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Circadian Pattern of Blood Pressure and Cardiovascular Autonomic Regulation During Different Phases of Pre- and Post-menopausal Women: A 24-hours & 7 days Study

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ABSTRACT:

Background: A significant difference in cardiovascular health exists between males and females, but marked differences can be observed in women of similar age groups also. Many studies were performed that suggested the role of several female sex hormones as a causal factor for increased cardiovascular risk but very less studies were present that directly focused on the role of circadian rhythmicity of blood pressure and cardiovascular autonomic regulation in postmenopausal women as well premenopausal women during different phases of menstrual cycle.

Objective: The present study is aimed to assess the twenty hours seven days circadian reproducibility of blood pressure and autonomic regulation of cardiovascular system providing alteration in the various menstrual phases in pre-menopausal and post-menopausal age groups.

Materials and methods: This was a comparative study of 50 pre-and 50 post-menopausal age group women done with the help of a structured questionnaire, ambulatory blood pressure monitoring (24-hour, 4-7 days), and autonomic nervous system monitoring and heart rate variability.

Results: The study shows significant changes in autonomic regulation of postmenopausal women compared to the premenopausal group, with significant differences between MESOR of Systolic BP, diastolic BP and HR. Increased circadian amplitude in postmenopausal women, suggestive of overall decreased chronobiological parameters of cardiovascular system in postmenopausal group.

Conclusion: Correlation of circadian patterns of Blood pressure and their correlation with autonomic regulation and heart rate variability could have clinical significance in the treatment and Pre-habilitation of cardiovascular diseases at earlier or primordial stage in postmenopausal as well as premenopausal women.

Keywords: Circadian rhythms, Menstrual phases, autonomic regulation, female sex hormones, Ambulatory blood pressure monitoring, heart rate variability

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INTRODUCTION

A gender-based difference in the regulation of blood pressure and heart rate in humans is very well known. Men are generally at greater risk for cardiovascular and renal disease than are age-matched, premenopausal women, studies using ambulatory blood pressure monitoring have shown that blood pressure is higher in men than in women at similar ages.[1] However, marked differences between the cardiovascular parameters of pre-and post-menopausal women can be seen, increasing the cardiovascular diseases after menopause and approaching the risk like that of men[1] suggesting that loss of ovarian function contributes to an increase in the risk of cardiovascular disease.[13,46] In relation to the cyclic phases of women, studies on the influence of female sex hormones on blood pressure regulation are conflicting. A normal menstrual cycle begins with the follicular phase, which is the period between menstruation and ovulation, second phase is the luteal phase, which is preceded by ovulation and followed by menstruation. For example, progesterone and estradial (estrogen) levels are lower during the follicular phase and higher during the luteal phase [2]. Some studies showed a difference between blood pressure and hormonal patterns

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in luteal and follicular phases in both normotensive and hypertensive premenopausal women, some reported high blood pressure in luteal phase some in the follicular phase or ovulatory phase.[3-5] Levels of high testosterone during the ovulatory and luteal phases were found in hypertensive premenopausal women.[6,7] Contrary to these some studies have reported decreased blood pressure during leutal phases[8] suggesting that additional information on the relative importance of female gonadal hormones in cardiovascular system must be further investigated with the fluctuations of BP during the menstrual cycle to understand the circadian pattern during the different phase.

Remarkable alterations in the homeostatic mechanisms cycle of the cardiovascular system occur during the menstrual and may be confounded by hormonal status[9,10]. In women, menopause is characterized by increases in blood pressure, as determined by the NHANES III study and others.[11,12] Interestingly, the blood pressure does not increase in the transitional phase from perimenopause to menopause,[13] but rather the increase in blood pressure after menopause takes an average of 5 to 20 years to develop, suggesting that lack of female hormones may not be the only contributing factor for the elevated blood pressure, numerous studies using ambulatory blood pressure monitoring techniques reported that blood pressure was not or very less affected by HRT (hormone replacement therapy) or the reduction in blood pressure with HRT was evident only at night or only in normotensive individuals.[5,14-17]

Concerning androgen levels after menopause, there is some controversy since studies have shown that serum testosterone levels in postmenopausal women may decrease slightly, may not change at all, or may actually increase.[18,19,47] Rats studies have also shown mixed results regarding the effects of androgens and hormonal changes on BP.[20,21] Blood pressure also increases with chronic testosterone administration in normotensive rats that stimulate the RAS (rennin angiotensin system), RAS, and vasopressin-degrading activities which leads to an increase in blood pressure in female rats.[6,21-23,51]

Postmenopausal women are found to have greater systolic blood pressure (SBP) than premenopausal women, however, findings about differences in diastolic blood pressure (DBP) and HR reactivity according to menopausal status are less or not clear.[24-26] Results from studies of the effects of HRT on cardiovascular reactivity in postmenopausal women are also potentially relevant.

