Correlation of hsCRP level with heart rate variability in prehypertensive subjects.

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Background of the study

High-sensitivity C-reactive protein (hs-CRP) is a common risk factor for developing cardiovascular disease.The objective of this study was to determine the relationship of C-reactive protein (CRP) and blood pressure (BP) across the range of BP categories including prehypertension. To evaluate the putative effect of systemic inflammation on heart rate variability (HRV), we analyzed in these patients the possible relationship among HRV parameters and high sensitivity C-reactive protein (hsCRP).

Methods: This cross-sectional study was conducted on 148 study subjects of both genders, with 74 prehypertensive subjects and 74 normotensive subjects. co-relation of hsCRP, and heart rate variability in prehypertensive and normotensive subjects was analysed

Results : The baseline parameters analyzed heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), mean arterial pressure (MAP), and rate pressure product (RPP). There was a significant difference between the groups ($p = 0.000$). In the control group, the mean hsCRP level is 5022.30 ng/ml, with an SD of 3361.50 ng/ml, while the preHTN group exhibits a significantly higher mean hsCRP level of 8998.73 ng/ml, along with an SD of 2945.60 ng/ml. We found There was significant difference in Standard Deviation of Normal-to-Normal intervals(SDNN),Root Mean Square of Successive Differences (RMSSD), NN50: normal-to-normal intervals that differ by more than 50 milliseconds , proportion derived from dividing NN50 (pNN50) , VLF: Very Low Frequency , Low-Frequency (LF) power , High-Frequency (HF) power components of prehypertensive subjects when compared to normotensive subjects.

Conclusion : Our study demonstrates a clear correlation between elevated C-reactive protein levels and blood pressure. Prehypertensive individuals were more likely to have a CRP rise than normal blood pressure individuals

Key words –hsCRP, Heart Rate Variability, Prehypertension

Introduction

About three quarters of all deaths from non-communicable diseases occur as a result of hypertension, which is also called cardiovascular disease.(1). A major contributor to mortality in low and middle income nations, hypertension has recently emerged as a major issue in public health. People of all ages experience hypertension, however it is more common among the elderly. In 2003, the term "prehypertension" was initially coined as one of the blood pressure categories by the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure(2). An independent strong positive linear connection with "cardiovascular disease (CVD)" morbidity and death exists for prehypertension, which is a precursor to hypertension. Additional research suggests a link between prehypertension and chronic renal illness(3, 4). In low- and middle-income nations, the percentage of young people with prehypertension is on the rise, and this condition progresses to hypertension as people get older (5) One out of four persons on Earth suffer from hypertension, and experts project that number will rise to 1.56 billion in 2025, a 60% increase from the current 1.36 billion (6).

The exact processes by which hypertensive individuals develop cardiovascular disease remain unclear; nevertheless, mounting evidence implies that inflammation may serve as a key mediator in this process. An increased risk of cardiovascular disease is an independent predictor of higher levels of inflammatory markers like C-reactive protein (CRP), making this finding all the more crucial. (7) Several atherogenic diseases, such as hyperglycemia, insulin resistance, and overt diabetes, have been associated with elevated CRP levels.(8)

A marker of chronic inflammation, C-reactive protein (CRP) has been linked to events related to coronary heart disease (CHD) and stroke. There has been conflicting evidence regarding CRP and hypertension in the research. The Multi-Ethnic Study of Atherosclerosis found a positive correlation between C-reactive protein and hypertension.(9)

The concentration of C-Reactive Proteins (CRP) in plasma increases one hundred times in reaction to injury, infection, or inflammation, compared to the minute quantities found in healthy individuals. As the first acute phase protein to be identified, C-reactive protein (CRP) is named for its capacity to precipitate the somatic C-polysaccharides of Streptococcus pneumonia.(10)In reaction to interleukin-6 (IL-6) and interleukin-1ß (IL-1ß), the liver mostly produces CRP. Its stability, short half-life (19 hours), and little value fluctuation between fresh and frozen versions make it an excellent biological marker. (11)

