Research Article

Comparative study of sympathetic activity in normal and preeclamptic pregnancy

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Abstract

Introduction: Abundant studies on the pathophysiologic mechanisms of Preeclampsia described that it is characterized by low circulating volume and high vascular resistance. This is exactly opposite of the hemodynamic changes that occur in normal pregnancy. It has been proposed that autonomic nervous system particularly sympathetic nervous system bring about these hemodynamic changes, but the exact role of autonomic control mechanism in pregnancy is poorly understood. So the study is conducted to evaluate and compare sympathetic functions in normal and preeclamptic pregnancy. **Aim and Objectives:** To compare the sympathetic activity in normal and preeclamptic pregnancy **Material and Methods**: Fifty normal pregnant and fifty preeclamptic pregnant females in the age group of 19-29 yrs were enrolled for the study after institutional ethical committee's clearance was obtained. The cold pressor test and handgrip test performed on both the groups. The systolic and diastolic pressor response during the maneuver is noted and response compared between above two study groups. **Result:** In our study, we found that mean value of systolic and diastolic pressure response is significantly increased in cold pressor test in preeclamptic pregnant females as compared to normal one whereas in Handgrip test only diastolic pressure response is significantly increased in preeclamptic females. **Discussion:** A significantly increased vasoconstrictive response to a cold stimulus seen in preeclamptic females is a sign of an increased vascular reactivity, which is attributed to increased sympathetic activity. Increased blood pressure response in handgrip test can be explained by muscle metaboreflex which is activated by accumulation of metabolites, which were increased in preeclampsia as compared to normal pregnancy**. Conclusion:** From the study, we conclude that there is sympathetic over activity in preeclampsia as compared to normal pregnancy. It would be helpful in both preventive and control measures for this most common disorder of pregnancy.

Keywords: Autonomic function test, Cold pressor test, Handgrip test, Preeclampsia, Pregnancy.

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INTRODUCTION

One of the well known complication, that commonly come across during pregnancy is Preeclampsia. Preeclampsia is defined as a pregnancy - specific disorder occurring after 20 weeks of gestation characterised by blood pressure of 140/90 mmHg or more for the first time in pregnancy, on two separate occasions and proteinuria of at least 0.3 g per 24 hours in a previously normotensive and non-proteinuric patient[1]. It occurs in up to 10% of all pregnancies and it is a major contributor to maternal morbidity and mortality, perinatal death, preterm birth and fetal growth restriction. It develops in the second half of pregnancy and resolves shortly after delivery.[2] Despite its prevalence and severity, no comprehensive theory or single factor has been suggested to explain the pathophysiology of this multi system disorder of pregnancy. Abundant studies described that preeclampsia is characterized by low circulating volume and high vascular resistance, which is exactly opposite of the hemodynamic changes that occur in normal pregnancy i.e. decrease in mean arterial pressure and systemic vascular resistance and marked increase in circulating

