ORIGINAL RESEARCH PAPER

Physiology

THE RELATIONSHIP BETWEEN HEART RATE VARIABILITY AND MEAN PLATLET VOLUME IN HYPERTENSIVE AND PRE-HYPERTENSIVE PATIENTS IN AJMER

KEY WORDS: Hypertension, Mean platelet volume, Heart rate variability

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ABSTRACT

Introduction- Hypertension is related to dysfunctional autonomic cardiovascular control and to abnormal activation of the sympathetic division. Platelet size has been demonstrated to reflect platelet activity and seems to be a useful predictive and prognostic biomarker of cardiovascular events. Mean Platelet Volume (MPV), is an important indicator of platelet activation, It may be an important diagnostic tool in both prehypertensive and hypertensive patients. HRV is the measure of the variation in time between successive heartbeats. HRV is extracted from an electrocardiogram (ECG) measurement by measuring the time intervals between the R-peaks of successive heartbeats. **Aim-** The study aimed to find out the relationship between mean platelet volume and heart rate variability. High HRV is commonly linked to young age, good physical fitness, and good overall health **Material & Methods-** This was a case control study conducted in neurophysiology laboratory attached to department of physiology J.L.N.Medical College Ajmer, Rajasthan, India between August 2023 and August 2024.The sample size was 150 with male and female, aged 30-50 years. Based on the blood pressure, the participants were divided into prehypertensive & hypertensive group, control group of 50 participants was also included. Blood pressure measurement done for all the participants. Time domain and frequency domain were recorded using five minutes recording used to analyzed heart rate variability. Student independent t test used to find out significant differences. Pearson correlation test used to find out correlation between HRV parameters and mean platelet volume in prehypertensive and hypertensive individuals. P value <0.05 considered significant. **Result –** Values of time domain in prehypertensive were significantly less than those in control group. The value of time domain in hypertensives were significantly less than those in prehypertensive and control group. In hypertensives, the mean value of LF was 68.70 ± 10.32 and it was increased (p< 0.01), then in prehypertensive individuals suggesting increased sympathetic activity in hypertension. The average values of LF/HF (2.17 ± 0.64) were significantly higher in hypertensive individuals (p< 0.01) than in prehypertensive individuals. The average value of mean platelet volume in prehypertensive individuals were 8.24 ± 0.57 was higher (p<0.01) than in controls The mean platelet volume in hypertensive individuals was 9.79 ± 0.88 which was higher (p<0.01) than in prehypertensive individuals. MPV is negatively correlated with RMSSD, with increase in MPV RMSSD decreases and statistically significant (r= -0.385, p= 0.004). Although the significant correlation of MPV was found with RMSSD in hypertensives only. **Conclusion-** In prehypertension and hypertension there is increased sympathetic and decreased parasympathetic activity which indicated by significant alteration in resting heart rate variability parameters. Increase in mean platelet volume is associated with sympathetic hyperactivity and decrease in parasympathetic activity in both prehypertensive and hypertensives since appropriate correlations were obtained between MPV and HRV indices.