Atherosclerosis begins and advances in part due to chronic low-grade inflammation; C-reactive protein, an acute phase protein, is a surrogate predictor of cardiovascular events in both healthy and coronary heart disease patients (12).Coronary risk assessment may benefit from including C-reactive protein testing (13).Yet, CRP might also help find people who are more likely to die suddenly from cardiac arrest (SCD).Variability in heart rate is a predictor of sudden cardiac

death (SCD) and an indication of autonomic dysfunction(14).We have explored the possibility of a connection between C-reactive protein and heart rate variability.

Materials And Methods

This analytical cross-sectional study did not proceed with any procedures until all patients had given written informed consent. The research was carried out in the department of physiology's research lab at Index Medical College & Hospital in Indore, M.P., India. The study was approved by the institute's scientific advisory committee and human ethics committee.

Participants

There were two groups involved in the research: one comprising healthy volunteers and the other comprised prehypertensive individuals recruited from the Outpatient Unit of the Department of General Medicine at Index Medical College & Hospital in Indore. In all, 320 participants gave their informed consent to participate in the screening. Using an automatic blood pressure monitor (CH432B, Citizen Systems Japan Co., Ltd, Tanashi, Tokyo, Japan) after 5 minutes of rest in a seated position, blood pressure was recorded three times in the outpatient department (5-minute intervals between each recording).For the final reading, we averaged these three recordings. After taking into account the inclusion (systolic BP < 140 mm Hg, diastolic BP < 90 mm Hg, aged 20-60 years) and exclusion (history of chronic illness, CVDs, diabetes, primary autonomic insufficiency, or kidney diseases; sportspersons; under medication for prehypertension and chronic illness) criteria, 148 subjects (74 considered normotensive and 74 prehypertensive) were recruited for the study. Each participant in the study was given a written explanation of the study's procedures and asked for their permission to participate in writing.

Methods

After a light meal, participants were instructed to report to the Department of Physiology at least two hours later, at approximately 9:00 A.M. Based on the 5-minute electrocardiography (ECG) recording while the subject was lying down, the resting heart rate variability (HRV) was calculated. The ML870 Power Lab 8/30 AD Instruments Data Acquisition Systems were used to digitize the ECG signals, which were then stored for offline analysis using the computer software Kubios HRV, version 2.1, Kuopio, Finland. After identifying the R-wave, the program calculated all of the RR intervals from the ECG data. After obtaining the oscillatory curve by plotting IBIs on a time scale, two methods—time-domain analysis and frequency-domain analysis—were used for analysis.

Following HRV, participants' venous blood was collected in a plain red vial while adhering to all aseptic protocols. After centrifugation, the serum was collected and kept for future use. hsC-reactive protein was measured .

The statistical analysis was carried out using the Windows version of the Statistical Package R. Mean ± SD is how the data is presented. A Kolmogorov-Smirnov test was used to analyze the data for normality. At $P \leq 0.05$, the null hypothesis was rejected.

Results

The table 1 , depicts a comparison between controls and the preHTN group, in terms of various cardiovascular parameters. The parameters analyzed include heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), mean arterial pressure (MAP), and rate pressure product (RPP). The analysis reveals that the preHTN group exhibits higher values for all parameters compared to the control group.