Along with reproductive hormones, pineal hormone melatonin regulates all the chronobiologic parameters of the body including reproduction and menstruation, and affects reproductive function, through the activation of receptor sites within the hypothalamic-pituitary-gonadal axis.[27,28] Most studies investigated the role of melatonin in hypothalamus and pituitary without directly focusing on its effect on ovary itself, as melatonin is found in the ovarian fluid suggesting a direct role in modulating physiological functions through activation of at least two pharmacological and molecularly distinct melatonin receptors, the MT1 and MT2.[28-30] During menopause, a decrease in nocturnal melatonin secretion has been observed and attributed to a low-estrogen environment.[31] Some studies reported increased melatonin levels during the luteal phase,[32] decreased melatonin amplitude during the luteal phase compared with the follicular phase,[33] or no difference between the menstrual phases.[29] It was showed that circadian, nocturnal administration of melatonin may postpone endocrine aging and maintain or reconstitute more juvenile sexual functions at a time of life when changes of ovarian cyclicity become evident (pre-, peri-menopausal and menopausal age) while another study reported that melatonin plays a role in inducing and timing the circadian rhythmicity of gonadotropin secretion during the follicular menstrual phase and eventually that in pubertal, amenorrheic and postpartum.[34,35] Some study the effect of melatonin on postmenopausal women with asthma and supported the hypothesis that high level of nocturnal melatonin may suppress levels of LH (Luteinizing Hormone).[36] So, nocturnal decline of melatonin levels with age may increase cardiovascular with reproductive problems. Many more studies have confirmed the protective role of melatonin on hypertension.[37,38]

Impaired circadian rhythm of cardiovascular autonomic regulation was observed in several studies on hypertension which include both premenstrual and post-menopausal women.[39] A detailed evaluation of circadian pattern of BP can be useful in diagnosing future cardiovascular risk. Since there is large variability in BP in health and MESOR-hypertension, not only within a day but also from one day to another, monitoring for 4 to 7 days is very useful and has been recommended nowadays by clinicians. Considering the extent of variability in blood pressure around the clock monitoring blood pressure for more than 24 hours is very useful to detect blood pressure over swinging patterns or circadian hyper-amplitude tension (CHAT), to reduce the false negative and false positive diagnosis of patients with borderline hypertension and altered Dipping and Non-Dipping patterns.[40] With ABPM a large number of blood pressure measurements can be taken over an extended period with the patient actively working which could decrease cardiovascular, cerebrovascular, and renal risk from the proper modeling of the circadian BP profile by the timed administration (chronotherapy) of antihypertensive medication, beyond the reduction of clinic-determined daytime or ABPM- determined 24 h mean BP levels.[41]

The present study is therefore designed to assess the circadian pattern of the blood pressure and autonomic regulation of cardiovascular system in premenopausal and postmenopausal women, differences in Ambulatory blood pressure (BP), and heart rate in a population of premenopausal and postmenopausal women. It will be a comparative study between pre and postmenopausal women. Premenopusal women of the age group 18 to 40 and postmenopausal women aged from 47 to 70 years will be included in the study. 24-hour four to seven days ABPM, autonomic parameters will be measured. The study may provide information on the different 24-hour/7-day circadian patterns of blood pressure and heart rate in pre and postmenopausal women during different phases of menstrual cycle could influence cardiovascular parameters in women of both groups.

METHODOLOGY

General Methods

***Registration of Volunteers*:** 50 premenopausal women (age group = 18-40 years), and 50 post-menopausal women (age group= 48-70) were recruited at King George Medical University Lucknow. The protocol of this study was approved by Committee of medical Ethics, Research cell KGMU (4061 /R.Cell-21) Lucknow and all the subjects were informed about the purpose and protocols of the study before undertaking the written informed consent from each of them.

Standard Format Informed Consent Form and Questionnaire

Each of the study participants were informed about the purpose of the study and agreed to take part in the study. The study complies with the declaration of Helsinki principles of medical ethics. The Detailed Consent form was provided to the participants in both English and Hindi language. Before enrolling any subject, a questionnaire regarding their routine, disease if any, and family history of any disease was made filled and only those participants was enrolled who justified all the inclusion criteria.

