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Original Article

Pressor response during normal Menstrual cycle.

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ABSTRACT

Aims: To study the blood pressure variations during different phases of the menstrual cycle using a set of autonomic function tests, Methods: The study included30 eumenorrheic, normal, normotensive, healthy females aged 18-30 yrs and a set of autonomic function tests were done to assess the pressor response during the three phases-menstrual phase, follicular phase and luteal phase of a single normal menstrual cycle. The subjects were selected based on predetermined exclusion-inclusion criteria. No controls of any kind (males or menopausal females) were included as the aim of the study was to compare pressor response among the three phases of a single menstrual cycle. Results: Across the menstrual cycle there was varied pressor response with higher values towards the luteal phase, when compared to the follicular and the menstrual phases. The statistically significant differences in the blood pressure parameters, resting blood pressure, postural variation in blood pressure and blood pressure response to cold pressor test were found between all the phases, with higher values towards the luteal phase. The results were obtained using ANOVA and student 't'-test, to study the significance of study parameters on continuous scale within each phases. Conclusion: There was varied pressor response across the menstrual cycle with higher values towards the luteal phase, as observed by the increased sympathetic outflow in the luteal phase compared to the increased parasympathetic outflow in the follicular phase. The baroreflex regulation of autonomic functions induced by posture changes is also modified during the normal, regular menstrual cycle. This altered regulation of the autonomic tone during the normal, regular menstrual cycle can be attributed to the cardio-protective effects of oestrogen in healthy young females in contrast to menopausal females.

1. Introduction

The menstrual cycle is not just a cycle of monthly periods, manifested as endometrial changes leading to a cyclical cervical bleeding which is concerned only with reproduction and its applied aspects of fertility. It is much more than a cycle of periods which itself is associated with other major systems in the body and having effect on more than hundreds of physical, psychological and behavioural changes.

The menstrual cycle which is secondary to the ovarian cycle is already proved to be purely a neuro-hormonal cycle controlled by the hypothalamo pituitary ovarian axis. This established hypothalamo pituitary ovarian axis and its cyclical hormonal changes during the three phases of the normal menstrual cycle have been proven as below[1]

1.Follicular phase: is primarily a phase of oestrogen, influenced by follicular stimulating hormone.

2.Luteal phase: is primarily a phase of progesterone influenced both by follicular stimulating hormone and luteinizing hormone.

3.Menstrual phase: the cervical bleeding phase, due to the withdrawal of hor monal effect on the endometrium.

Changes in the neuroendocrine system depending on the ovarian hormones have an important bearing in the control of reproductive and non reproductive functions having an effect on

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changes in cognition, behaviour and cardiovascular functions. The objective assessment of all these changes are difficult as majority of these changes are subjective qualities. But the literature reveals proven established correlation of these changes in case of premenstrual distress syndrome[2]. In this regard an objective assessment of the autonomic function tests appears to give some valuable information on sympatho-vagal discharge and the cardiovascular pressor response.

Similarly certain autonomic changes have also been reported during the three different phases of the menstrual cycle, more so during the premenstrual or luteal phase reflecting the influence of ovarian hormonal changes on blood pressure regulation and certain other neuro cardiovascular reflexes in women [3-6].

Normal blood pressure is under the control of autonomic nervous system. The sympathetic nerves that constrict arterioles and veins increasing the heart rate and stroke volume, discharge in a tonic fashion and the blood pressure is adjusted by variations in the rate of this tonic discharge. Spinal reflex activity affects blood pressure, but the main control of blood pressure is exerted by groups of neurons belonging to the autonomic nervous system in the medulla oblongata-the vasomotor area and the ventrolateral medulla[7].

Therefore the pressor response at any given point of time is a direct reflect of the sympatho-vagal discharge on heart, which can be assessed by the autonomic function tests. Although the autonomic function tests are criticized on the ground that they do not give a direct measure of the autonomic activity, there are some results which correlate well with overall dysfunction of autonomic nervous system, secondary to endocrinal abnormalities like diabetic neuropathy[8].