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volume, heart rate and cardiac output. It has been proposed that autonomic nervous system bring about these hemodynamic changes. Cardiovascular adaptations during pregnancy are triggered by decrease in systemic vascular résistance. It results into a feedback response of increase in cardiovascular sympathetic drive to meet the higher circulatory demands of pregnancy. Defect in this feedback response results into preeclampsia.[3] In short, the marked increase in sympathetic activity in latter months of pregnancy help to return the arterial pressure to non pregnant levels, but when there is excessive increase in sympathetic activity, hypertension develops[4]. Earlier study by Hans P. Schobel *et al*[5] indicated that increase in peripheral vascular resistance and blood pressure seen in preeclampsia, was mediated by a substantial increase in sympathetic vasoconstrictor activity. The higher cardiac output in early pregnancy of women, developing preeclampsia later is due to significantly higher heart rate, which has been regarded as an early sign of increased sympathetic activity.[2] If preeclampsia (toxemia in pregnancy) is considered as an impairment of these hemodynamic alterations, one might expect differences in autonomic control mechanism of preeclampsia[6]. Methods for the assessment of autonomic circulatory control in humans have therefore been of great interest for researchers involved in the field of cardiovascular physiology in pregnancy. Schobel *et al*[5] measured postganglionic action potentials in sympathetic nerve fibers in patients with preeclampsia. Greenwood *et al* found that vasomotor sympathetic activity increased in women with normal pregnancy and was even greater in hypertensive pregnant women.[7,8] The potential involvement of the autonomic nervous system particularly sympathetic nervous system using non invasive methods like cardiovascular reflex test in preeclampsia has, as far as we know, not been investigated much in Indian studies. Since the sympathetic nervous system also has an important adaptive influence on the circulation, we decided to evaluate sympathetic nervous function in preeclampsia, using standard noninvasive cardiovascular reflex test. i. e. cold pressor test and handgrip test. [9,10] These noninvasive methods have the advantage of minimal risk for the mother and the fetus and repeated measurements can be possible in case of any error in values during procedure.[2]

AIMS AND OBJECTIVE

To compare the sympathetic activity in normal and preeclamptic pregnancy.

METHODS

It is a cross-sectional study, conducted between December 2009 and October 2011 on two groups of subjects. Group I - Normal pregnant group (n =50) and Group II – Preeclamptic pregnant group (n =50)**.** Thus a total of 100 subjects were included in the study and the selection criterion was:

Preeclamptic pregnant Group (Group II)

Diagnosed cases of Preeclamptic pregnant females (n=50) in the third trimester of pregnancy in the age group of 18 to 29years, visiting Obstetrics and gynecology OPD (antenatal clinic) were selected for study. Preeclampsia is defined as a pregnancy - specific disorder occurring after 20 weeks of gestation characterised by blood pressure of 140/90 mmHg or higher and proteinuria of at least 0.3 g per 24 hours in a previously normotensive and non proteinuric patient.[1] All subjects selected were primigravida with no other complication of pregnancy.

Exclusion Criteria

Females with

a) Age group other than 18-29
b) Previous history of hypertension, hypotension, CVD, Diabetes mellitus, chronic renal failure, obesity, liver diseases, thyrotoxicosis, vascular **diseases.**
c) Multigravida, those < 28 weeks of gestation, multiple pregnancy, known cases of intrauterine growth retardation and Eclampsia (In case of pregnant subjects)
d) Smoking and alcoholics
e) Subjects taking drugs such as hypnotics or autonomic blockers were excluded from the study.

These exclusion criteria were applied to both study groups so as to exclude direct or indirect effects of the above mentioned factors on the parameters assessed.

Normal normotensive pregnant group (Group I)

For comparison separate group of normal normotensive pregnant females(n=50)of same trimester(third trimester),all primigravida belonging to the same age group(18-29yeras), similar height and weight, and having same ethnic group as that of preeclamptic pregnant group were enrolled in this group. The selection of this group was based on detail history, physical examination as same as that used for the preeclamptic pregnant group. They met same exclusion criteria as that of preeclamptic pregnant group.

Procedure

Before starting the study work, all participants were given detailed information about the project and every effort was taken to solve their queries. This was an attempt to establish a good rapport with the subjects and relieve their anxiety. Written informed consent was obtained from every subject. The subjects were instructed not to have coffee, tea cola 12 hours before the tests and were asked to have light breakfast two hours before the tests.[11,12] The

subjects were asked to report either in the OPD or in the ward of Obstetrics and gynecology as per their convenience in the morning hours for measurement of anthropometric parameters. BP was measured with sphygmomanometer by the standard auscultatory Riva Rocci method and heart rate with the help of ECG machine with lead II, explained in details below. The cardiovascular autonomic tests performed are detailed below in the order of execution. These tests were demonstrated to the subjects.