INTRODUCTION

A mean arterial pressure greater than 110 mmHg (Normal is about 90 mmHg) is considered to be hypertensive (This level of mean pressure occurs when the diastolic blood pressure is greater than about 90 mmHg and systolic pressure is greater than about 135 mmHg).(1) In general hypertension has been divided into primary or essential hypertension and secondary hypertension, in 90% of hypertensive patients, no specific cause of hypertension can be isolated and are grouped under primary hypertension.(2) Hypertension is one of the most important preventable contributors to disease and death in the United States, leading to myocardial infarction, stroke, and renal failure when it is not detected early and treated appropriately. According to JNC VII criteria, raised blood pressure is classified into prehypertension and hypertension. Prehypertension was defined as a systolic blood pressure of 120–139 mmHg and/or a diastolic blood pressure of 80–89 mmHg. (3) Prehypertension is a precursor of clinical hypertension and is closely related with the increased incidence of cardiovascular disease. Studies documented the role played by the autonomic nervous system in modulating cardiovascular functions and in controlling blood pressure. Origin, progression, and outcome of hypertension are related to dysfunctional autonomic cardiovascular control and to abnormal activation of the sympathetic division. (4) Sympathetic activation participates in the development of hypertension-related target organ damage, such as left ventricular diastolic dysfunction, left ventricular hypertrophy and arterial remodeling and hypertrophy. Platelet size has been demonstrated to reflect platelet activity and seems to be a useful predictive and prognostic biomarker of cardiovascular events. It is associated with a variety of prothrombotic and proinflammatory diseases. Increased MPV was observed in cardiovascular diseases, cerebral stroke, respiratory diseases, chronic renal failure, intestine diseases, rheumatoid diseases, diabetes, and various cancers. Decreased MPV was noted in tuberculosis during disease exacerbation, ulcerative colitis, SLE in adult, and different neoplastic diseases. (5) A high MPV value may reflect the presence of active large platelets which contain more dense granules that are metabolically and enzymatically more active than small ones, leading to high thrombus burden lesions that result in fatal or non-fatal cardiovascular events. Platelet activity is increased in essential hypertension. (6) Mean platelet volume is an important platelet production index that may be indirectly related to platelet function. (6) Shear stress in hypertension causes endothelial damage resulting in thrombus formation. As a result, in hypertensive patients, due to the consumption of small platelets, the number of thrombocytes decreases and

MPV increases. Thus, MPV is significantly higher in hypertensive patients than in normotensive subjects. (6) Studies suggested that MPV, an indicator of platelet activation was significantly higher in patients with prehypertension and hypertension when compared with control subjects and MPV was also higher in patients with hypertension than in patients with prehypertension. (7) The heart rate is the number of heart beats per minute. Heart rate variability (HRV) is the fluctuation in the time intervals between adjacent heart beats.HRV indexes neurocardiac function and is generated by heart-brain interactions and dynamic non-linear autonomic nervous system (ANS) processes. HRV is an emergent property of interdependent regulatory systems which operate on different time scales to help us adapt to environmental and psychological challenges. HRV reflects regulation of autonomic balance, blood pressure (BP), gas exchange, gut, heart, and vascular tone, which refers to the diameter of the blood vessels that regulate BP, and possibly facial muscles. (8) Medulla oblongata controls HR through the vagus, the tenth cranial nerve: vagal tone reduces HR by inhibiting the sinoatrial node, the heart's pacemaker.HR is an involuntary mechanism, the medulla oblongata receives information from the rest of the brain: including the central autonomic network (CAN), with the prefrontal cortex playing a leading role. (9,10) Indeed, the cortical regulation of the CAN has been well described; there are both direct and indirect pathways (involving the cingulate and insula cortices, amygdala, hypothalamus and medulla oblongata) linking the frontal cortex to autonomic motor circuits responsible for both the excitatory and inhibitory effects on the heart. Therefore, the moment-to-moment control of HR reflects complex interactions between physiology, emotion and cognition. (9,10) Three approaches are used to monitor HRV: time-domain and frequency-domain measures are linear in nature, whereas complexity measures offer a nonlinear approach. The simplest approach is to summarize differences in the interbeat interval as a mean and SD, so-called time-domain measures. Second, a spectral analysis allows frequency domain indices to be calculated and describes the interbeat intervals as a complex sum of waveforms. The variance in HR is distinguished in terms of the underlying rhythms that occur at different frequencies. There is growing evidence that frequency-domain indices measure the functioning of the autonomic nervous system.