There is a general agreement that blood pressure rises with advancing age and also the systolic blood pressure and the diastolic blood pressure are lower in young women than in young men, until age 55-65, after which they become comparable[7]. Also there is a higher incidence of ischaemic heart disease in women after menopause, which suggests a close association between ovarian hormone levels and the cardiovascular status[9].

Similarly it has been established that there is an association between idiopathic orthostatic intolerance and syncope to the hormonal alterations in a normal menstrual cycle[10-12].

The presence of oestrogen receptors in the heart, vascular smooth muscle and autonomic brain centres-nucleus tractus solitarius and ventrolateral medulla, suggest a possible combined involvement of autonomic nervous system and ovarian hormones in the regulation of cardiovascular system.[13].

Therefore an attempt has been made to study the pressor response during different phases of the normal menstrual cycle using a set of autonomic function tests , the results of which is of a great value in the field of diagnostics and therapeutics of modern gynaecology and neurology.

2.Materials and Methods:

The study was conducted in the Department of Physiology, DR.B.R.Ambedkar Medical College, Bangalore. The ethical clearance was obtained from the Institutions ethical committe. The subjects were informed about the study and written consent was obtained from all subjects. The study included 30 normal, normotensive, non-pregnant, healthy-women aged 18-30 years, having normal regular menstrual cycles. The subject selection was based on the predetermined exclusion-inclusion criteria.

2.1.Inclusion criteria:

- Women aged between 18 to 30 years.
- Eumennorheic i,e. regular normal menstrual cycles of 26-34 days.
- Normotensive (<140/90 mm of Hg).

2.2.Exclusion criteria:

- Pregnancy.
- H/o irregular cycles
- H/o menorrhagia.
- H/o hypertension.
- H/o endocrine disorders.
- H/o postural symptoms.
- H/o syncopal attacks.
- H/O any medication during the study (including oral contraceptive pills).

Since the study was to compare the pressor response during the different phases of the same menstrual cycle, subject controls of any kind (males or menopausal women) was not taken. The stage of the cycle on entry was calculated from the date of onset of the last menstrual period.

The three phases of the study are [1];

1. Menstrual phase: Day 1 to day 5.

2. Proliferative / Follicular phase: Day6 to day14 (including ovulatory phase).

3. Secretory / Luteal phase: Day15 to day28 (including pre-menstrual phase).

Each subject was studied across six weeks, during which time atleast one full normal menstrual cycle will be completed. The recordings of the pressor response based on the set of autonomic functions chosen were made on specified days of a single menstrual cycle, preferably during morning in all three phases, during which the subjects were told to abstain from coffee, tea and smoking 12 hrs before the measurement.

All blood pressure measurements were done using a sphygmomanometer by the standard Riva-Rocci method (auscultatory), wherein the appearance and disappearance of the Korotkoff sounds were recorded as the systolic and diastolic blood pressures respectively.[14].

The autonomic function tests studied were [14];

1. Resting blood pressure; The subject was asked to rest in supine position for 15 minutes and at the end of 15 minutes blood pressure was recorded in this resting position. The subject was asked to relax during the procedure.

2. Blood pressure from supine to standing position (Postural Challenge Test): The subject was asked to lie down quietly for 10 minutes, then the subject is asked to stand up quietly, unaided within 5 seconds and remain standing quietly for 1 minute, the systolic and the diastolic blood pressure was measured at the end of 1 minute.

3. Cold pressor test: The subject was asked to be in the sitting position on a chair and the resting blood pressure was measured. Then their hands were placed in freezing (5°c) water for 1 minute. At the end of one minute,systolic and diastolic blood pressures were measured, prior to removing the hands from the cold water because of intolerant pain.