Anthropometric Measurements

Standing Height

Standing Height of the subject was measured by simply making the subject stand against a wall on which the measuring scale was inscribed. The subject would stand on bare feet on a flat floor against the wall with both the feet parallel and with heels, buttocks and occiput touching the wall. The head was held erect with eyes aligned horizontally and ears vertically without tilt. Then with the help of plastic ruler, the top most point of the vertex was noted on the wall.[13]

Weight

Weight was measured with KRUPS weighing machine in light weight garments without foot wears.

Recording of blood pressure

The arterial blood pressure of each subject was recorded in the right brachial artery in sitting position with the patient's arm at approximate heart level.[14] The subjects were instructed to come after a night's restful sleep, no strenuous physical activity to be performed for atleast 1 hour before recording the blood pressure. The entire procedure was explained and the patient made comfortable to allay rise in blood pressure due to anxiety, excitement or stress.[1,15,16] The blood pressure was measured with sphygmomanometer by the standard auscultatory Riva-Rocci method from the right upper arm. The systolic pressure was recorded as appearance of the Korotk off sounds (phase I) and the diastolic blood pressure recorded as the disappearance of the Korotkoff sounds (phase V)[17]) Two readings were taken with a 15 minute rest period in between and the arithmetic average of the two readings was noted as the blood pressure of the subject.[18,19]

Heart rate

The subject was asked to relax in supine position for 30 minutes. The resting heart rate was recorded on a standard ECG from lead II, at a paper speed of 25 mm/sec. Two readings were taken with a 15 minute rest period in between and the arithmetic average of the two readings was noted as the heart rate of the subject

HR=1500/R-R interval[9]

Materials

Sympathetic function tests will be carried out by using

1. Electro cardiograph
2. Sphygmomanometer
3. Hand grip dynamometer
4. Cold water (4-5 degree cel)
5. Thermometer

Tests for sympathetic functions

1. Cold pressor test
2. Handgrip test

Cold Pressor Test: (CPT)

The subject was seated comfortably and HR and BP were recorded in the same manner as mentioned above before the test. The CPT was performed by immersing the subject's one hand up to the wrist in ice cold water (4-5 degree celcius) for 1 minutes[20,21,22] Subjects were asked to avoid isometric contraction and performance of a Valsalva maneuver or hold expiration during the CPT.[23] The maximum reading of systolic and diastolic pressures was noted and compare with pretest readings[22] Rise in the systolic and diastolic blood pressure was calculated by subtracting pretest reading from this maximum reading.

Hand grip Dynamometer Test (HGT)

The subject was seated comfortably and HR and BP were recorded in the same manner as mentioned above before starting the test. The subjects were explained about the procedure through self demonstration. The subjects were asked to perform Maximum Voluntary Contraction (MVC) by gripping the handgrip dynamometer, as hard as possible for few seconds and maximum force exerted was noted down. After giving rest for few minutes the subjects were made to perform test at 30% of maximal voluntary contraction by gripping the hand dynamometer for 3-5 minutes or till the subject could sustain the effort comfortably[24] Systolic and diastolic blood pressure was recorded on the non exercising arm at interval of 30 seconds during the period of exercise. Rise in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at the point just before the release of hand grip were noted. The response was considered as the difference between maximum BP obtained during exercise and the pre-exercise reading.[24] A rise in DBP of less than 10 mm Hg was defined as abnormal, 11-15 mm Hg as borderline and 16 mm Hg or more as normal[25,26]

Statistical analysis[27,28]

Statistical analysis of the observations was carried out using SSPS version 17.0. The data was expressed in terms of mean and standard deviation and inferential statistics was determined using the one way analysis of variance (ANOVA), Bonferroni's multiple comparison tests and z test as appropriate. Also correlation between different parameters was determined by Pearson's correlation coefficient. Statistical significance was tested at 5% and

expressed in terms of 'p' value with $p<0.05$ = statistically significant.