Table 1: Between group comparison of cardiovascular Parameters

Sl.no	Parameter	Control (n=74) (Mean $\pm$ SD)	preHTN (n=74) (Mean $\pm$ SD)
1	HR (bpm)	84.39 $\pm$ 6.32	86.86 $\pm$ 4.04**
2	SBP (mmHg)	109.54 $\pm$ 5.56	123.84 $\pm$ 2.43***
3	DBP (mmHg)	73.68 $\pm$ 3.93	84.16 $\pm$ 4.18***
4	PP (mmHg)	35.86 $\pm$ 7.06	39.68 $\pm$ 5.12***
5	MAP (mmHg)	85.63 $\pm$ 3.09	123.84 $\pm$ 2.43***
6	RPP	9247.00 $\pm$ 868.09	10763.54 $\pm$ 659.58***

HR: Heart Rate SBP: Systolic Blood Pressure DBP: Diastolic Blood Pressure PP: Pulse Pressure MAP: Mean Arterial Pressure RPP: Rate Pressure Product

**=P<0.01   (Statistically (Moderate) significant)   *** = P<0.00 (Statistically (Highly) significant)

Table 2 presents a comparative analysis of heart rate variability (HRV) parameters between individuals with preHTN and a control group, offering insights into autonomic function and its potential implications for cardiovascular health. Prehypertension, a condition associated with an increased risk of developing hypertension and cardiovascular diseases, is investigated here. Notable differences are observed in several HRV parameters, including reduced overall HRV (SDNN), diminished parasympathetic activity (RMSSD), enhanced parasympathetic modulation (NN50 and pNN50), increased Very Low Frequency power (VLF), higher normalized Low-Frequency power (LFnu), decreased normalized High-Frequency power (HFnu), and a higher LF:HF ratio in prehypertensive individuals compared to healthy controls.

Table 2: Between group comparison of heart rate variability

Sl.no	Parameter	Control (n=74) (Mean ± SD)	preHTN (n=74) (Mean ± SD)
1	SDNN	38.52 ± 24.41	31.65 ± 16.78*
2	RMSSD	67.38 ± 70.35	33.65 ± 19.95***
3	NN50	13.49 ± 15.53	22.42 ± 27.63*
4	pNN50	3.92 ± 5.22	6.35 ± 8.12*
5	VLF (ms2)	66.76 ± 93/71	127.85 ± 204.01*
6	LFnu	48.37 ± 13.71	63.64 ± 17.61***
7	HFnu	51.32 ± 13.69	36.30 ± 17.59***
8	TP	1333.03 ± 1841.25	1117.65 ± 1583.16
9	LF:HF	1.13 ± 0.74	2.65 ± 2.01***

SDNN: Standard Deviation of Normal-to-Normal intervals   RMSSD: Root Mean Square of Successive Differences   NN50:   normal-to-normal intervals that differ by more than 50 milliseconds pNN50: proportion derived from dividing NN50 by the total number of normal-to-normal intervals   VLF: Very Low Frequency   LFnu: normalized measure of the Low-Frequency (LF) power component   HFnu: normalized measure of the High-Frequency (HF) power component.
**= P<0.01   (Statistically (Moderate) significant)   *** = P<0.00 (Statistically (Highly) significant)

Table 3: Between group comparison of Inflammatory marker (hsCRP)

Sl.no	Parameter	Control (n=74) (Mean ± SD)	preHTN (n=74) (Mean ± SD)
1	hsCRP (ng/ml)	5022.30 ± 3361.50	8998.73 ± 2945.60***