2.Materials and Methods:

A comparative evaluation study of the pressor response during the three phases-menstrual phase, follicular phase and the luteal phase was undertaken wherein repeated measures analysis of variance (ANOVA) has been used to find the significance of study parameters between three phases. Student t test (two tailed dependent) has been used to find the significance of study parameters on continous scale within each group.[15,16].

2.4. Significant figures

+ Suggestive significance (P value: 0.05<P<0.10)

* Moderately significant (P value:0.01<P 0.05)

** Strongly significant (P value : P0.01)

2.5. Statistical software:

The Statistical software namely SPSS 15.0, Stata 8.0, MedCalc 9.0.1 and Systat 11.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

3. Results:

Table-1 gives the comparison of Resting BP, Postural BP and CPT between the Menstrual Phase (MP), Follicular Phase (FP) and Luteal Phase(LP) and it shows an increase of blood pressure towards the luteal phase, suggestive of sympathetic dominance.

Table 1: Comparison of Resting BP, Postural BP and CPT between the Menstrual Phase (MP), Follicular Phase (FP) and Luteal Phase(LP).

Autonomic Function tests	MP	FP	LP	P value	MP vs FP	MP vs LP	FP vs LP
Resting SBP	103.4±5.31	99.2±5.55	109.2±3.99	<0.001**	0.009**	<0.001**	<0.001**
Resting DBP	69.2±3.66	68.4±2.54	72.00±4.17	<0.001**	0.281	0.001**	<0.001**
Postural SBP	97.13±6.34	93.07±6.6	99.80±6.13	<0.001**	<0.001**	<0.001**	<0.001**
Postural DBP	63.33±3.69	62.07±3.04	62.60±3.53	0.272	0.070+	0.412	0.492
CPT: SBP	117±5.84	112.93±5.84	123±5.84	<0.001**	<0.001**	<0.001**	<0.001**
CPT:DBP	88.8±5.55	85.33±4.05	90.6±5.31	<0.001**	<0.001**	<0.001**	<0.001**

* moderately significant,**strongy significant

SBP-systoic blood pressure, DBP-diastolic blood pressure, CPT-cold pressor test

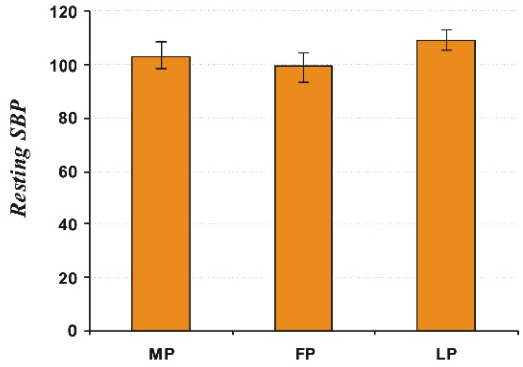
Table 2: Comparison of mean difference and 95% Confidence Interval of restingBP, postural BP and CPT, between Menstrual Phase (MP), Follicular Phase (FP) and Luteal Phase(LP).

Autonomic Function tests	MP vs FP		MP vs LP		FP vs LP	
	Mean ± SD	95%CI	Mean ± SD	95%CI	Mean ± SD	95%CI
Resting SBP	4.2±8.26	1.12 to 7.28	-5.8±3.91	-7.26 to -4.3	-10±6.56	-12.45 to -7.55
Resting DBP	0.8±3.99	-0.69 to 2.29	-2.8±4.29	4-4.4 to -1.2	-3.6±4.44	-5.26 to -1.94
Postural SBP	4.07±2.32	3.2 to 4.93	-2.67±1.92	-3.38 to -1.95	-6.73±3.04	-7.87 to -5.6
Postural DBP	1.27±3.69	-0.11 to 2.65	0.73±4.83	-1.07 to 2.54	-0.53±4.2	-2.1 to 1.03
CPT: SBP	4.07±3.46	2.77 to 5.36	-6±4.43	-7.65 to -4.35	-10.07±5.37	-12.07 to -8.06
CPT:DBP	3.47±3.48	2.17 to 4.77	-1.8±1.92	-2.52 to -1.08	-5.27±3.3	-6.5 to -4.03

95% confidence interval provides the significance if it does not include the 0, if 95% confidence interval includes 0 then the results are not significant at 5% Level of significance.

