenstrual symptoms (5). Women with SPAF score of more than ten and less than thirty were identified. Females with excessive irregular flow, pregnancy, those on hormonal contraceptive, thyroid dysfunction, diabetes mellitus, hypertension, cardiac and pulmonary diseases, history of neurological disorder and chronic renal failure were excluded. The participants were explained in detail about study protocol and written informed consent was obtained from them.

The subjects were advised to have lunch at 1.00 pm

and come for tests at least three hours after lunch with empty bowel and bladder. The subjects were instructed to avoid caffeine and nicotine 12 hours before the test. The subjects were told to refrain from taking medication known to influence the cardiovascular system viz. anticholinergics, antihistaminic, over the counter cough and cold medications, diuretics, opiods, sympathomimetics and parasympathomimetics 48 hours prior to study. The autonomic function and baroreceptor reactivity parameters were recorded in both study and control groups during 1-5 days prior to onset of menstrual (luteal phase) and 8-10 days after menstruation (follicular phase) (12).

Autonomic function tests:

The subjects were asked to lie comfortably on a couch and relax for 5 or 10 min in a darkened room. They were informed about the procedure to alleviate anxiety. Appropriate transducers were connected to monitor the respiration and ECG (lead II). A room temperature of 23°C with 25-35% humidity was maintained (13). Basal supine heart rate and blood pressure was recorded by oscillometric method using automated blood pressure monitor Omron MX3, India. Following which, the lead II ECG was recorded for next 5 minutes in total resting condition for short term HRV analysis.

Short term HRV:

Short-term HRV recording was performed using lead II electrocardiogram (ECG), following the standard procedure as per the recommendation of task force. The data acquisition was performed using a 16-bit, Power Lab 8/30 data acquisition system (New South Wales, Australia) with AcqKnowledge 3.8.2 software. Sampling rate was kept at 500 samples/s per channel. HRV analysis of the RR tachogram was performed for frequency domain (by power spectral analysis using fast Fourier transformation) and time domain measures using the software from the Biomedical Signal Analysis Group ver. 1.1 (Kuopio, Finland). The frequency domain indices included low frequency (LF; 0.04-0.15 Hz), high frequency (HF; 0.15-0.4 Hz), total power (TP), LF in normalized units (LFnu), HF in normalized units (HFnu) and the ratio of LF to HF (LF-HF ratio). The time domain measures included mean RR (mean of RR interval), standard deviation of RR interval (SDNN), the square root of the mean of the sum of the squares of the differences between adjacent NN intervals (RMSSD), the number of pairs of adjacent NN intervals differing by more than 50 msec in the entire recording (NN50) and the percentage of NN50 counts, given by NN50 count divided by total number of all NN intervals (pNN50) (7).

Heart rate response to standing 30:15 ratio (a measure of baroreceptor reactivity):

After recording ECG in supine position the subject was asked to stand, preferably within 3 seconds with a continuous ECG monitoring. During standing, the ratio of longest RR interval at 30th beat to shortest RR interval at 15th beat (30:15 ratio) was computed.

Heart rate response to deep breathing E: I ratio:

Before performing this test the subject was asked to sit comfortably and the procedure for deep breathing was explained and demonstrated. Procedure includes six breaths per minute. Recorded metronome was used in such a way that it could deliver counts making six cycles of breathing per minute. During the maneuver respiration was monitored using respiratory transducer. E:I ratio, the ratio of longest RR interval during expiration to the shortest RR interval during inspiration averaged over 6 cycles of respiration was calculated. Heart rate variation during deep breathing was calculated by measuring maximum & minimum R-R interval during expiration & inspiration respectively, expressed as beats per minute. Then the difference between maximum & minimum heart rate was calculated (HRB).

BP response to sustained isometric hand grip:

Subjects were instructed regarding sustaining the handgrip at one third of their maximum voluntary contraction for 4 minutes. The maximum DBP attained during the manoeuvre was noted. $\Delta DBP_{(ihg)}$ is the difference between this highest DBP recorded during sustained handgrip and baseline DBP.