hsCRP: High Sensitive C reactive Protein **= P<0.01   (Statistically (Moderate) significant) *** = P<0.00 (Statistically (Highly) significant)
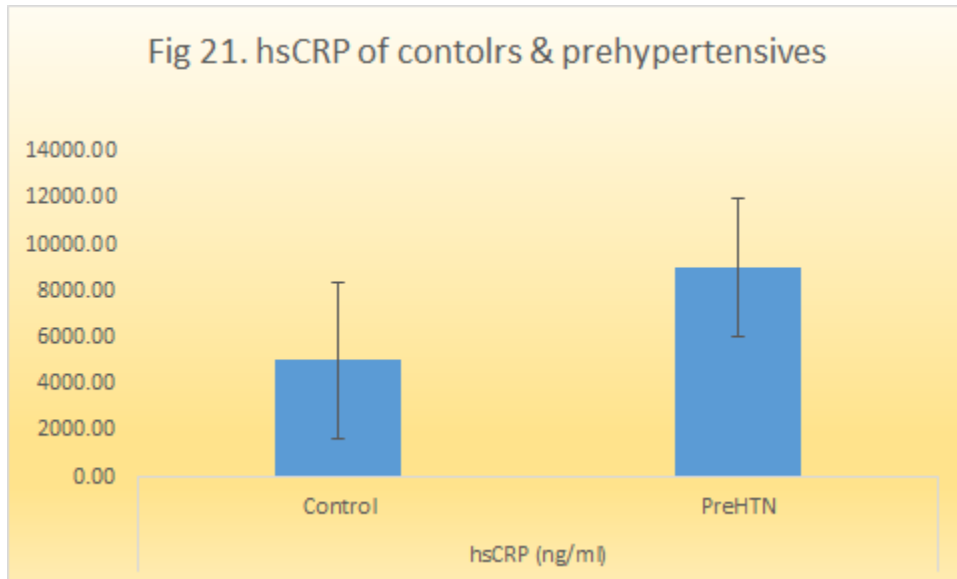
Fig -1 CRP of Controls & Prehypertensive

Table 3 & Fig 1, presents a comparative analysis of the inflammatory marker High-Sensitive C-reactive Protein (hsCRP) in control group and the pre-hypertension (preHTN) group. The table showcases the mean values and standard deviations (SD) of hsCRP levels measured in ng/ml for each group. In the control group, the mean hsCRP level is 5022.30 ng/ml, with an SD of 3361.50 ng/ml, while the preHTN group exhibits a significantly higher mean hsCRP level of 8998.73 ng/ml, along with an SD of 2945.60 ng/ml. The substantial difference in hsCRP levels is underscored by the signifying an exceptionally low p-value of less than 0.00, indicating a highly significant statistical distinction between the two groups.

Table 6: Correlation between CRP and HRV parameters in preHTN

Sl.no	Parameter	hsCRP (ng/ml) (r value)
1	LF nu	0.54
2	HF nu	- 0.54
3	LF:HF	0.52

LFnu: normalized measure of the Low-Frequency (LF) power component   HFnu: normalized measure of the High-Frequency (HF) power component. hsCRP: High Sensitive C reactive Protein HRV: Heart Rate Variability.

Fig 30. Association of hsCRP with LF nu in preHTN

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Fig 31. Association of hsCRP with HF nu in preHTN