The high-frequency measure is more easily understood as it is said to reflect parasympathetic nervous systems. (11,12) In contrast, low frequency is less readily interpreted as it is influenced by both the parasympathetic nervous system (PNS) and baroreceptor activity. A frequently considered index is the LF/HF ratio, which is said to reflect the balance between PNS and the sympathetic nervous system activity. (13,14) The autonomic nervous system (ANS) modulates HR. Activation of the sympathetic nervous system increases HR and decreases HRV, whereas parasympathetic nervous activity decreases HR and increases HRV. (15) HRV is extracted from an electrocardiogram (ECG) measurement by measuring the time intervals between the R-peaks of successive heartbeats, which is considered the gold standard. HRV in healthy individuals is strongest during resting periods, whereas during stress and physical activity, HRV is decreased. The magnitude of heart rate variability is different between individuals. High HRV is commonly linked to young age, good physical fitness, and good overall health. (16,17)

MATERIAL AND METHOD

It was a Case Control Study,conducted over one Year duration (August 2023 to August 2024) at Jawahar Lal Nehru Medical College and Associated Group of Hospitals fifty prehypertensive and fifty hypertensive subjects aging 30-50 years selected from the non-communicable disease clinic, department of General Medicine, JLN medical college, Ajmer. Fifty healthy controls selected from the group of technicians, staffs, residents and patient's attendants.

Sample Size Calculation

Prevalence of Hypertension assumed to be 22% according to seed the approximate sample size calculated to be140, which further rounded off to 150.

Study Tools

Hematological parameter (Mean Platelet Volume), Heart Rate Variability Parameters (Time domain indices-MeanRR,SDNN, RMSSD, NN50, Pnn50), (Frequency domain measures- LF, HF, LF/HF)

Inclusion Criteria

Hypertensive Subjects with minimum period of 1 -5 years. Prehypertensive and hypertensive individuals in the age group of 30 to 50 years including both genders. Subject without any cardiovascular complications. Subject who has given written informed consent. The subject come from indoor and outdoor department of J.L.N hospital.

Exclusion Criteria

Subjects having Diabetes mellitus,Endocrine disorders, Renal failure, Smoking history, Alcoholism history, Bronchial asthma, Neurological disorders, Pregnancy, Subjects who have not given written informed consent were excluded from study.

Study Procedure

Subject allowed to sit comfortably for 5 minutes, blood pressure measurements done by both palpatory and auscultatory methods in sitting position in upper arm. Blood sample collection done using aseptic techniques, venous blood collected by venipuncture at cubital fossa, blood transferred to sterile EDTA vials and sent for complete blood count. Complete blood count done at central laboratory department of pathology by complete blood count machine ABX Micro 60 Hematology Analyser-HORIBA.MPV recorded from complete blood count reports.

The SA node receives inputs mainly from parasympathetic and sympathetic nervous system. Other determinants which also influence the input are hormone, baroreceptor reflex, sleep – wake cycle, thermoregulator, stress and meals. Analysis of HRV is done with the R-R intervals by time domains & frequency domains.

Heart rate variability assessed by computerized machine RMS polyrite. Subject asked to be seated make himself/herself comfortable and relaxed for 5-10 minutes. Informed and written consent obtained from subjects. The laboratory room kept calm with temperature around 25-28 degree Celsius. Prior to the procedure subject asked to empty bladder and have breakfast. Recording done in supine, awake and eye closed position. Heart rate and blood pressure were recorded for all the subjects. The ECG findings with normal sinus rhythm for a period of 5 minutes were taken for analysing HRV. The Task Force European Society of Cardiology guidelines were followed while recording and analysing HRV data. Time domain and frequency domain indices are used to analyse heart rate variability. For calculating time domain indices each QRS complex is identified and the normal to normal (N-N) intervals (the intervals between adjacent QRS complex) is determined.

Statistical Analysis

Mean, standard deviation, and p value were used to explain the characteristics of the study. Data analysis was done using SPSS software version 20. Student independent t test used to find out significant differences. Pearson correlation test used to find out correlation between HRV parameters and mean platelet volume in prehypertensive and hypertensive individuals. P value <0.05 considered significant.