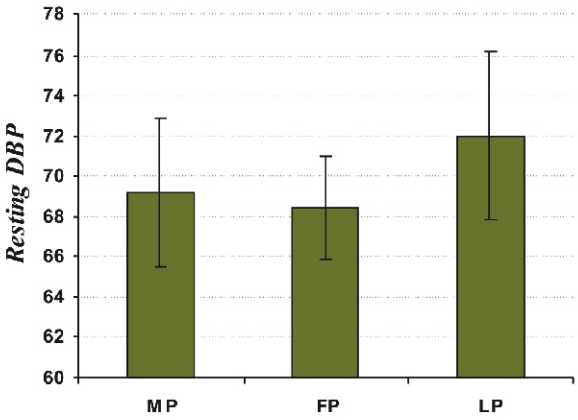
SBP-systoic blood pressure, DBP-diastolic blood pressure, CPT-cold pressor test

Graph 1: Comparison of resting SBP between the phases-MP,FP and LP.



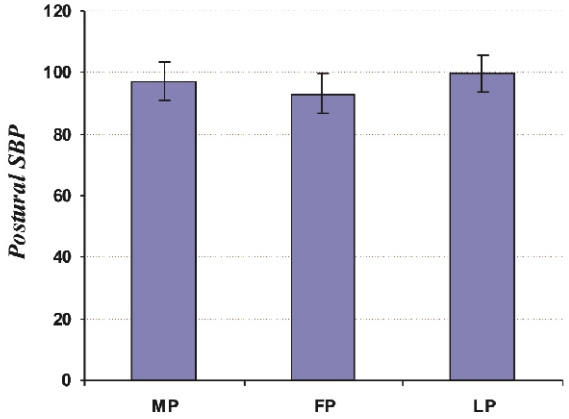
SBP-Systolic blood pressure, MP-menstrual phase, FP-follicuar phase, LP-lutea phase

Graph 2:Comparison of resting DBP between the phases-MP,FP and LP.



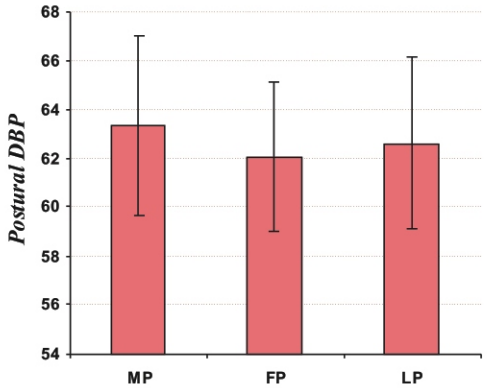
DBP-diastolic blood pressure, MP-menstrual phase, FP-follicuar phase, LP-lutea phase

Graph 3: Comparison of postural SBP between the phases-MP,FP and LP.



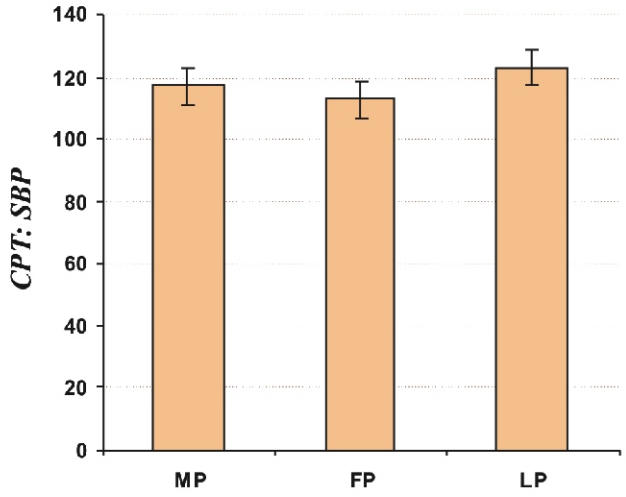
SBP- systolic blood pressure, MP-menstrual phase, FP-follicuar phase, LP-lutea phase

