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A STUDY OF SYMPATHETIC FUNCTION TESTS DURING DIFFERENT PHASES OF MENSTRUAL CYCLE IN NORMAL HEALTHY FEMALES

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ABSTRACT: AIMS AND OBJECTIVES: The present study was designed to study the sympathetic function tests during the follicular, luteal and menstrual phases of the menstrual cycle in normal healthy eumenorrheic females. **MATERIALS AND METHODS:** Thirty females in the age group of 18-25 years were recruited for the study. Sympathetic non-invasive autonomic function tests were performed that is Isometric handgrip exercise test, cold pressor test and postural challenge test. **STATISTICAL ANALYSIS:** Results were analyzed by ANOVA with SPSS version 17.0 using unpaired 't' test. **RESULTS:** showed that during the luteal phase, there is a significant increase in the resting systolic (119.1 ± 4.41) and diastolic (74.43 ± 4.26) blood pressure, as compared to menstrual (SBP 116.11 ± 4.23 & DBP 72.13 ± 3.44) and follicular phase (SBP 110.23 ± 4.46 & DBP 69.13 ± 3.13) showing the sympathetic dominance ($p < 0.05$). The systolic and diastolic blood pressure also showed significant increase ($p < 0.05$) with the application of the stimulus [viz. isometric handgrip exercise, cold pressor tests and postural challenge test] during the luteal phase as compared to both follicular and menstrual phase. However, In the follicular phase, both the systolic and diastolic blood pressure decreased with the application of the stimulus [viz. isometric handgrip exercise (Follicular phase SBP 112.16 ± 3.12 , DBP 70.16 ± 1.18), cold pressor tests (SBP 121.41 ± 3.27 , DBP 80.43 ± 4.12) and postural challenge test (SBP 100.23 ± 4.41 , DBP 60.14 ± 3.32)] as compared to the menstrual (IHG SBP 120.15 ± 3.11 , DBP 74.24 ± 2.14 , CPT SBP 125.17 ± 3.29 DBP 86.22 ± 4.16 , postural challenge SBP 105.17 ± 4.17 , DBP 62.41 ± 3.11) and luteal phase (IHG SBP 124.12 ± 2.21 , DBP 78.12 ± 3.23 , CPT SBP 129.21 ± 3.12 DBP 90.23 ± 4.46 , postural challenge SBP 109.21 ± 4.61 , DBP 65.12 ± 3.22) showing the parasympathetic predominance. The decrease is statistically significant ($p < 0.05$). **CONCLUSIONS:** Our study shows that blood pressure in the resting state and during the stressful maneuvers like cold pressor test, isometric handgrip exercise and standing from lying posture was highest during luteal phase of the menstrual cycle and lowest in the follicular phase. This correlates to the symptoms of premenstrual syndrome which has hormonal and neural basis.

KEYWORDS: follicular phase, luteal phase, autonomic nervous system, menstrual cycle.

INTRODUCTION: The biological activity of the menstrual cycle is created by the coordination among hypothalamic, hypophyseal and ovarian hormones.¹

The established hypothalamic, hypophyseal and ovarian axis and its cyclical hormonal changes during the three phases of normal menstrual cycle are as follows.²

Follicular Phase: is mainly a phase of oestrogen, influenced by follicular stimulating hormone. Luteal phase: primarily a phase of progesterone influenced both by follicular stimulating hormone and luteinizing hormone.

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Menstrual Cycle: The cervical bleeding phase, due to the withdrawal of hormonal effect on endometrium. The fluctuations in hormonal levels affect not only the female reproductive tract but also many other tissues of the body.

Reproductive hormones primarily estrogen, may modulate cardiovascular function through a number of mechanisms, including stress induced activation of the hypothalamic pituitary adrenal and sympatho-adrenomedullary systems.^{3,4} Chapman et al reported that endogenous progesterone was known to have hypertensive effect, whereas administration of estrogen promoted vasodilator effect by increased prostacyclin and nitric oxide synthesis.⁵

Variations in the autonomic nerve function may also be related to these fluctuations⁶. Some women may experience some physical, psychological and behavioral symptoms which occur in late luteal phase of menstrual cycle as premenstrual syndrome.⁷ The physiological changes observed during the luteal phase of menstrual cycle are known to mimic early pregnancy.⁵

Hassan et al³ reported that significant decrease in mean blood pressure during mid-luteal phase was due to decrease in total peripheral resistance. Dunne et al demonstrated a high blood pressure at the onset of menstrual cycle as compared to other phases.⁸

Normally, blood pressure is under the control of autonomic nervous system. The sympathetic nerves discharge in a tonic fashion that constricts the arterioles and veins increasing the heart rate and stroke volume. Blood pressure is adjusted by variations in rate of this tonic discharge.⁹ The behavioral and psychological changes in response to hormonal imbalance during premenstrual phase, pregnancy and menopause involve limbic system and hypothalamus.

