Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 06, 2024

TITLE: FREQUENCY DOMAIN ANALYSIS OF HEARTRATE VARIABILITY IN GESTATIONAL HYPERTENSIVE AND NORMOTENSIVE PREGNANT WOMEN

Authors : Adhilakshmi.A[1], Nirmala.N[2],Premaleela.KGN[2],Karthika Priyadarshini U[3]

Affiliation: [1] ASSISTANT PROFESSOR, Department of Physiology,Indira Gandhi Medical College and Research Institute,Puducherry

[2] PROFESSOR(RETD), Department of Physiology and Department of Obstetrics and Gynecology,SriVenkateswaraa Medical College and Research Centre,Puducherry respectively

[3] ASSISTANT PROFESSOR, JIPMER,Puducherry

Corresponding author:Dr.Adhilakshmi.A,Assistant Professor,Department of Physiology Indira Gandhi Medical College and Research Institute,Puducherry

Hypertensive disorders of pregnancy constitute an enigmatic and clinically challenging group of pregnancy complications worldwide and the third leading cause of maternal mortality and morbidity. Gestational hypertension does not complicate pregnancy but progresses to preeclampsia if not detected early.Detection of predictors of preeclampsia in gestational hypertensive women will reduce maternal and foetal complications thereby reducing the mortality and morbidity rates.The aim of our study was to analyse the heartrate variability in Gestational hypertensive women in comparison with Normotensive pregnant women.The study was conducted on 30 normotensive pregnant(control group) and 30 gestational hypertensive women(study group). Heartrate variability was recorded using the instrument PHYSIOPAC-PP4, MEDICAID system and HRV indices were analysed in both groups.Frequency domain analysis of HRV showed significant increase in LFnu ($p<0.001$), decrease in HFnu ($p<0.001$) and high LF-HF ratio ($p<0.001$) in the study group compared to control group.Total Power was decreased in the study group. This study showed significant sympathovagal imbalance in gestational hypertensives. HRV analysis, a noninvasive screening method can be used for assessment of sympathovagal imbalance and early detection of preeclampsia.

KEYWORDS; GH-Gestational hypertension,HRV-Heartrate variability,PE-Preeclampsia,LF-Low Frequency,HF- High Frequency

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INTRODUCTION

Hypertensive disorders of pregnancy complicate 6-8% of pregnancies worldwide and form one of the deadly triad, along with hemorrhage and infection.[1, 2]
It is a significant cause of maternal, foetal and neonatal mortality and morbidity and can also lead to long-term health problems like chronic hypertension, kidney failure, or nervous system disorders. [3, 4] The incidence of pregnancy induced hypertension in India is about 7-10% of all antenatal admissions.[5] Prakash et al in 2006 in a hospital based study reported HDP in 5.38%[6]
Globally, about 3,50,000 women die every year from pregnancy related causes and
hypertensive disorders in pregnancy contribute to approximately 12% of the maternal deaths worldwide and World Health Organization estimates that at least one woman dies every seven minutes from complications of hypertensive disorders of pregnancy.[7,8] Pregnancy induced hypertension contributes to 15.6% maternal mortality in India [9,10]
Pregnancy induced effects on cardiovascular function in the resting state are increase in Heartrate, StrokeVolume and Cardiac output. Systolic pressure remains stable throughout pregnancy whereas diastolic blood pressure decreases till 28 weeks and then increases towards nonpregnant levels by term. This results because of an integrated effect of renin angiotensin aldosterone axis, oestrogen mediated contractility, autonomic changes in the heart, baroreflex mechanism and aldosterone mediated altered vascular reactivity[11, 12] In women who develop Gestational hypertension or Preeclampsia, BP is stable during the first half of pregnancy and then continuously increases until delivery.[13]
Though etiological factor is not known, hypertension in pregnancy and its complications can be minimized by early detection and prompt action In a developing country like India with inadequate care for antenatal mothers, this entity on many occasions remains undetected till major complications supervene..

Very few studies have explored hypertensive disorders of pregnancy in India and those done so far have focussed on assessment of alterations in various parameters only after the onset of disease. The progression of gestational hypertension to preeclampsia has not been elucidated in any study. Prediction of preeclampsia at an early stage with the help of Heart rate variability (HRV) is of utmost importance taking into account the endangering situation the mother and the foetus are exposed to due to hypertension.