Methodology

i) ***Monitoring of health records*:** The health records of each subject was maintained following the general observations, like the presence or absence of headache, insomnia, hyperactivity, irritbility, nausea, sleeping limbs, dizziness, constipation, shaky hands, stomach cramp, drowsiness, sweating, hunger, weakness, and sore eyes during the period of treatment. If any of these symptoms occur subject was told to inform us and stop the supplementation.

ii) ***Ambulatory Blood pressure monitoring*:** The twenty-four-hour, around-the-clock automatic measurements of SBP, DBP and heart rate at 30 min day time and 60 min night time interval for continuous four days was obtained by ABPM device and software (A&TD TM-2430, Japan). The result of these ABPM records was compared using standard statistical methods. **ABPM in premenopausal** women was measured two times once during the Follicular phase (i.e. days between 1th-14th of 28-day cycle) second ABPM will be done during Leutal Phase (i.e. 15^{th} – 28^{th} day of 28-day cycle). **In postmenopausal women** (Age 47-70 years), 24 hours 4-7 days continuous ABPM was recorded.

iii) ***Autonomic Nervous system monitoring and heart rate variability* (HRV):** Autonomic nervous system monitoring and HRV was done by using standard noninvasive autonomic nervous system battery of test including HRV once in both pre- and post-menopausal women.

Determination of Menstrual Cycle Phase: Only women who had experienced a regular menstrual cycle over the preceding 6 months were recruited. Details of previous menstrual history along with subject-monitored basal body temperature were used to identify phases of the menstrual cycle. Ovulation was indicated by a sustained increase in basal body temperature of at least 0.3°C after the luteinizing hormone surge and confirmed by sex hormone levels (estradiol and progesterone) measured on the study days. Menstrual cycle length was calculated from the first day of menses (*day 1*) to the day preceding the next menses. The average cycle length was 27 ± 2.1 days with ovulation occurring at day 14 ± 0.9. Measurements were made in the same or consecutive cycles.

Ambulatory Blood Pressure Monitoring

Twenty-four hours 4-7 days Ambulatory blood pressure monitoring of the subjects was done with anautomated ABPM device, A&D TM-2430 model (manufactured by A&D Company Japan). ABPM of premenopausal subject was done three times, initially during menstrual phase, follicular phase, and leutal phase. ABPM of Postmenopausal subject was done once.

MESOR

MESOR (midline-estimating statistic of rhythm), is a time structure or chronome-adjusted mean,

Predictable change or Double Amplitude

The double amplitude is a measure of total extent of change within a day or the circadian amplitude, of reproducible variability within a day, predictable by the linear curve fitting which yields added parameters like mesor and acrophse (Halberg 2002).

Acrophase

Acrophase is a measure of timing of overall high values recurring in each cycle (Halberg et al 2002)

Autonomic Nervous System Battery of Tests

Autonomic nervous system analysis of the subject was performed by Cardiac Autonomic Neuropathy Analysis System, (CAN) of CANWIN (Lifeline meditech, Bangalore India). Both Sympathetic and Parasympathetic autonomic nervous system response of the patient was analyzed. Heart Rate Variability (HRV) was analsed by Vario Win – HR -HRV Analysis.

Parasympathetic Function Test

1) **Resting HR –** Subjects were allowed be in resting positions at least for 15 min before measurement. It was made sure that subject has not taken any substance having caffeine or tobacco before and during the test. Heart rate was measured by clinic stethoscope for 2 minutes. The number of times heart beats when patient was at complete rest was analysed by this test.

2) ***Deep Breathing- Expiration and Inspiration Ratio*:** In each subject the ratio of total time taken in expiration to the total time taken in Inspiration was measured to analyze the E: I ratio.

3) ***Response to standing*:** 30:15 ratio - The Stand Ratio (also known as the 30:15 ratio) was calculated as the ratio of the slowest heart rate (found around beat 30) and the quickest heart rate (found around beat 15) in each subject.

4) ***Valsalva Maneuver*:** In each subject Valsalva maneuver was performed by attempting to forcibly exhale while keeping the mouth and nose closed to evaluate the condition of heart. Standard Valsalva maneuver was performed on each subject, in the supine position, allowed to take a full inspiration and exhale forcibly for 10 seconds at a pressure of 40 to 60 mm Hg against a fixed resistance.

Sympathetic Function test:

1) ***Postural Hypotension*:** A drop in blood pressure (hypotension) due to a change in body position (posture) was evaluated in each subject by allowing them to move to a more vertical position: from sitting to standing or from lying down to sitting or standing was examined in all the subjects. Blood pressure, heart rate, O2 saturation, and the occurrence of dizziness or palpitations were recorded prior to and 1-, 3- and 5-min following seating.