Statistical analysis:

Statistical analysis was done using SPSS statistics software version 19 (SPSS, Chicago, USA). The normally distributed continuous data was presented as Mean±SD. Difference of means between luteal and postmenstrual phases were compared using students paired *t* test. The difference was considered statistically significant if probability of chance was less than 0.05 ($p<0.05$).

Results

Age and anthropometric measurements

Table I shows mean age group and anthropometric measurements of sixty study subjects.

Basal cardiovascular parameters

HR in luteal phase was significantly higher than follicular phase (p value<0.001). The SBP was significantly higher in luteal phase than follicular phase (p value = 0.002) (Table II).

Short term HRV analysis

On analysis of time domain indices, mean HR was significantly lower in follicular phase than luteal phase (p value<0.001). RMSSD, NN50, pNN50 (p value 0.001), were significantly higher in follicular phase than luteal phase (Table III).

The frequency domain indices follicular VLF, LF, HF and TP were significantly lower in luteal phase than follicular phase (Table IV). LF (nu) and LF/HF ratio was significantly higher with concomitant decrease in HF (nu) in luteal phase than follicular phase (Fig. 1).

TABLE I : Age and anthropometeric measurements of the subjects.

Parameters	*Study group (n=60)*
Age (years)	19.23±0.86
Weight (kg)	52.24±9.09
Height (cms)	156.81±4.37
BMI (kg/m^2)	21.40±3.57

Values are expressed as Mean±SD. BMI: Body Mass Index.

TABLE II : Comparison of basal supine cardiovascular parameters between luteal and postmenstrual phases.

Parameters	*Luteal (n=60)*	*Follicular (n=60)*
HR (beats/min)	74.68±9.66	70.00±8.68***
SBP (mmHg)	102.93±7.36	99.43±7.93**
DBP (mmHg)	67.88±6.93	66.42±6.94

Values are expressed as Mean±SD; analysis was done by Student's paired t test. *P<0.05; **P<0.01; ***P<0.001.

TABLE III : Comparison of time domain indices between luteal and postmenstrual phases.

Parameters	*Luteal (n=60)*	*Follicular (n=60)*
Mean HR	79.16±9.00	75.08±9.75***
SDNN (ms)	0.05±0.02	0.06±0.06
RMSSD (ms)	45.59±20.84	65.25±35.39***
NN50	98.90±66.14	129.73±75.83**
pNN50	27.13±18.71	37.062±22.96**

Values are expressed as Mean±SD; analysis was done by Student's paired t test. *P<0.05; **P<0.01; ***P<0.001 Mean HR: Mean Heart rate; SDNN: standard deviation of NN intervals ; RMSSD: square root of the mean squared differences of successive NN intervals; NN50: number of pairs of adjacent NN intervals differing by more than 50 ms; pNN50: percentage of NN50.