The aim of our study was to identify hypertensive women from the antenatal OPD and to analyse and compare the heart rate variability in gestational hypertensive and normotensive pregnant women

MATERIALS AND METHODS

The study was a case control study carried out after obtaining the institutional ethical committee clearance.

Pregnant women in the age group of 21-40years attending maternity OPD,

30 Normotensive pregnant women of more than 20 weeks gestation with

Systolic BP:100-118mmHg and Diastolic BP :60-78mmHg(Group I)

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30 Gestational Hypertensive women of more than 20 weeks gestation with Systolic BP ≥ 140mmHg and Diastolic BP≥ 90mmHg (Group II) were included in the study

Pregnant women with Gestational age<20weeks,Pretensives,Severe preeclampsia,Eclampsia, Multiple pregnancy, Gestational Diabetes, Pregnant women with renal diseases, Hypertension prior to pregnancy and on drugs were excluded from the study.

A written informed consent was obtained from those fulfilling the inclusion criteria willing to participate.Baseline assessment was done.Gestational age was determined by means of last menstrual period and confirmed by ultrasound report

Bloodpressure: Measured with a mercury sphygmomanometer with the women in the sitting posture after a rest of 10 minutes, the arm cuff at heart level and diastolic pressure designated at the 5th Korotkoff sound(JNC criteria).

Hypertension in pregnancy is defined as a systolic blood pressure of 140 mmHg or greater or a diastolic blood pressure of 90 mmHg or greater. These measurements must be present on at least two occasions at least 6 hours apart, but not more than 1 week apart. Includes gestational hypertension,preeclampsia,eclampsia

Gestational hypertension: Subjects having systolic blood pressure of 140 mmHg or greater or a diastolic blood pressure of 90 mmHg or greater. These measurements must be present on at least two occasions at least 6 hours apart after 20 weeks of gestation; had no history of hypertension, had no albuminuria and no systemic abnormality earlier (NHBPEP) [14].

HRV recording: Before recording HRV instructions were given to the subjects HRV was recorded between 9 am and 11 am in our physiology research laboratory avoiding too bright light or noise and room temperature was maintained. Subjects were allowed to take a supine rest of 10 minutes and basal heart rate (BHR) and BP (diastolic and systolic) were recorded. Recording of short-term HRV was carried out as per the recommendation of the Task Force on HRV.[15, 16]

For this purpose, electrocardiogram (ECG) electrodes were connected and Lead II ECG was acquired during supine rest using PHYSIOPAC MEDICAID SYSTEMS,CHANDIGARH.The data was transferred from PHYSIOPAC to a windows‑based PC with AcqKnowledge software Ectopics and artefacts were removed from the recorded ECG. RR tachogram was extracted from the edited 256‑s ECG using the R wave detector in the AcqKnowledge software and saved in ASC‑II format. HRV analysis was done using the Kubios HRV analysis software version 2.0,2008 (Biosignal Analysis and Medical Imaging Group). The R-R interval data obtained with the ECG monitoring system was subjected to Fast Fourier Transformation and analysed for parameters in the frequency domains - LFnu, HFnu, LF/HF ratio, TP

STATISTICAL METHODS

Data was analyzed using SPSS Version 16. The conventional level of $p < 0.05$ was considered as statistically significant. Normality assumption for parametric tests was tested by the skewness and kurtosis values of the distribution. Homogeneity of variance was tested by Levene test in cases of 't' test. Differences in BP, BMI among the two groups were compared using unpaired't' test. Chi square test was done to compare differences in proportions.

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RESULTS AND DISCUSSION

Hypertension in pregnancy is accompanied by marked maternal cardiovascular changes and the autonomic nervous system balances these changes and maintains cardiovascular homeostasis.