RESULT

[Table-1]: Values of different time domains in control versus prehypertensive

Time domain	Control		Prehypertensive		p value
	Mean	SD	Mean	SD	
Mean RR	0.75	0.09	0.62	0.05	<0.01*
SDNN	67.03	11.91	35.96	6.35	<0.01*
RMSSD	61.22	8.83	33.69	6.51	<0.01*
NN50	85.76	29.81	35	29.72	<0.01*

[Table-2]: Values of different time domains in prehypertensive versus hypertensive

Time domain	Prehypertensive		Hypertensives		p value
	MEAN	SD	MEAN	SD	
RR	0.62	0.05	0.52	0.09	<0.001*
SDNN	35.96	6.35	24.47	6.82	<0.001*
RMSSD	33.69	6.51	16.02	7.95	<0.001*
NN50	35	29.72	9.34	8.44	<0.001*
pNN50	12.07	7.26	2.38	1.84	<0.001*

[Table-3]: Values of different frequency domains in control versus prehypertensive

Frequency domain	Control		Prehypertensive		p value
	Mean	SD	Mean	SD	
LF n.u	36.30	8.83	61.45	7.52	0.00**
HF n.u	57.10	9.04	38.70	6.98	0.00**
LF/HF	0.60	0.13	1.62	0.42	0.00**

[Table-4]: Values of different frequency domains in prehypertensive versus hypertensives

Frequency domain	Prehypertensive		Hypertensive		p value
	Mean	SD	Mean	SD	
LF n.u	61.45	7.52	68.70	10.32	0.00**
HF n.u	38.70	6.98	37.55	6.34	0.016**
LF/HF	1.62	0.42	2.17	0.64	0.00**

[Table-5]: Value of mean platelet volume in control versus prehypertensive

Parameter	Control		Prehypertensive		
MPV	Mean	SD	Mean	SD	p value
	6.32	0.31	8.24	0.57	0.00**

[Table-6]: Value of mean platelet volume in prehypertensive versus hypertensive

Parameter	Prehypertensive		Hypertensive		
MPV	Mean	SD	Mean	SD	p value
	8.24	0.57	9.79	0.88	0.00**

[Table-7]: Correlation between Mean MPV and time domains in prehypertensive

Time domain	Correlation coefficient	P value
Mean RR	-0.325	0.21
SDNN	-0.289	0.098
RMSSD	-0.061	0.569

[Table-8]: Correlation between Mean MPV and frequency domains in prehypertensive

Time domain	Correlation coefficient	P value
LFn.u	0.163	0.295
HFn.u	-0.497	0.04
LF/HF	0.236	0.223

[Table-9]: Correlation between Mean MPV and time domains in Hypertensive

Time domain	Correlation coefficient	P value
Mean RR	-0.232	0.149
SDNN	-0.105	0.312
RMSSD	-0.385	0.004**

[Table-10]: Correlation between Mean MPV and frequency domains in Hypertensive

Time domain	Correlation coefficient	P value
LFn.u	0.296	0.065
HFn.u	-0.301	0.102
LF/HF	0.158	0.219

DISCUSSION

Present study included prehypertensive and hypertensive individuals, heart rate variability used to assess autonomic functions in study groups. The study aimed to find out the relationship between mean platelet volume and heart rate variability.

When systolic and diastolic blood pressure compared in prehypertensive (SBP 130 ± 3.01, DBP 83.32 ± 3.01) and control groups (SBP 112± 5.79, DBP 73.6 ± 3.30), the mean values were high in prehypertensive group in comparison to control groups. Prehypertensive with high blood pressure more likely to develop hypertension.