Most of the behavioral and emotional patterns are exhibited through autonomic nervous system. Therefore, it is worthwhile to assess autonomic functions during various phases of menstrual cycle.^[8,10,11] Moreover, there are few studies in the cardiorespiratory functions in different phases of the menstrual cycle among the healthy Indian women. Thus the objective of our study is to elucidate the autonomic functions during follicular, luteal and menstrual phases of the cycle in young healthy females.

MATERIALS & METHODS: The present study was a cross-sectional study, conducted in Santosh Medical College, Ghaziabad. Ethical approval was taken from the research committee of the institution before starting the study.

Thirty apparently healthy female volunteers in the age group of 18-25 years with h/o regular menstrual cycle were studied in follicular, luteal and menstrual phases of menstrual cycle. Menstrual history including age of menarche, regularity of cycles, h/o dysmenorrhea, h/o premenstrual symptoms like irritability, headache were collected. Women subjects with age >above 25 years, h/o irregular menstrual cycles, use of contraceptive pills, h/o diabetes or hypertension or any other chronic illness, on medication and smokers were excluded from the study. Informed consent was taken from all the subjects.

Height was measured using a standard stadiometer with the subject standing in erect posture. The readings were taken to the nearest 0.1 cm. Weight was recorded in kilograms using a calibrated weighing machine (Avery) scale with a capacity of 120 kgs and a sensitivity of 0.05 kg. The BMI was calculated as the weight in kilograms divided by the square of the height in meters [weight (kg)/height (m²)].¹²

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The following tests were performed for assessment of sympathetic activity:

Resting blood pressure of all the subjects was measured by auscultatory method with the help of mercury sphygmomanometer (DIAMOND). Before recording the blood pressure, subjects were allowed to rest for 10 minutes in a quiet room to reduce the anxiety. First Korkoff sound indicated systolic blood pressure (SBP) and fifth Korkoff sound indicated diastolic blood pressure (DBP).

Cold pressor test: Procedure of the cold pressor test (CPT) was explained to all the students participating in the study. After recording resting blood pressure, subjects were asked to dip left arm in the cold water (temp at 2-4° C) for 2 minutes and blood pressure was recorded from the right arm. Blood pressure was once again recorded 5 minutes after hand was taken out from the cold water.²⁰

Isometric Handgrip Exercise Test: After recording basal blood pressure, subjects were asked to perform isometric handgrip exercise. Subjects were told to hold the handgrip spring dynamometer in the right (or dominant hand) to have a full grip of it. Handles of the dynamometer were compressed by the subject with maximum effort for few seconds. This whole procedure was repeated thrice with rest in between to prevent fatigue. Mean of the three readings was referred as maximal isometric tension (Tmax). Then, the subjects were asked to perform isometric handgrip exercise at 30% of Tmax for 2 minutes. During the test, blood pressure was recorded from the non-exercising arm. Blood pressure was again recorded 5 minutes after completion of the exercise.

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 quietly, unaided within 5 seconds and remain standing quietly for 1 minute, the systolic and diastolic blood pressure was measured at the end of 1 minute.

Statistical Analysis: Results were analyzed by ANOVA with SPSS version 17.0 using unpaired 't' test.

RESULTS:

Variables	Mean±SD
Age(yrs)	20.72±1.20
BMI(kg/m ²)	21.67± 0.97

Table 1: Mean ± SD of the anthropometric variables

Table 2: Statistical analysis of sympathetic function tests [Isometric Handgrip Exercise Test, Cold Pressor Test and Postural Challenge Test] during different phases of the menstrual cycle.

Parameters	Menstrual phase	Follicular phase	Luteal phase
Resting SBP(mmHg)	116.11± 4.23	110.23 ± 4.46	119.1 ± 4.41
Resting DBP(mmHg)	72.13±3.44	69.13±3.13	74.43±4.26
IHG SBP(mmHg)	120.15±3.11	112.16±3.12	124.12±2.21
IHG DBP(mmHg)	74.24±2.14	70.16±1.18	78.12±3.23
CPT SBP(mmHg)	125.17±3.29	121.41±3.27	129.21±3.12
CPT DBP(mmHg)	86.22±4.16	80.43±4.12	90.23±4.46
Postural SBP(mmHg)	105.17±4.17	100.23±4.41	109.21±4.61
Postural DBP(mmHg)	62.41±3.11	60.14±3.32	65.12±3.22

Table 2

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Data presented in Table 2 shows that during the luteal phase, there was significant increase in the resting systolic and diastolic blood pressure showing the sympathetic dominance. Both systolic and diastolic blood pressure also showed significant increase ($p < 0.05$) with the application of the stimulus [isometric handgrip exercise, cold pressor tests and postural challenge test] during the luteal phase. In the follicular phase, both the systolic and diastolic blood pressure decreased with the application of the stimulus [isometric handgrip exercise, cold pressor tests and postural challenge test] and without the stimulus, the decrease is statistically significant ($p < 0.05$).