OBSERVATION AND RESULTS

Following anthropometric parameters were assessed and autonomic function tests were carried out in each of the study groups.

Anthropometric parameters

1. Standing height
2. Weight
3. Body mass index (BMI)
4. Arterial blood pressure

Table 1: Table showing the distribution of cases in the study group

Group I Normal pregnant group	Group II Preeclamptic group
50	50

Table 2: Table showing groupwise comparison of age of subjects

Group I Normal pregnant group	Group II Preeclamptic group	Group I vs Group II
23.08 ± 2.76	23.58 ± 2.90	p>0.05 NS

The above table shows the age (in years) of the two groups of subjects expressed in terms of mean and standard deviation. There was no statistical difference in the mean age of pregnant (Group I) and preeclamptic pregnant women (Group II).

Table 3: Table showing group wise comparison of height, weight and BMI of subjects

	Group I Normal pregnant	Group II Preeclamptic pregnant	Group I vs Group II
Height (metres)	1.55 ± 0.04	1.54 ± 0.03	p>0.05 NS
Weight (Kg)	59.68 ± 4.94	60.52 ± 2.59	p>0.05 NS
BMI (Kg/m^2)	24.69 ± 2.342	25.41 ± 1.604	p>0.05 NS

The above table shows the mean height, weight and BMI of the two groups of subjects with their standard deviation. There was no statistical difference ($p>0.05$) in the heights, weights and BMI of normal pregnant and preeclamptic groups.

Table 4: Table showing the gestational age of the pregnant subjects i.e. Group I and Group II

	Group I Normal pregnant	Group II Preeclamptic pregnant	Group I vs Group II
Gestational Age (weeks)	31.62± 2.303	31.92 ± 1.861	p>0.05 NS

The above table shows the comparison of the gestational age of the pregnant groups of subjects, namely the normal pregnant group (Group I) and the preeclamptic group (Group II). There is no significant difference between the two groups with respect to this parameter.

Table 5: Table showing group wise comparison of the blood pressure of subjects

	Group I Normal pregnant	Group II Preeclamptic Pregnant	Group I vs Group II
Systolic blood pressure (mm Hg)	113.9± 7.655	154.8±4.675	p<0.001***
Diastolic blood pressure (mm Hg)	70.72 ± 6.058	100.4± 9.510	p<0.001***
Mean arterial pressure (mm Hg)	85.12± 4.392	118.5± 6.401	p<0.001***

This table gives the systolic, diastolic blood pressure and the mean arterial pressure expressed in terms of mean and standard deviation of the two groups of subjects. The preeclamptic group showed a significant increase in the systolic, diastolic and mean arterial pressure as compared to normal pregnant ($p < 0.001$).

Table 6: Table showing groupwise comparison of Resting Heart rate of subjects

	Group I Normal pregnant	Group II Preeclamptic	Group I vs Group II
Resting Heart rate	87.3+14.01	91.1+5.79	p>0.05 NS

This table gives the resting HR expressed in terms of mean and standard deviation of the two groups of subjects. Preeclamptic group showed increase in HR as compared to pregnant group but it was found to be non significant.

Table 7: Table showing group wise comparison of the sympathetic activity of the subjects in two groups

Response of sympathetic function tests	Group I Normal pregnant	GroupII Preeclamptic Pregnant	Group I Vs Group II
Increase in SBP during CPT(mmHg)	13.52+4.908	15.92+5.450	P<0.05 *
Increase in DBP during CPT(mmHg)	9.040+3.574	10.96+3.923	P<0.05 *
Increase in SBP during Hg(mmHg)	13.4+4.005	14.96+-4.106	p>0.05 NS
Increased in DBP during Hg(mmHg)	11.68+-3.733	13.96+-4.703	P<0.05 *

DISCUSSION

In the present study, no significant difference in age, height, weight or BMI was found amongst the groups studied indicating that the groups were comparable.