The association between alteration in autonomic cardiovascular control and development of hypertension in pregnancy has been investigated by some studies. Heartrate variability is an useful noninvasive and powerful tool to assess the cardiac autonomic functions and has the advantage of carrying minimum risk to the mother and foetus and possibility of repeated measurements.The following tables show the age,parity and trimesterwise distribution of subjects

Table 1: Comparison of age between control group (normotensive pregnant woman) and subjects of study group (gestational hypertensive)

	CONTROL GROUP Mean ± SD	STUDY GROUP Mean ± SD	P VALUE
AGE in years	26.23 ± 4.12	23.69 ± 4.12	0.597

Table 2: Parity-wise distribution of control group and study group

PARITY	CONTROL GROUP N (%)	STUDY GROUP N (%)
PRIMIGRAVIDA	14	16
MULTIGRAVIDA	19	11
TOTAL	30	30

P= 0.194

Table 3: Trimesterwise distribution of control group and study group

TRIMESTER	CONTROL GROUP N (%)	STUDY GROUP N (%)
2nd TRIMESTER	11	8
3rd TRIMESTER	19	22
TOTAL	30	30

P=0.405

Table 4: Comparison of BMI between control group and study group

PARAMETER	CONTROL GROUP MEAN ± SD	STUDY GROUP MEAN ± SD	P VALUE
BMI	21.66 ± 3.24	27.27± 3.32	0.475

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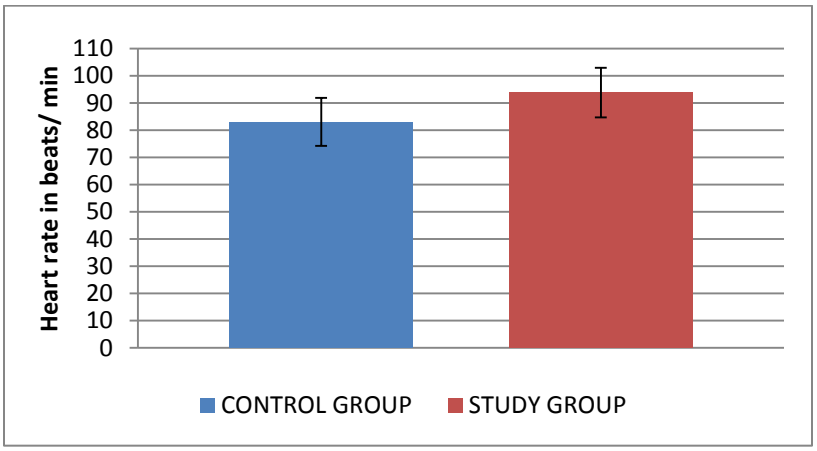
Table 5: Comparison of vital parameters between control and study group

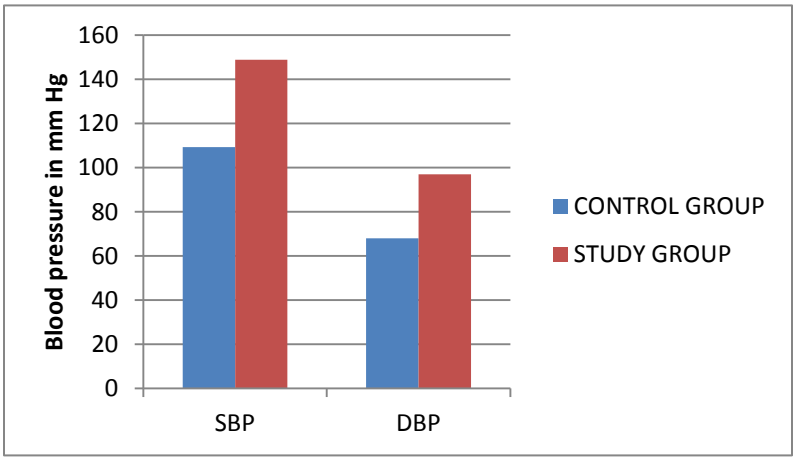
PARAMETERS	CONROL GROUP MEAN±SD	STUDY GROUP MEAN± SD	P value
HR	83.05 ± 8.83	93.80 ± 9.12	<0.001
SBP	109.25 ± 7.17	148.80 ± 7.53	<0.001
DBP	68.0 ± 4.60	96.93 ± 6.05	<0.001

Figure 5 a: Comparison of Heart rate between control and study group



In our study a high basal heart rate (HR) was observed in gestational hypertensive women compared to gestational normotensive women.The difference in HR was statistically significant between the groups (Table5, Fig5a) .GKPal et al in their study on hypertensive pregnant women have found similar results.Significantly higher heart rate is regarded as an early sign of increased sympathetic activity and lower vagal tone