Mean resting heart rate was higher in prehypertensive group (91.6±6.43) in comparison to control group (73.32±3.99) and was still higher in hypertensive group (99±5.96). This finding is similar to that shown by Singh et al 1998 (17). Increased heart rate in prehypertensive and hypertensive is due to increased sympathetic discharge. As baroreceptor reflex regulate blood pressure for short term, continuous elevated blood pressure in prehypertensive and hypertensive make baroreceptors less sensitive to pressure change which leads to reduced afferent impulse to vasomotor centre in medulla leading to increased cardiac and vascular sympathetic centre activity (increases heart rate).

Heart rate variability is used to assess autonomic functions in control, prehypertensive and hypertensive groups, five minutes period heart rate variability used to analyse time domain and frequency domain parameters and comparison made in all three groups.

Time domain parameters used were mean RR, SDNN, RMSSD, NN 50, pNN50. The mean value of SDNN, RMSSD, NN50, pNN50 in prehypertensive were 35.96±6.35,33.69±6.51,35±29.72, 12.07±7.26 respectively. The mean Values of time domain in prehypertensive were significantly less than those in control group(p<.0.01). Similar findings were observed by Nambiar S et al (18), GK PAL et al (19).

The mean value of SDNN, RMSSD, NN50, pNN50 in hypertensive were 24.47±6.82, 16.02±7.95, 9.34±8.44, 2.38±1.84 respectively. The mean Values of time domain in hypertensives were significantly less than those in prehypertensive and control group(p<0.001). Similar findings were observed by Huikeri et al 1996 (20), Radaelli et al 1994 (21). RMSSD, pNN50 are sensitive makers of parasympathetic activity and the mean values of time domain were reduced in both prehypertensive and hypertensive patients as compare to control subjects ,may due to increased sympathetic activity and decreased parasympathetic activity. LF, HF and LF/HF ratio were analysed as frequency domain. Mean values of LF and HF in prehypertensive were 61.45 ± 7.52 and 38.7 ± 6.98 respectively. These values were significantly (p < 0.01) higher and lower respectively in comparison to controls, decrease in HF value is due to reduced parasympathetic activity. The mean value of LF/HF was 1.62 ± 0.42 and it was markedly increased in prehypertensive individuals (p<0.01) than in controls. All these indicate imbalance sympathetic and parasympathetic divisions in prehypertension. These findings were like that observed by GK Pal t al (2010) (19) Nambiar et al, (18) Urooj et al. (22)

The increased LF/HF may be due to proportionate rise in sympathetic activity and reduction in parasympathetic activity. In hypertensives, the mean value of LF was 68.70 ± 10.32 and it was increased (p< 0.01), then in prehypertensive individuals suggesting increased sympathetic activity in hypertension. The mean value of HF n.u was 37.55 ± 6.34 and was markedly reduced in hypertensive individuals (p < 0.01) than in prehypertensive individual. This implies reduced parasympathetic activity in hypertension. The average values of LF/HF (2.17 ± 0.64) were significantly (p<0.01) higher in hypertensive individuals (p< 0.01) than in prehypertensive individuals. These findings are like those observed by Nirmala Natarjan et al (A study on analysis of HRV in

hypertensive individuals), Virtanen R et al, (23) Xie et al, (24) Urooj et al, (22) Menezes J R et al. (25)

The average value of mean platelet volume in prehypertensive individuals were 8.24 ± 0.57 was higher ($p<0.01$) than in controls The mean platelet volume in hypertensive individuals was 9.79 ± 0.88 which was higher ($p<0.01$) than in prehypertensive individuals. These findings were like that observed by Nadar et al,(26) Gomi et al, (27) Varol et al. (28) They demonstrated that mean platelet volume was increased in prehypertensive and hypertensive individuals than in normal individuals. Guven et al (29) also reported that mean platelet volume was markedly increased in prehypertension than in normal individuals. Inanc T et al noticed a positive relationship between mean platelet volume and blood pressure. (30)

In prehypertensive mean platelet volume (MPV) is negatively correlated with SDNN, with increase in MPV SDNN decreases and statistically not significant ($r= -0.289$, $p= 0.098$) also MPV is negatively correlated with RMSSD with increase in MPV RMSSD decreases and statistically not significant ($r= -0.061$, $p= 0.569$).