Blood pressure

There is a significant increase in the systolic blood pressure, diastolic blood pressure and mean arterial blood pressure of the preeclamptic group as compared to normal pregnant.

Resting Heart rate

Resting heart rate of two groups is given in table no. 6. The preeclamptic pregnant group shows increase in mean resting heart rate as compared to the normal pregnant group, but it is non significant.

Cold pressor test

Table no.7 depicts the rise in systolic blood pressure (SBP) and diastolic blood pressure (DBP) respectively during cold pressor test (CPT) in two groups of subjects. The mean rise in SBP of the normal pregnant (group I) and preeclamptic group (group II) were 13.52 mmHg and 15.92 mmHg respectively. Thus, group II shows significant rise in SBP as compared to group I. Similarly, group I and group II showed 9.04 mmHg and 10.96 mmHg of mean rise in DBP respectively during CPT. Thus there is significant rise in DBP in group II as compared to group I. The finding of the present study is in conformity with findings of *Nandini kapoor 2011[24] *Woisetschlager 2000[29], *Rodolfo Gomez[30] A significantly increased vasoconstrictive response to a cold stimulus seen in preeclamptic women compared to normal pregnant women is a sign of an increased vascular reactivity and increased vascular reactivity is attributed to increased sympathetic activity.[20,31] Thus, preeclamptic women show increased sympathetic activity as compared to normal pregnant women. This increased vasoconstrictor response in preeclampsia might be explained by the increase responsiveness to vasoconstrictors like catecholamines i.e. nor epinephrine as compared to normal pregnancy.[32,33] Cold pressor test is a potent reflex stimulus capable of increasing muscle sympathetic nerve activity[34,35] and plasma norepinephrine levels. in both arm and leg[25]. This released norepinephrine binds to membrane-bound post-junctional α-adrenergic receptors on the vascular smooth muscle and bring about vasoconstriction[36]. Now, sensitivity of this vasculature to nor epinephrine is increased in pregnancy induced hypertension compared to normal pregnancy[32,33]. Thus, increase vascular reactivity in preeclampsia may be the reason for increased blood pressure response to CPT as compared to normal pregnancy.

Hans P schobel (1996) *et al* [5] explained the possible mechanisms increasing sympathetic muscle nerve activity in preeclampsia. **Kanayama *et al* (1997)**[37] has done animal experiments to study effects of cold stimulus on non pregnant and pregnant rats. A significant increase in urinary protein excretion was observed in the cold-stimulated pregnant rats, in contrast to the control rats. The concentrations of norepinephrine and epinephrine in the cold-stressed pregnant rats were markedly higher than those in the control rats.

Handgrip test

Table no.7 depicts the rise in systolic blood pressure (SBP) and diastolic blood pressure (DBP) respectively during handgrip tests in two groups of subjects. The mean rise in systolic blood pressure of the normal pregnant (group I) and preeclamptic group (group II) were 13.4 mmHg and 14.96 mmHg respectively. The group II shows significant increase in response as compared to group I. Similarly mean rise in DBP were 11.68 mmHg and 13.96 mmHg in normal pregnant and preeclamptic pregnant group respectively. Thus there is non significant increase in diastolic response of preeclamptic group as compared to normal pregnant group. The finding of the present study is in conformity with findings of--- *PhilipN baker 1994[38], *Nandini kapoor 2011[24], *Tomoda S 1994[39] *Degani S 1985[40.] Blood pressure response to hand grip test used as a measure of cardiac sympathetic activity[2] which is significantly increased in preeclampsia as compared to normal pregnant, suggesting increased sympathetic activity in preeclampsia. Handgrip exercise is characterized by increase in blood pressure and heart rate. It occurs due to the changes in the autonomic efferent activity caused reflexly i.e muscle metab reflex[41] Reflex mechanism occurs by the stimulation of somatic afferents, sensitive to metabolites produced within the contracting muscle and result into general sympathetic activation and vagal withdrawal. It is explained in flowchart given below.