Figure 5b: Comparison of Blood pressure between the groups



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Systolic (SBP)and diastolic blood pressure(DBP) was significantly higher in the gestational hypertensive women compared to gestational normotensive women(Table5,Fig5b).SBP is an index of cardiac output that is related to stroke volume which in turn depends on venous return and myocardial contractility.DBP is an index of peripheral vascular resistance which reflects basal sympathetic tone.[17] The hypertensive subjects had significantly high systolic and diastolic blood pressure which could be due to their increased sympathetic tone as pregnancy induced hypertension is primarily a state of sympathetic activity.Our result is consistent with studies by Rang et al[18]

Mean sympathetic activity during rest appeared to be three times higher in preeclamptic women compared to healthy pregnant women. Increase in Systemic vascular resistance is mediated by a marked increase in sympathetic vasoconstriction activity in hypertensive pregnancies[19]

Spectral analysis studies have shown decreased baroreflex sensitivity in preeclamptic women compared to healthy pregnant women. In all hypertensive conditions baroreflex is reset towards the elevated blood pressure. It indicates that rather than opposing the blood pressure elevations this mechanism acts to maintain it. This reflex mechanism may be the reason for the sympathetic activation in hypertensive pregnancy[20,21]

According to a study by Faber et al,baroreflex sensitivity blood pressure variability and heartrate variability were analysed on GH,PE and chronic hypertension and compared with controls and was markedly altered in all the three groups with hypertensive pregnancies compared with healthy pregnant women.HRV was significantly impaired in GH and unaltered in chronic hypertension and PE.[22]

Frequency domain analysis of HRV has gained popularity with broad application as a functional indicator of the autonomic nervous system. LF nu indicates sympathetic modulation of heart functions.HF nu reflects vagal modulation of SA nodal discharge.In our study LF nu was increased and HF nu was decreased in the study group LF nu, HF nu and LF-HF ratio were stastistically significant in our study in gestational hypertensive compared to normotensive pregnant group. (Table 6),(Fig 6a, 6b)

Table 6: Comparison of LF nu, HF nu, LF/HF ratio and Total power

PARAMETER	CONTROL GROUP	STUDY GROUP	P VALUE
LF nu	49.53 ± 13.92	68.03 ± 9.08	< .0001
HFnu	49.08 ± 15.37	31.73 ± 9.05	< .0001
LF-HF RATIO	1.14 ± 0.66	2.53 ± 1.53	< .0001
TOTAL POWER (ms^2)	1344 ±1120.83	1207 ± 1117.63	0.638

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Figure 6 a: Comparison of LFnu and HF nu between the groups

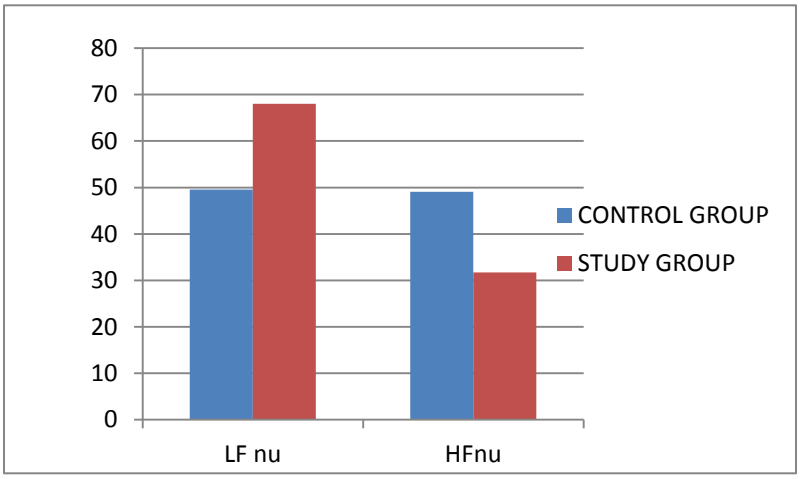
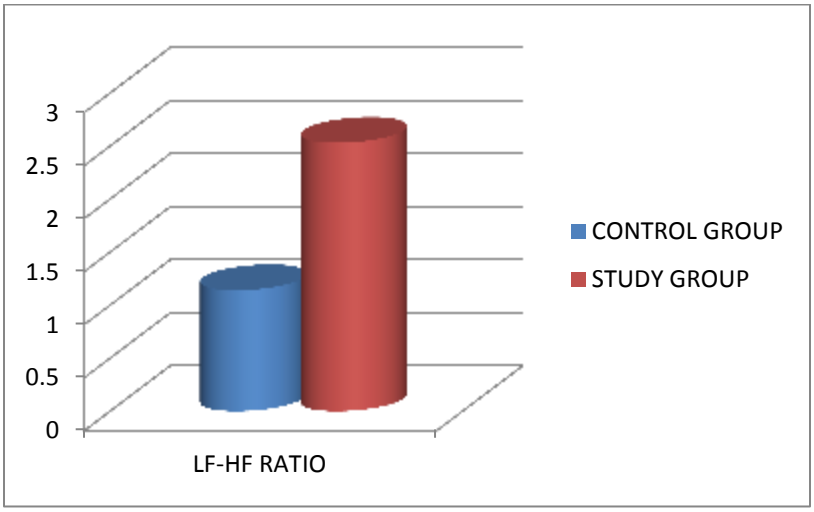