2) ***Sustained Handgrip*:** Cardiovascular responses to sustained hand grip were investigated in all the subjects. The subject was allowed to holds the handgrip dynamometer in the hand with the arm at right angles and the elbow by the side of the body. The handle of the dynamometer is adjusted if required - the base should rest on first metacarpal (heel of palm), while the handle should rest on middle of four fingers. When ready the subject squeezes the dynamometer with more than 30% of maximum isometric effort, which was maintained for about 5 seconds. No other body movement was allowed. Systolic blood pressure before and after the sustained handgrip was evaluated.

Heart Rate Variability

Heart Rate Variability (HRV) was analyzed by Vario Win – HR -HRV Analysis and following parameters were evaluated -

- **Time Domain Parameters**: Measurements assessed with Time Domain Parameters are in milliseconds (ms): Heart Rate (R-R m/s): a mean heart rate value on entire (5 minutes) was recorded, SDNN : Standard deviation of all NN intervals, RMSSD: square root of the mean of the squares of differences between adjacent intervals ,SDSD: Standard deviation of all NN intervals, pNN50: Percentage of differences between adjacent NN intervals that are greater than 50 ms; a member of the larger pNNx family (circulation 1996, Mietus 2002)
- **Frequency Domain Parameters:** Measurements assessed with Frequency Domain Parameters are in milliseconds square ($ms^{2)}$: Total Power, Very Low Frequency (VLF), Low Frequency (LF), Normalized Low Frequency (LF norm), High Frequency (HF),Normalized High Frequency (HF norm), LF/HF ratio: (normalized units).

RESULTS

Clinical Observations

Table 1 illustrates the basal clinical observations of the subjects. Out of 150 subjects recruited during the initial experiment (80 premenopausal, 15 left out and 70 postmenopausal women 20 dropped the study. Therefore, data of 100 subjects are included in the analysis (data of 50 subjects was given in I^{st} year report). There were 25 premenopausal and 25 postmenopausal women subjects. In II^{nd} year data of 50 subjects are also included. The subjects included in our study were of 18 to 75 years of age (mean 65.44 ± 13.54).

Mean casual blood pressure of the premenopausal subjects recorded by mercury sphygmomanometer was systolic BP 120 ± 12.32 and diastolic BP 78.26 ± 7.1, Postmenopausal women systolic BP was 139.35 ± 6.23 and diastolic 86.63 ± 2.33. Mean pulse rate of the premenopausal subject measured manually by using radial artery of premenopausal subjects was 71.21 ± 11.20 beats per minute (b/m) and postmenopausal women was 82.20 ± 9.11.

Table 1: Basal Clinical characteristics and observation of subjects

S.no	Clinical characteristics	Premeno-pausal	Postmeno-pausal
1	No. of subjects	50	50
2	Average age (years) ± SE	28.02 ± 14.2	61.02 ± 9.32
3	Height (cm) ± SE	154.73 ± 3.52	153.49 ± 2.38
4	Weight (kg) ± SE	59.23 ± 9.32	64.68 ± 9.64
5	Body mass index (BMI) (kg/m^2) ± SE	23.42 ± 2.50	24.16 ± 2.89
6	Casual Systolic blood pressure (mmHg)	120.57 ± 12.32	135.42 ± 9.12
7	Casual diastolic blood pressure (mmHg)	78.26 ± 7.1	91.63 ± 5.33
8	Casual Heart beats (beats per minute)	71.21 ± 6.23	75.12 ± 4.23

Values represent the mean ± SE of 50 subjects (55 Premenopausal and 55 postmenopausal women).

Ambulatory Blood pressure Monitoring in pre- and post-menopausal women

Average 7-day values of the mean (MESOR) and of double amplitude (2A) for systolic BP (SBP), diastolic BP (DBP) and heart rate (HR) were determined for each subject.

MESOR

There was a significant difference between MESOR of Systolic B.P, Diastolic B.P and H.R of postmenopausal women ($p<0.05$, 0.01) and premenopausal women. However, no significant changes were found in the MESOR of premenopausal women during menstrual and leutal phases. Significantly high MESOR was noted during ovulatory phase (130.55/80.24) ($p<0.05$) and lowest during leutal phase (118.26/70.12). A significant heart rate was noted during ovulatory phase however which were not significant (Table 2).

Table 2: MESOR of 7-day/24-hour ambulatory blood pressure monitoring in premenopausal women.