Fig. 1: Bar diagram showing comparison of resting DBP in different phases of menstrual cycle.

Figure 1

Fig. 2: Bar diagram showing comparison of resting SBP in different phases of menstrual cycle.

Figure 2

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Fig. 3: Comparison of DBP response to isometric handgrip exercise test in different phases of the menstrual cycle.

Figure 3

Fig 4: Comparison of SBP response to isometric handgrip exercise test in different phases of the menstrual cycle.

Figure 4

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Fig. 5: Comparison of DBP response to cold pressor test in different phases of the menstrual cycle.

Figure 5

Fig. 6: Comparison of SBP response to cold pressor test in different phases of the menstrual cycle.

Figure 6

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Fig. 7: Comparison of Postural DBP in different phases of the menstrual cycle.

Figure 7

Fig. 8: Comparison of Postural SBP in different phases of the menstrual cycle.

Figure 8

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DISCUSSION: In the present study, significant increase in the resting systolic and diastolic blood pressure was observed in the luteal phase as compared to the menstrual phase in contrast to the significant decrease in the follicular phase. In the follicular phase, estrogen promotes vasodilatation by stimulating the release of prostacyclin and nitric oxide and inhibits the production of vasoconstrictors like angiotensinogen II and endothelins.^{12,13}

Estrogen increases density as well as the function of presynaptic α_2 adrenoreceptors in the follicular phase that causes a significant decrease in the secretion of noradrenaline¹⁴. Estrogen causes smooth muscle relaxation and thus vasodilatation by stimulating the opening of calcium activated potassium channels by nitric oxide¹⁵ and cyclic guanosine monophosphate pathway that causes vasodilatation.¹⁶ Estradiol might also be associated with increase in acetylcholine concentration.¹⁷

This may be the cause of decreased sympathetic activity during follicular phase as compared to luteal phase.¹⁸

During the luteal phase, progesterone may increase cardiac excitability by opposing effects of estrogen.¹⁹ Progesterone also exerts an inhibitory effect on the cardiovagal baroreflex responses.²⁰

Estradiol peaks during luteal phase and this helps in increasing progesterone receptors. This increased action of progesterone hormone during the luteal phase may be responsible for increased sympathetic activity. It has been shown that ovarian steroids in the normal menstrual cycle may alter the autonomic nervous system activity with parasympathetic predominance in the follicular phase and sympathetic dominance in the luteal phase that raises the resting blood pressure.²¹

Our study showed a statistically significant difference in postural change of systolic and diastolic blood pressure in all the three phases of menstrual cycle. On sudden change of posture from supine to standing, there is peripheral pooling of blood in the dependent parts of the body; this decreases the venous return and cardiac output so the systolic blood pressure decreases. This via the sino-aortic reflex, which operates within seconds, stabilizes the blood pressure.³

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 increases in the premenstrual phase. Thus, it was concluded that baroreflex regulation of autonomic functions is modified by postural change during the menstrual cycle.²²

Our study showed that the systolic and diastolic blood pressure response to cold pressor test was significantly higher in the luteal phase as compared to the menstrual and follicular phases and the difference was statistically significant ($p < 0.05$). Increased sympathetic activity induced by cold water stress causes norepinephrine release and elevation of blood pressure. Increase in blood pressure might also be contributed by release of endothelins, prostaglandins and angiotensin II.²³

Women's pain threshold was significantly higher during the second phase of the menstrual cycle indicating increased levels of ovarian steroids and endorphins.²⁴

Normally during isometric handgrip exercise, there is increase in the concentrations of metabolites like lactic acid and adenosine that are detected by metabolite-sensitive nerve endings within the skeletal muscle interstitium. These substances increase the discharge of group IV (metaboreceptor) afferent fibers, initiating a potent reflex that increases sympathetic nerve activity.

This leads to vasoconstriction, which contributes to the rise in BP,²⁵ it is shown that there is a marked influence of estrogen on the blood flow through the hand and forearm; especially on the venous tone, yet the effects of progesterone on peripheral blood flow are questionable.²⁶

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It is possible that under the influence of estrogen, the normal blood flow response to known vasodilators may be reduced or reversed that will decrease the endurance for isometric exercise.²⁷

In the menstrual phase due to blood loss, blood pressure is lesser than during luteal phase without and with the application of the stimulus [viz. isometric handgrip exercise, cold pressor tests and postural challenge test]. However, blood pressure in this phase is more than the follicular phase, that may be due to fall in estrogen levels.^{6,13}

CONCLUSIONS: Our study shows that blood pressure in the resting state and during the stressful maneuvers like cold pressor test, isometric handgrip exercise and standing from lying posture was highest during luteal phase of the menstrual cycle and lowest in the follicular phase. This correlates to the symptoms of premenstrual syndrome which has hormonal and neural basis.

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