Figure 6 b: Comparison of LF HF ratio between the groups



LF-HF ratio which reflects increased sympathetic tone was significantly high in study group compared to control group in our study (Fig 6b) which is similar to studies by GKPal et al. Increased LF –HF ratio was also seen in a study conducted by Cheryl Yang et al on preeclamptic women and normal pregnant women and concluded that pregnancy is associated with a facilitation of sympathetic regulation and an attenuation of parasympathetic influence of heartrate and such alterations are enhanced in preeclamptic pregnancy[23] LF-HF ratio is an index of sympathovagal balance between sympathetic and parasympathetic activities of an individual in resting supine condition. Total Power was decreased in gestational hypertensive group in our study which represents parasympathetic control of CVS similar to other studies (Fig 6c)

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Figure 6 c: Comparison of Total power between the groups

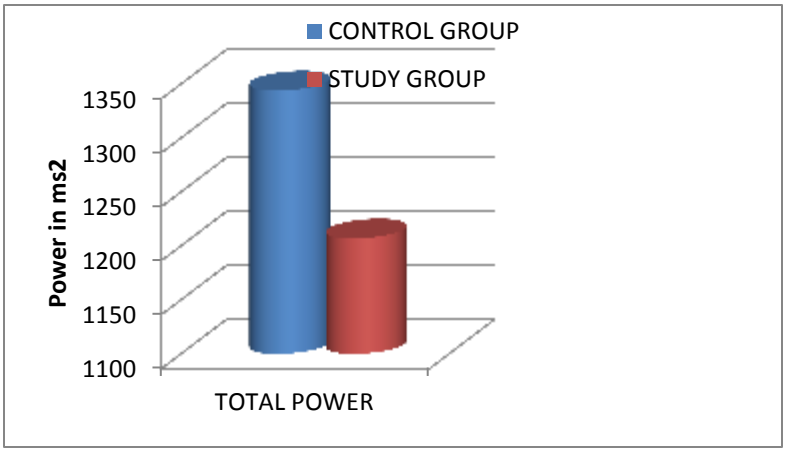
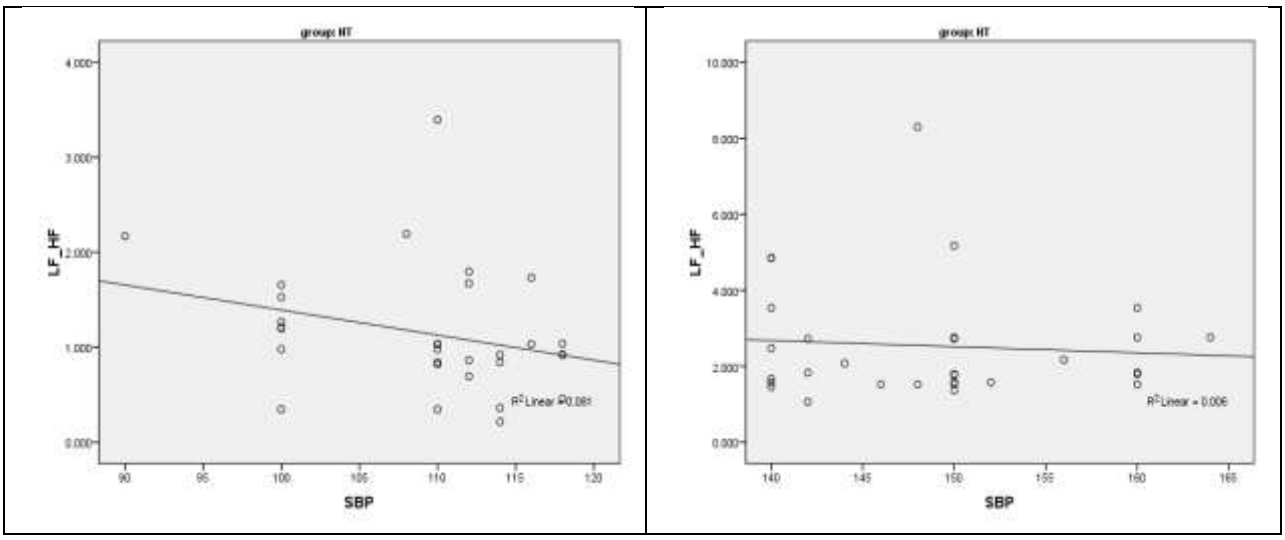