	SBP (mmHg)	DBP (mmHg)	HR (b/m)
Menstrual Phase	120.11 ± 1.65	76.42 ± 2.31	71.42 ± 1.33
Ovulatory phase	130.55 ± 2.32*	80.24 ± 4.66	78.23 ± 3.26*
Leutal phase	118.21 ± 4.21	77.52 ± 2.66	70.0 ± 0.86
Postmenopausal Women	140.23 ± 14.02*Δ	89.42 ± 9.22*Δ	79.52 ± 6.23*

Values represent the mean ± SE of 50 premenopausal and 50 postmenopausal women.

* Significant at the level of $p < 0.05$

Δ Significant at the level of $p < 0.01$

Double Amplitude (Predictable change)

The circadian amplitude, of reproducible variability within 7 days increased significantly in postmenopausal women (Table 3, and Figure 1). In premenopausal women, there were no significant changes noted in menstrual and leutal however significant changes in double amplitude of blood pressure and heart rate were noted during ovulatory phase (Table 3)

Table 3: Double Amplitude (Predictable change) of 7-days/24-hour ambulatory blood pressure monitoring in premenopausal women.

	SBP (mmHg)	DBP (mmHg)	HR (b/m)
Menstrual Phase	10.22 ± 1.67	12.44 ± 0.77	10.10 ± 2.10
Ovulatory phase	18.02 ± 3.15*	20.14 ± 1.42*	15.26 ± 2.86*
Leutal phase	17.23 ± 2.32	18.26 ± 2.26	12.26 ± 1.26
Postmenopausal women	24.55 ± 2.36*	14.22 ± 1.20	17.33 ± 0.759*

Values represent the mean ± SE of 50 premenopausal and 50 postmenopausal women.
* Significant at the level of $p < 0.05$
Δ Significant at the level of $p < 0.01$

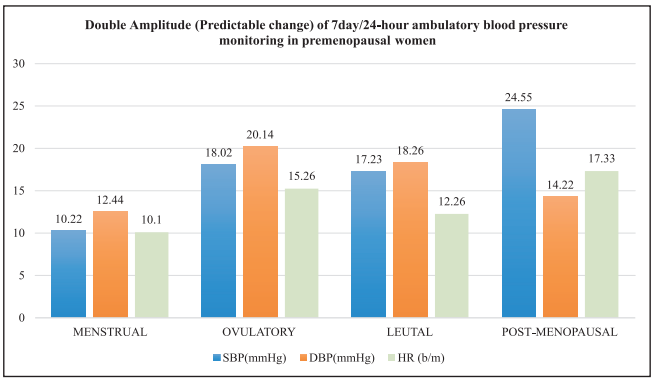


Figure 1: Double Amplitude (Predictable change) of 7day/24-hour ambulatory blood pressure monitoring in premenopausal women.

Acrophase

The circadian pattern of timing of overall high values recurring in each cycle showed no significance in any of the groups. In Postmenopausal women maximum S.B.P was noted during 13:00 hours. In premenopausal women, the pattern was almost similar between 14:00 to 16:00 hours. No significant changes were observed between the different phases of menstrual cycle. Thus, all the groups showed normal acrophase patterns (Table 4, and figure 2).

Table 4: Acrophase of 7day/24-hour ambulatory blood pressure monitoring.

	SBP (mmHg)	DBP (mmHg)	HR (b/m)
Menstrual Phase	14.50 ± 0.233	15.10 ± 1.23	17.33 ± 1.411
Ovulatory phase	14.22 ± 0.142	14.32 ± 0.863	15.00 ± 1.35
Leutal phase	16.05 ± 0.85	15.50 ± 0.84	16.10 ± 2.30
Postmenopausal women	13.20 ± 2.36	14.68 ± 0.240	13:30 ± 1.67

Values represent the mean ± SE of 50 premenopausal and 50 postmenopausal women.
* Significant at the level of $p < 0.05$
Δ Significant at the level of $p < 0.01$

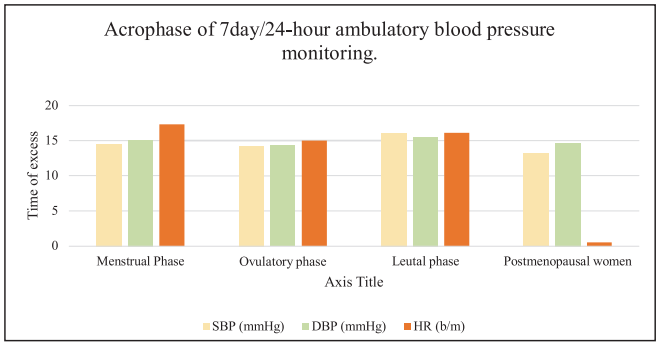


Figure 2: Acrophase of 7day/24-hour ambulatory blood pressure monitoring

Autonomic Nervous System Battery of Test

Parasympathetic Nervous system Tests

Resting HR

There was no significant difference between different phases of menstrual cycle in premenopausal women resting HR**.** In postmenopausal women, number of resting heart rate b/sec was normal but increased significantly as compared to premenopausal women (Table 5).