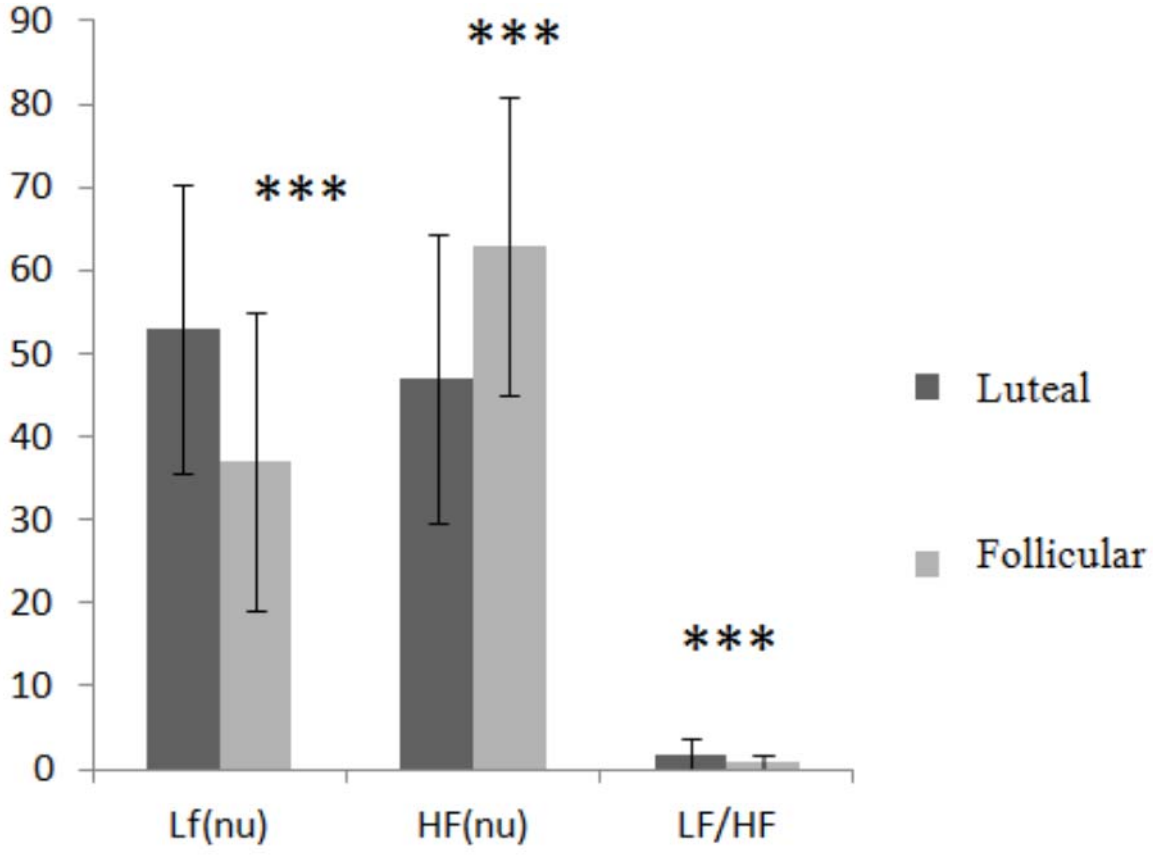
TABLE IV : Comparison of frequency domain indices between luteal and postmenstrual phases.

Parameters	*Luteal (n=60)*	*Follicular (n=60)*
VLF (ms^2)	101.25±94.913	160.85±168.460**
LF (ms^2)	348.417±254.975	287.183±217.139*
HF (ms^2)	354.783±304.509	652.100±584.397***
TP (ms^2)	804.450±559.079	1099.7±850.409**

Values are expressed as Mean±SD; analysis was done by Student's paired t test *P<0.05; **P<0.01; ***P<0.001. Mean HR: Mean Heart rate; SDNN: standard deviation of NN intervals; RMSSD: square root of the mean squared differences of successive NN intervals; NN50: number of pairs of adjacent NN intervals differing by more than 50 ms; pNN50: percentage of NN50; VLF: very low frequency; LF: low frequency; HF: high frequency; TP: total power.

HR and BP response during CAFT

Parameters 30:15 and E/I ratio were higher in follicular phase but is not statistically significant. $\Delta DBP_{(ihg)}$ is significantly higher (p value <0.001) in luteal phase when compared with follicular phase (Table V).



*P<0.05; **P<0.01; ***P<0.001.

Fig. 1 : Comparison of frequency domain indices between luteal and postmenstrual phases.

TABLE V : Comparison of baroreceptor reactivity and other reactivity tests luteal and postmenstrual phases in all 60 subjects.

Reactivity tests	*Luteal (n=60)*	*Follicular (n=60)*
30:15	1.556±0.208	1.578±0.175
E/I	1.414±0.175	1.457±0.185
HRB	29.805±5.49	31.67±4.33
$\Delta DBP_{(ihg)}$	16.166±7.309	12.4±6.28***

Values are expressed as Mean±SD; analysis was done by Student's paired t test *P<0.05; **P<0.01; ***P<0.001. 30:15 - ratio obtained after analyzing HR response to standing an index of baroreceptor reactivity; E/I ratio: ratio obtained from analyzing HR response to deep breathing test; HRB: Heart rate variation to deep breathing; $\Delta DBP_{(ihg)}$: diastolic rise when isometric handgrip test was performed.