Table 7: Correlation of LF-HF ratio with SBP, DBP and BHR of control and study groups

PARAMETERS	CONTROL GROUP		STUDY GROUP	
	r VALUE	p VALUE	r VALUE	p VALUE
SBP	-0.285	0.126	-0.08	0.676
DBP	-0.163	0.389	-0.128	0.5
BHR	-0.049	0.797	0.168	0.375

Figure 7 a: Correlation of LF-HF ratio with SBP in the control and study groups



There was a weak negative correlation between the Systolic Blood pressure and LF HF ratio both in the control group (r = -0.285, p = 0.126) and in the study group (r = -0.080, p = 0.676). This association was not found to be statistically significant. (Figure 7 a)

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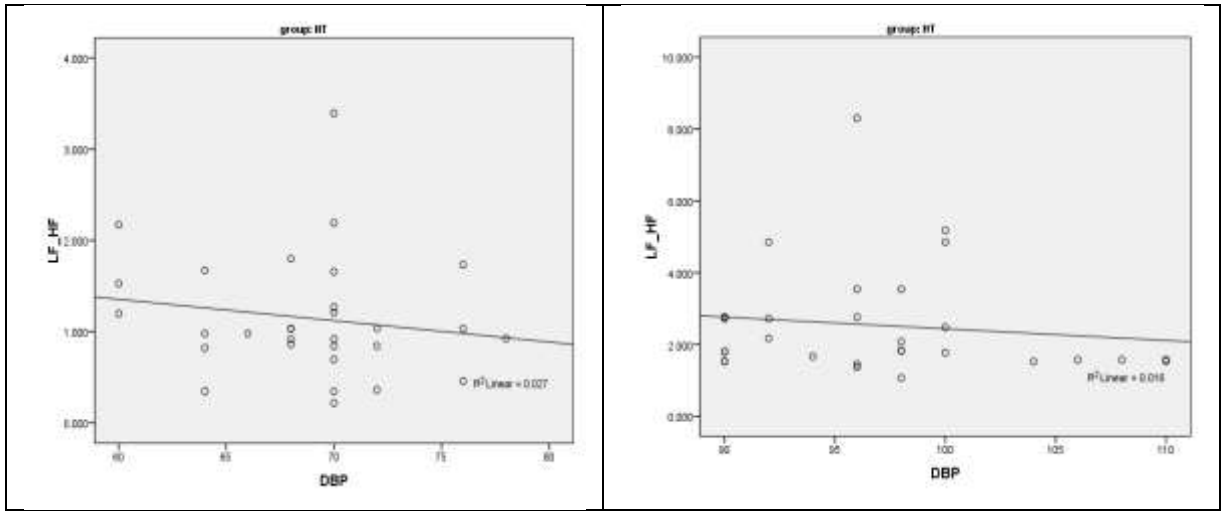
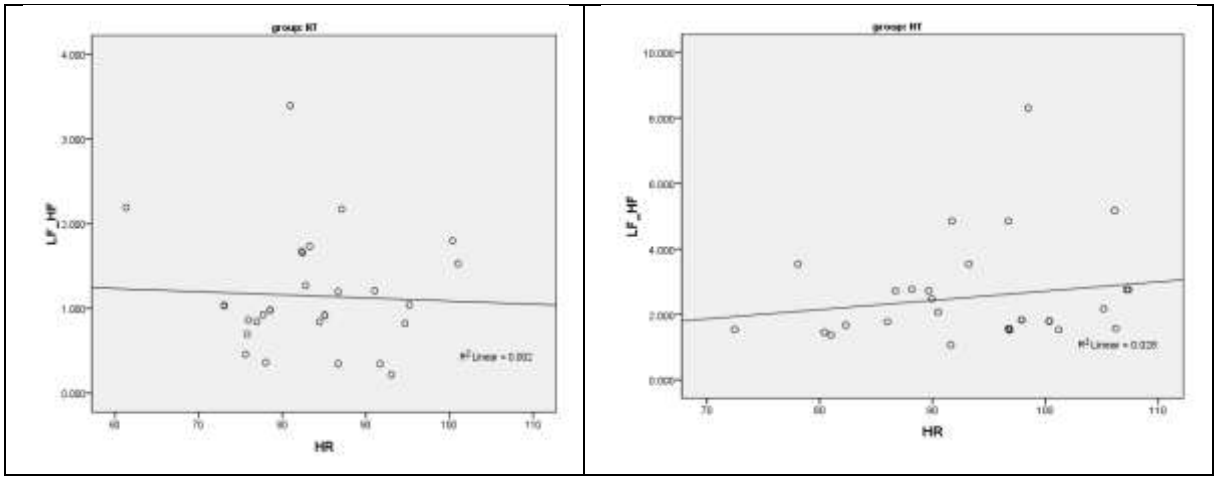
Figure 7 b: Correlation of LF-HF ratio with DBP in the control and study groups



There was a weak negative correlation between the Diastolic Blood pressure and LF HF ratio both in the control group (r = -0.163, p = 0.389) and in the study group (r = -0.128, p = 0.500). This association was not found to be statistically significant. (Figure7 b)

Figure 7 c: Correlation of LF-HF ratio with BHR in the control and study groups



There was a weak negative correlation between the basal heart rate and LF HF ratio in the control group (r = -0.049, p = 0.797), whereas a weak positive correlation was seen in the study group (r = 0.168, p = 0.375). This association was not found to be statistically significant. (Figure 7 c)

Muscle sympathetic nerve activity using microangiographic studies in gestational hypertensive women in the third trimester by Greenwood et al also showed that women with GH had increased sympathetic discharge compared to their normal counterparts.He attributed it to activation of Renin Angiotensin system,hyperinsulinemia which produces sympathetic activation

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and reduction in vasopressin levels.[24] The sympathovagal balance is maintained by by the interaction of three major factors namely central neural regulation, peripheral inhibitory and excitatory reflex mechanisms

From the analysis we conclude that pregnancy is associated with sympathetic hyperactivity and this is exaggerated in gestational hypertensive women and also vagal withdrawal contributes to sympathovagal imbalance which is a feature of hypertensive pregnancies.

CONCLUSION

Hypertensive disorders of pregnancy remain a major problem in developing countries. The rate of progression depends on gestational age at time of diagnosis; the rate reaches 50% when gestational hypertension develops before 30 weeks' gestation. A predictor of PE HRV analysis which is a noninvasive procedure is important in detecting the function and integrity of Autonomic Nervous System would make intervention,close surveillance,early diagnosis and timely delivery possible there by reducing the maternal and foetal mortality of the disorder also bring a relief to heavy burden on the healthcare delivery system.

LIMITATIONS

Since preeclampsia is a very heterogenous disorder a predictive test should use different markers of importance that reflect different aspects of pathogenesis.

Pretensive pregnant women were excluded.

Followup of the patients was not done

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