E: I Ratio

There was no significant difference between different phases of menstrual cycle in premenopausal women E:I ratio. There was no change in E:I ratio in postmenopausal women.

(Response to standing) 30:15 Ratio

There was no significant difference between 30:15 ratio. The slowest heartbeat and fastest heartbeat during standing were normal during the test in all the subjects. There were no changes during different phases of menstrual cycle and postmenopausal women (table 5)

Valsalva Manuver

The blood pressure responses to the Valsalva maneuver in pre and postmenopausal women are shown in figure and table 5. No changes were observed in blood pressure responses to the Valsalva maneuver.

Table 5: Parasympathetic Nervous System tests response of premenopausal subjects

	Menstrual Phase	Ovulatory Phase	Leutal Phase	Postmenopausal
RestingHR(b/min)	72.40 ± 3.21	70.22 ± 10.20	72.11 ± 9.42	77.42 ± 2.60*
E:I Ratio	1.21 ± 0.03	1.01 ± 0.03	1.01 ± 0.85	2.30 ± 0.98
30:15 Ratio	1.00 ± 0.01	1.00 ± 0.05	1.20 ± 0.011	1.02 ± 0.02
Valsalva manuveur ratio	1.56 ± 0.03	1.88 ± 0.04	1.07 ± 0.041	1.52 ± 0.02

Values represent the mean ± SE of 50 premenopausal and 50 postmenopausal women.
* Significant at the level of $p < 0.05$ Δ Significant at the level of $p < 0.01$

Sympathetic Nervous System Tests

Postural hypotension

There was no significant decrease in Blood pressure (hypotension) due to a change in body position (posture) when a person moves to a more vertical position from sitting to standing or from lying down to sitting or standing in all the subjects. Blood pressure, heart rate were normal during the test and there were no symptoms such as saturation, occurrence of dizziness or palpitations when recorded prior to and 1-, 3- and 5-min following seatings (Table 6).

Sustained handgrip

There was a significant change in cardiovascular responses to sustained hand grip in postmenopausal subjects as compared to premenopausal. There were no changes observed during different phases of menstrual cycle (Table 6).

Table 6: Sympathetic Nervous system Tests response of premenopausal subjects.

	Menstrual phase	Ovulatory phase	Leutal Phase	Postmenopausal women
Postural Hypotension (Decrease in systolic B.P after standing/mmHg)	9.66 ± 0.85	10.02 ± 0.09	10.02 ± 0.22	10.26 ± 0.22
Sustained Handgrip (Increase in diastolic B.P after sustained hand-grip/ mmHg)	16.55 ± 2.30	16.22 ± 1.33	17.66 ± 1.22	17.33 ± 2.06*

Values represent the mean ± SE of 50 premenopausal and 50 postmenopausal women.
* Significant at the level of $p < 0.05$
Δ Significant at the level of $p < 0.01$

Heart Rate Variability

Time domain parameters

There were no significant changes during different phases in premenopausal subjects. Postmenopausal subject showed lower HRV in the time domain (SDNN, RMSSD, pNN50, R- R m/s) parameters. Significant changes were observed in SDNN, RMSSD, and R-Rm/s parameters in postmenopausal subjects (Table 7, and Figure 3).

Table 7: Time domain parameters of HRV in premenopausal subjects.

	Menstrual Phase	Leutal// phase	Ovulatory phase	Postmenopausalwomen
SDNN (m/s)	27.20 ± 1.26	26.32 ± 2.31	30.26 ± 1.46	19.63 ± 1.33*Δ
RMSSD (m/s)	26.39 ± 0.59	26.33 ± 0.62	32.22 ± 1.08	19.02 ± 1.20*Δ
pNN50	7.00 ± 0.32	9.60 ± 0.55	9.44 ± 0.72	9.00 ± 1.20
R-R m/s	789.30 ± 20.35	881.76 ± 22.30	856.22 ± 19.94	633.22 ± 18.66*Δ

Values represent the mean ± SE of 50 Premenopausal women and 50 postmenopausal women.
* Significant at the level of $p < 0.05$
Δ Significant at the level of $p < 0.01$