Graph 4:Comparison of postural DBP between the phases-MP,FP and LP



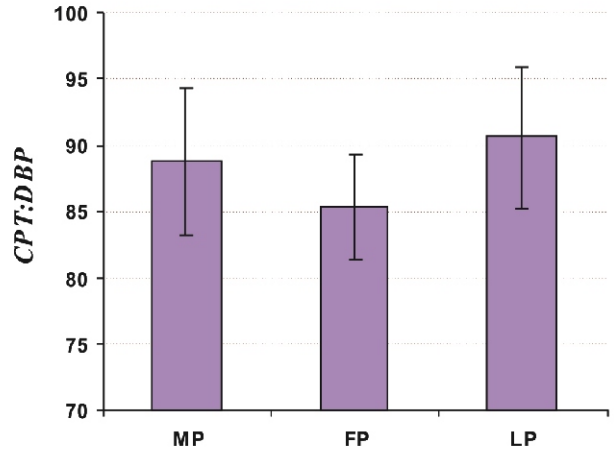
DBP=diastolic blood pressure, MP-menstrual phase, FP-follicuar phase, LP-lutea phase

Graph 5: Comparison of SBP response to cold pressor test (CPT) between the phases-MP,FP and LP.



CPT-Cold pressor test,s SBP-ystolic blood pressure,MP-menstrual phase,FP-follicuar phase,LP-lutea phase

Graph 6: Comparison of DBP response to cold pressor test (CPT) between the phases-MP,FP and LP.



CPT-Cold pressor test,DBP-diastolic blood pressure,MP-menstrual phase,FP-follicuar phase,LP-lutea phase

4.Discussion:

4.1.Resting blood pressure:

In the present study,the mean differences in the systolic blood pressure (SBP) between the three phases-menstrual,follicular and luteal phases showed statistically significant differences P<0.001,being highest in the luteal phase.

The mean differences in diastolic blood pressure (DBP) was statistically significant only between two phases:-menstrual & luteal phase and follicular & luteal phase.

The results were consistent with each of the earlier studies, which showed increase in SBP during luteal phase.There exists a significant difference between the SBP in the pre and postmenstrual phase, being higher in the premenstrual phase i,e.lutealphase, which can be explained on the basis of increased salt and fluid retention induced by ovarian steroids and a higher sympathetic nervous system activity[3].

The mean level of SBP varied with the phase of the menstrual cycle, being higher on days 17-26, the part of the luteal phase during which the peak of progesterone levels develops than during the luteal phase as a whole and significantly higher than the mean for all other days of the cycle.[17]. The sympathetic baroreflex sensitivity defined as the slope relating R-R interval and systolic blood pressure was greater during the mid luteal phase than the early follicular phase. The hormonal fluctuations that occur during the normal menstrual cycle mainly increased norepinephrine (NE) in midluteal phase may be responsible for this altered sympathetic outflow[18]. Sympathetic predominance in the luteal phase of menstrual cycle[19]. Also the administration of exogenous progesterone and the combined oral contraceptive pills are known to induce hypertension.[17].

Thus it is possible to conclude that the changes in the ovarian steroids in the normal menstrual cycle may alter the autonomic nervous system activity with parasympathetic pre dominance in the follicular phase and sympathetic predominance in the luteal phase which rises the SBP, but more proven results on DBP variation between the three phases is not found.

4.2. Blood pressure from supine to standing(Postural blood pressure):

In the present study, changes in blood pressure from supine to standing position was noted.There was a statistically significant difference in postural change of systolic blood pressure between all the three phases of the menstrual cycle.