In hypertensives MPV is negatively correlated with SDNN, with increase in MPV SDNN decreases and statistically not significant ($r= -0.105$, $p= 0.312$) also MPV is negatively correlated with RMSSD, with increase in MPV RMSSD decreases and statistically significant ($r= -0.385$, $p= 0.004$). Although the significant correlation of MPV was found with RMSSD in hypertensives only, negative correlation of MPV with SDNN and RMSSD indicate decrease in parasympathetic activity with increase in MPV in hypertensive and prehypertensives.

In prehypertensives MPV is negatively correlated with HF, with increase in MPV HF decreases and statistically not significant ($r= -0.497$, $p= 0.04$). H.F is a marker of parasympathetic activity. Hence this shows that increased MPV may lead to reduce parasympathetic activity in these individuals. MPV is positively correlated with LF, with increase in MPV, LF increases and statistically not significant ($r= 0.163$, $p= 0.295$). This implies that as mean platelet volume increases it may lead to sympathetic overactivity and increase in LF. In a study conducted by Mills Dc et al he showed that increased level of adrenaline activates platelets leading to increased mean platelet volume. Hence there occurs a positive correlation between sympathetic activity and mean platelet volume.

In hypertensives MPV is negatively correlated with HF, with increase in MPV HF decreases and statistically not significant ($r= -0.301$, $p= 0.102$). MPV is positively correlated with LF, with increase in MPV, LF increases and statistically not significant ($r= 0.296$, $p= 0.065$). HF indicate parasympathetic activity while LF indicate sympathetic activity. These findings indicate that as MPV increases, there is decrease in parasympathetic activity and sympathetic overactivity in hypertensives. Lande K et el (31) in his study showed that mean platelet volume is altered in sympathetic overactivity producing changes in HRV.

Present study showed that increase in mean platelet volume is associated with increased sympathetic activity and decrease in parasympathetic activity in both prehypertensive and hypertensives. Hence, MPV may also be used as an indicator of sympathovagal imbalance or sympathetic hyperactivity along with HRV in those individuals.

Limitations Of The Study

Mean platelet volume depends on other parameters also like time interval between venous sample collection and sample analysis, anticoagulant used in sample collection vial, sample storage temperature, analysis method. Platelet activation may be caused by other factors which are not measured in this study. Sample size of present study was small. The correlation between mean platelet volume and HRV parameters could have been established if the study was conducted among larger sample size. Study conducted at single city hospital hospital only.

CONCLUSIONS

The present study showed that in prehypertension and hypertension there is increased sympathetic and decreased parasympathetic activity which indicated by significant alteration in resting heart rate variability parameters.

Autonomic alteration occurs early in disease as shown by changes in HRV indices in prehypertensive. With the disease progression autonomic alteration (increased sympathetic and decreased parasympathetic activity) increases as variation in HRV parameters were more in hypertensive in comparison to prehypertensive. Due to increased sympathetic activity Mean platelet volume increased in prehypertensive and hypertensives and both are at risk of developing cardiovascular & cerebrovascular complications. Increase in mean platelet volume is associated with sympathetic hyperactivity and decrease in parasympathetic activity in both prehypertensive and hypertensives since appropriate correlations were obtained between MPV and HRV indices. Early diagnosis of hypertension in the prehypertensive state is important since sympathetic hyperactivity occurs early and it is associated with target organ damage, increasing their risk of developing cardiovascular complications. Increase in mean platelet volume which predicts cardiovascular and cerebrovascular complications may also be used as an indicator of sympathetic overactivity in prehypertensive and hypertensive individuals. When compared to HRV, mean platelet volume is a simple and easy way of evaluating the cardiovascular risk and hence it can be included in the routine blood investigations of prehypertensive and hypertensive individuals to detect the complications at the earliest during their follow up.

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