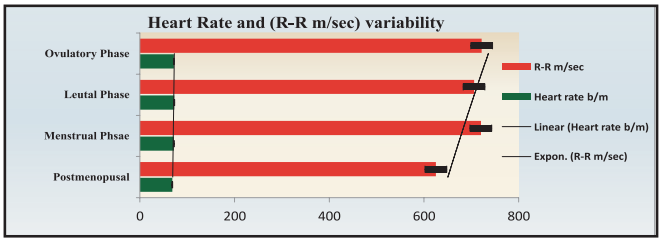
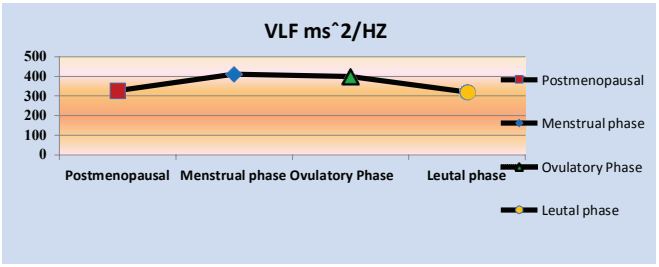
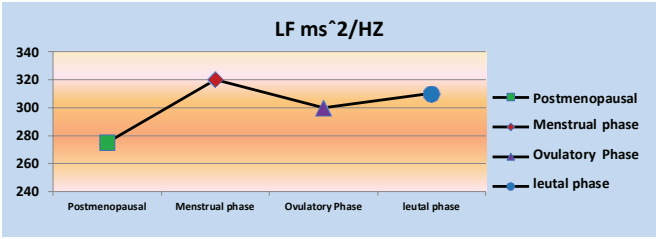


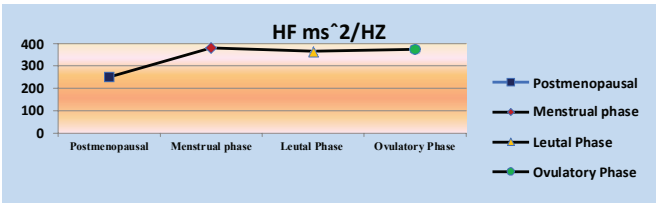
Figure 3: Heart Rate and (R-R m/sec) variability in premenopausal and postmenopausal subjects. Graph represents MESOR of Heart rate (green) and R-R (red) of 100.

Frequency Domain Parameters

There was a significant decrease in all frequency domain parameters of postmenopausal women. Low HRV was observed in the frequency domain (VLF, LF, HF and LF/HF ratio) parameters during. VLF was higher in premenopausal subjects compared to postmenopausal. There were no changes in VLF during different phases of menstrual cycle. LF was higher during menstrual phase but changes were not significant. No significant changes observed in HF and LF: HF ratio (Figure 4).







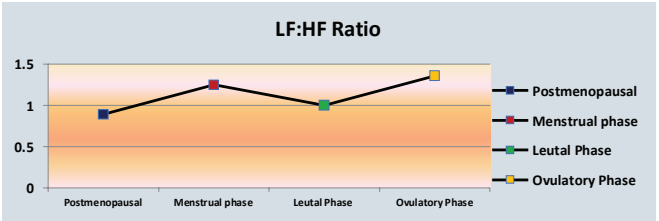


Figure 4: Changes in Frequency domains of HRV of premenopausal and postmenopausal women. (A) VLF ^2/sec, (B) LF^2/sec (C) HF^2/sec (D) LF/HF ratio.