The diastolic blood pressure response to change of posture was only of suggestive of significance between menstrual-follicular phases, and there was no significant difference between follicular-luteal phase. There was a statistically significant difference in DBP response to posture. On sudden change from supine to standing position, there is peripheral pooling of blood in dependent part , this decreases venous return and cardiac output, so the systolic blood pressure which is dependent on left ventricular ejection also decreases. This via the sino-aortic reflex, which operates within seconds, stabilizes the blood pressure [20]. The sympathetic baroreflex sensitivity defined as the slope relating R-R interval and systolic blood pressure was greater during the mid luteal phase than the early follicular phase. The hormonal fluctuations that occur during the normal menstrual cycle mainly increased norepinephrine (NE) in mid luteal phase may be responsible for this altered sympathetic outflow [21]. SBP was significantly higher in the ovulatory phase than in the follicular and luteal phase but resting DBP did not differ significantly between the phases. Also the rate pressure product (RPP) was higher during the ovulatory phase than during the menstrual and follicular phase, suggesting a pattern of menstrual cycle related variation in cardio vascular functioning which an be related to the established actions of the ovarian steroids.[22]. Significant correlations were observed between the plasma oestradiol concentration and the cardiovagal baroreflex sensitivity. The cardiovagal baroreflex sensitivity during the early follicular phase was significantly greater than those of the

mid luteal phase and also when compared to men,indicating parasympathetic dominance in the follicular phase[23]. The plasma renin activity and the concentrations of fluid regulatory hormones, aldosterone and plasma norepinephrine (NE) levels increased along the luteal phase which contributes to the increased cardiovagalbaroreflex sensitivity[24]. The parasympathetic activity is predominant in the follicular phase, resulting in an impairment of baroreflex caused by posture changes. Moreover, baroreflex control of the sympathetic component, not the parasympathetic component increases in the premenstrual phase, while the reflex response of the sympathetic component is less in the ovulatory phase compared with the menstrual or luteal phase concluding that the baroreflex regulation of autonomic functions induced by changing position is modified during the normal menstrual cycle. A difference in the balance of the ovarian hormones along the menstrual cycle may be responsible for these changes of autonomic functions during the menstrual cycle[25]. Therefore we can conclude that there is an increased postural difference in SBP along the menstrual cycle, with more being in the luteal phase which could be attributed to the increased sympathetic activity in the luteal phase.

4.3.Cold Pressor Test:

In the present study, the mean systolic blood pressure response to cold pressor test was higher in the luteal phase compared to menstrual and follicular phases. Also the difference of systolic blood pressure between the three phases of the menstrual cycle were statistically significant P <0.001.In this test the relationship between increased muscle sympathetic nerve activity and increase in fore arm vascular resistance provoked by immersion of hand in ice cold water is studied. This intervention produces an increase in sympathetic vasoconstriction outflow by activation of thermal and nociceptive afferents from the immersed hand.T his hypothesis is supported by the finding that there is increase in plasma levels of nor epinephrine without any change in the levels of adrenal catecholamines in response to local cooling. Womens pain threshold was significantly higher during the second phase of the menstrual cycle indicating increased levels of ovarian steroids and endorphins[26].Diastolic blood pressure response to cold presssor test, in the luteal phase was higher compared to the other phases of the menstrual cycle. Only mean diastolic blood pressure difference was statistically significant between menstrual and follicular phases, possibly because the dominant sympathetic activity during the luteal and menstrual phase would result in an increase in systolic and diastolic blood pressure observed during these phases[27].

5.Conclusions:

From the above study, we can conclude that,the regulation of autonomic tone is modified during the normal,regular menstrual cycle,with highest sympathetic outflow in the luteal phase,compared to the follicular phase and increased parasympathetic outflow in the follicular phase,compared to the luteal phase.The baroreflex regulation of autonomic functions induced by posture changes is also modified during the normal,regular menstrual cycle.This altered regulation of the autonomic tone during the normal,regular menstrual cycle can be attributed to the cardio-protective effects of oestrogen in healthy young females in contrast to menopausal females.

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