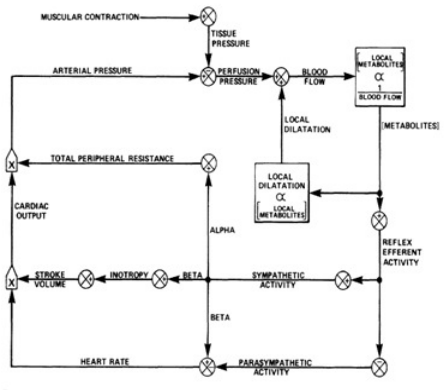

FIGURE 3. *The principle mechanisms available for arterial pressure elevation as a result of isometric contraction are summarized in a diagrammatic form.* ⊗ *is the symbol used for addition and subtraction, for example:*

ARTERIAL PRESSURE ⊗ PERFUSION PRESSURE

TISSUE PRESSURE

shows that perfusion pressure is enhanced by increasing arterial pressure and diminished by increasing tissue pressure. ⊠ *represents multiplication, for example:*

STROKE VOLUME ⊠ CARDIAC OUTPUT

HEART RATE

indicates that cardiac output equals heart rate times stroke volume. Fur further review of control systems nomenclature see Guyton.[17]

This reflex stimulation (along with cortical irradiation) increases heart rate, causes arterial vasoconstriction in non exercising skeletal muscle, and increases cardiac output[41]. As explained in flow chart, concentration of local metabolite is inversely proportional to blood flow. Handgrip contraction causes decrease in skin blood flow. This decrease in blood flow is more in preeclampsia as compared to normal pregnancy[42] resulting in more local metabolites production, which reflexly causes more stimulation of efferent sympathetic activity in preeclampsia as compared to normal pregnant. Other possible mechanisms given by some of the following studies. **JOHN R. STRATTON *et al***[35] showed that plasma catecholamines, which are marker of general sympathetic nervous system activation, increases during handgrip exercise**.** Preeclamptic group shows increased responsiveness to these vasoconstrictors due to increase sensitivity of vasculature to vasoconstrictors[32,33] whereas in pregnancy this responsiveness to vasoconstrictor is lost[32] Thus, preeclamptic group shows significant increase blood pressure response, as sign of increased reactivity to stressor (handgrip) as compared to normal pregnant, suggesting increased sympathetic activity in preeclampsia as compared to normal pregnancy. Similar results were found in study by Nandini kapoor *et al*[24] **John P Greenwood (2001) *et al***[7] suggested some central role for increase sympathetic activity in hypertensive pregnancy. Pregnancy which later on, develops hypertension showed peripheral sympathetic hyperactivity[2,43].

SUMMARY AND CONCLUSIONS

The data obtained was subjected to statistical analysis. The findings of the present study are summarized as follows:

- The preeclamptic group is associated with a significant rise in the systolic, diastolic and mean arterial pressure as compared to normal pregnancy.
- Blood pressure response (i.e. rise in SBP and DBP) to cold stimuli and handgrip (i.e. rise in DBP) is significantly increased in preeclamptic group as compared to normal pregnant.
- Preeclampsia is associated with hyperactivity of sympathetic function.
- The development of preventive strategies not only requires knowledge of pathophysiology mechanism of the disease, but also availability of methods of early detection and means of interventions and correction of pathophysiological changes.
- Analysis of changes in baroreflex functioning serially in pregnancy and preeclampsia could be field of interest that should be further explored.
- As preeclampsia is found to be autonomic dysfunction disorder, then recent technique like pranayam and yoga could be beneficial in prevention of progress of disease as yoga practices bring about stable ANS equilibrium with tendency towards parasympathetic nervous system dominance and also cardiovascular efficiency is increased as many cardiovascular diseases are associated with it.
- Next to the application of preventive strategies, early prediction using the same autonomic functions could also be useful for targeting obstetrics care at those most likely to benefit.

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