MAIN FINDINGS AND DISCUSSION

Our results of study on 50 premenopausal and 50 postmenopausal shows significant changes in autonomic regulation of cardiovascular system of postmenopausal women when compared to premenopausal women. There was a significant difference between MESOR of Systolic B.P, Diastolic B.P and H.R of postmenopausal women and premenopausal women. The circadian amplitude, of reproducible variability within 7 days increased significantly in postmenopausal women (tables 2 and 3). Our findings indicate that there was a significant decrease in overall chronobiological parameters of SBP, DBP and HR in postmenopausal women. We tried to explore the autonomic changes in cardiovascular system through different battery of tests of autonomic nervous. We found that Postmenopausal women have irregular pattern of sympathetic, parasympathetic autonomic tone and also very low heart rate variability as compared to premenopausal. Our results have indicated that there was mixed variability in Parasympathetic tone which can be explained based on the fact that there was no significant difference between resting HR and 30:50 ratio but there were significant changes in E:I ratio and valsalva maneuver in postmenopausal women. Heart rate exhibits a distinct circadian pattern with a progressive rise in the early morning, which parallels the surge in sympathetic nerve activity. Ratio of lowest heart beat and highest heart beat (30:50 ratios) was found to be normal. It is well established that there has been a significant relationship between the autonomic nervous system and cardiovascular irregularity. Our results indicate significant changes in both Time domain and frequency domain Measures of HRV in postmenopausal women. In time domain measures our initial findings indicate that postmenopausal subjects have lower HRV (SDNN, RMSSD, pNN50, R-R m/s) parameters during initial observations before melatonin supplementation. These measures carried significant prognostic information concerning cardiovascular abnormalities and indicate that reduced cardiac vagal tone is a factor associated with an increased risk of cardiovascular fatal events.[42,51] Increased level of inflammatory markers found during initial observation could be associated with low HRV. Studies have found low HRV to be associated with higher levels of the inflammatory risk markers interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor–alpha (TNF- α) and with inflammatory-procoagulant markers such as fibrinogen, [43] as well as with platelet activation. Low HRV and elevations in proinflammatory or procoagulant markers generally have been described as though they are independent pathways. However, both inflammatory and coagulant responses can be modulated by ANS activity and a cholinergic anti-inflammatory pathway was recently proposed in which there is vagal efferent inhibition of proinflammatory cytokine release, thereby reducing systemic inflammation.[44,48] Low HRV, reflecting reduced vagal activity, should therefore be associated with higher levels of both proinflammatory and procoagulant markers. Recent studies have found a relationship between HRV activity and increased markers of inflammation in other high-risk patients, including those with heart failure and with acute coronary syndrome.[45] All these parameters may be associated with low level of melatonin, as many authors have reported disturbed cardiac autonomic activity in patients whose melatonin levels are low especially in higher age group people.

In premenopausal women, however, no significant changes were found in the MESOR of premenopausal women during menstrual and leutal phases. The highest MESOR was noted during ovulatory phase (130/80) and lowest during the leutal phase i.e., 118/77. Significant heart rate MESOR was noted during ovulatory phase. There were no significant changes noted in menstrual and leutal phases, however significant changes in double amplitude of blood pressure and heart rate were noted during ovulatory phase. No changes were found in acrophase. There were no significant changes in autonomic nervous system battery of test (viz parasympathetic and sympathetic tests and HRV analysis) examined during different phases of menstrual cycle. Results obtained from data from 50 postmenopausal and 50 premenopausal women demonstrate that Postmenopausal women have decreased cardiac functions i.e. High BP, Low estrogen and high testosterone levels are predictors of future cardiovascular risk. We suggest Ambulatory blood pressure monitoring in postmenopausal can demonstrate future cardiovascular risk, several patterns of BP behavior that may be relevant to clinical management—isolated systolic and isolated diastolic hypertension, post-prandial hypotension, autonomic failure, etc. Taking ABPM into account in the total risk stratification should help clinicians avoid overtreatment in patients who have a low cardiovascular risk and, conversely, under treatment in those at high cardiovascular risk. According to the European guidelines for the management of hypertension, being a woman aged ≥65 years represents an independent risk factor. There is nowadays ample evidence indicating that an abnormally elevated BP during ABPM is associated with a heightened risk of experiencing target-organ damage. No doubt the wide use of ABPM in risk stratification would have important implications for the cost-effective diagnosis and treatment of hypertension, and time-based medications. As clear from limited data there is a specific difference in cardiovascular parameters during different phases of menstrual cycle. We think that detailed chronobiologic evaluation of Blood Pressure variability during reproductive phases is useful in studying circadian waveform of blood pressure and diagnosis of future cardiovascular risk. This could have two advantages- First is that knowledge of circadian variations among different phases of the reproductive cycle in young women can help in risk assessment of Pre-Hypertension and Pregnancy loss due to preëclampsia. Since there is a large variability of BP, not only within a day, but also from one day to another, monitoring for 4-7 days is very useful and has been recommended nowadays by clinicians. Considering the extent of hour-to-hour and day-to-day variability in blood pressure around the clock monitoring of blood pressure for more than 24 hours is very useful to detect blood pressure over swinging patterns or circadian hyper amplitude tension (CHAT), to reduce number of false negative and false positive diagnosis like white coat hypertension in diagnosis of patients with borderline hypertension and dipping and non-dipping patterns.[40] Secondly correlation of circadian pattern of Blood pressure and their correlation with autonomic regulation and heart rate variability could have clinical significance in the treatment and Pre-habilitation of cardiovascular diseases at earlier or primordial stage. The results may provide information on the different 24 hours /7days circadian pattern of blood pressure and heart rate in pre and postmenopausal women and also to what extent the difference in levels of sex hormones and melatonin during different phases of menstrual cycle could influence cardiovascular parameters in women of both groups in future as these results are not perhaps sufficient and more subjects are recruited and will be studied in the coming year.

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