Discussion

The variations in autonomic balance during menstrual cycle, which likely had evolved as an adaption for reproduction, may contribute to catamanial variations in disease independent of hormonal variations especially when the degree of variation is more (14). The study was conducted to assess the autonomic status of women with mild PMS using short-term heart rate variability (HRV) analysis and conventional autonomic function tests (CAFT).

In our study, it was observed that baseline cardiovascular parameters (HR and SBP) were significantly higher in luteal phase compared to follicular phase. A considerable increase in mean HR with reduction in NN50, RMSSD and pNN50 in the luteal phase reflected decreased cardiovagal drive in the luteal phase when compared follicular phase (7).

It was further substantiated by findings of frequency domain, in which TP, the index of overall HRV was significantly reduced in the luteal phase (p<0.01). In luteal phase, the TP was maximally contributed by LF (43.3%) which was reduced (26.11%) in follicular

phase. A significantly increased LFnu, LF-HF ratio in luteal phase further showed increased sympathetic drive and decreased vagal tone (7). This finding of ours refutes the findings of Leicht AS et al, who had studied only 5 women had reported that there is no change in HRV across the menstrual cycle (15). Our findings are consistent with findings of Matsumoto et al who had also got similar results with HRV in women with PMS (16).

Several bodies of evidence also suggest that progesterone in luteal phase, contributes to the pathophysiology of PMS (17, 18, 19). Delay in physiological withdrawal of ovarian hormones, estrogen and progesterone in the luteal phase associated with low plasma levels of LH and FSH was evident in the women with PMS (20, 21, 22). This increased ovarian hormones in the luteal phase causes increased water and salt retention (mainly progesterone) along with exaggerated increase in renin activity and aldosterone which accelerates the HR and SBP (13, 20). Also in the follicular phase, predominated by estrogen, which increases density and function of presynaptic d2 adrenoreceptors resulting in significant decrease in norepinephrine induced responses. Estrogen also stimulates the opening of calcium activated potassium channels by nitric oxide mediated cGMP dependent pathway. Thus relaxes vascular smooth muscle and promoting vasodilatation during the follicular phase. Estradiol is associated with increase in acetylcholine concentration and has facilitating effect on cardio-vagal function. It has also been reported that estradiol increases the number and sensitivity of progesterone receptor, thus increasing action of progesterone hormone during the luteal phase (23).

The 30:15 ratio (a measure of baroreceptor reactivity) during the orthostatic stress test did not show a significant difference between the phases. This could be because inspite of fluid retension, progesterone exerts inhibitory effect on the cardiovagal baroreflex responses (23). Also reduced plasma shift on standing during the luteal phase was prominent in the women with PMS leading to decreased activation of baroreceptors (20).

Even though there was reduction in E: I ratio in luteal phase, it was not significant. Probably the subjects had mild PMS and could be significant in severe PMS. An increase in $\Delta DBP_{(ihg)}$ increased sympathetic reactivity in the luteal phase. Hence, in the present study, in females with mild premenstrual syndrome, there was a significant alteration in autonomic modulation in the form of decreased HRV, decreased parasympathetic drive and reactivity and increased sympathetic drive and reactivity in the luteal phase when compared with the follicular phase.

Research has shown that allopregnanolone, plays an important physiological modulatory role in changing the sensitivity of $GABA_A$ receptors for GABA thus playing an important role in stress (19, 24, 25).

Hence we conclude that autonomic changes during the luteal phase may also be responsible for the psychological and somatic changes during the luteal phase in women with PMS. Women having PMS are advised to undergo stress reduction programs and nonpharmaceutical treatment like yoga, meditation etc for physical and psychological symptom relief (26).

Limitation

Continuous BP monitoring could not be done, which would have helped us in recording the BP changes during lying to standing.

Conclusion:

In the present study, there was an overall reduction in HRV with both the time and frequency domain indices showing decreased vagal tone and the conventional autonomic function tests showing an increased sympathetic reactivity and decreased parasympathetic reactivity in the luteal phase of the menstrual cycle. In addition to autonomic function test, our findings could have been strengthened with simultaneous measurement of estrogen and progesterone levels, which forms the future scope of our study.

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