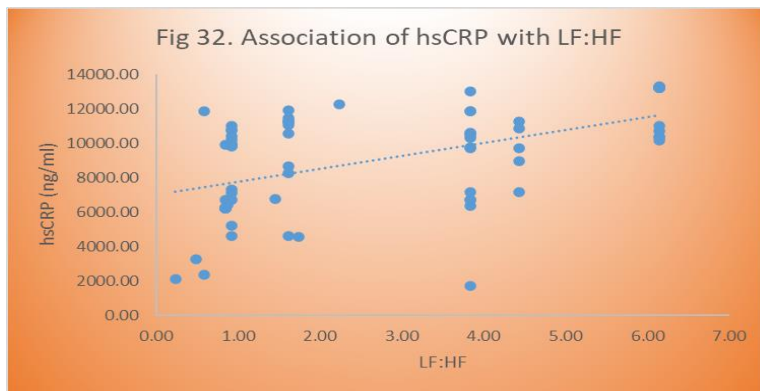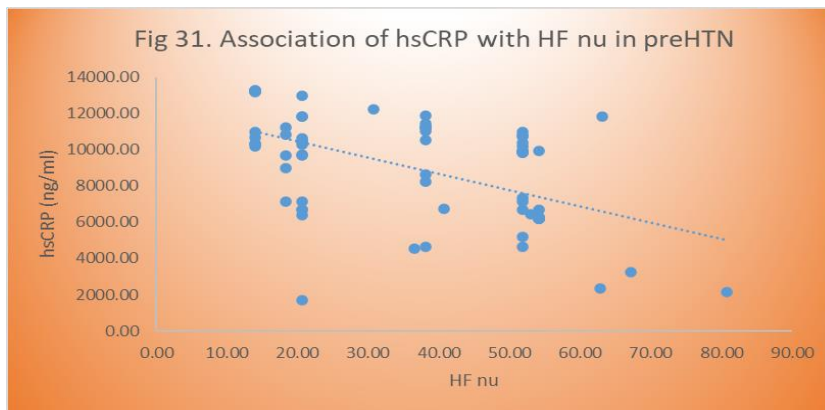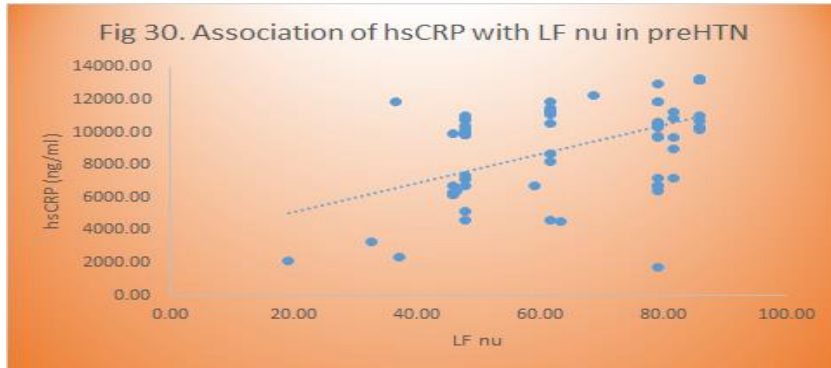Fig 32. Association of hsCRP with LF:HF

Table 6 & Fig 2-4 shows that, In individuals with prehypertension (preHTN), the results showed significant correlations: a positive relationship between hsCRP and LF nu (r = 0.54, p < 0.01), a negative association between hsCRP and HF nu (r = - 0.54, p < 0.01), and a positive correlation with LF:HF (r = 0.52, p < 0.01). These findings suggest that elevated hsCRP levels are linked to altered autonomic balance and potentially increased cardiovascular risk in prehypertensive individuals. This highlights the clinical importance of monitoring hsCRP and HRV in this population, shedding light on the influence of systemic inflammation on cardiac

autonomic modulation and encouraging further research to explore underlying mechanisms and potential therapeutic implications.

Discussion

This study set out to do three things: evaluate cardiac autonomic function using HRV, quantify inflammation with C-reactive protein, and investigate the link between the two.This study's most important conclusion is that prehypertensive young individuals exhibited CV risk markers, higher C-reactive protein levels, and reduced cardiovagal regulation. The two groups of participants were statistically indistinguishable with respect to age and sex. This study found that compared to normotensive patients, hypertension patients had a slightly higher mean body mass index (BMI), which was statistically significant (P<0.05).One major indicator of future CV morbidity is reduced cardiovagal modulation. The findings of this study revealed decreased cardiovagal modulation in prehypertensive young adults. Factors that increase the risk of cardiovascular disease include being overweight or obese, not getting enough exercise, having high blood pressure, total cholesterol, triglycerides, and a decrease in cardiovagal modulation (15).There was a statistically significant difference in CV risk variables between young adults with prehypertension and normotension, according to our study. We observed a slight correlation between prehypertension and cardiovagal modulation, but after adjusting for CV risk variables, we were unable to pinpoint the precise relationship between MAP (prehypertension) and RMSSD. Prehypertension has less of an effect on cardiovagal modulation, or vice versa.

The significant increase in high-sensitivity C-reactive protein (CRP) levels between the prehypertensive and control groups in our study points to a strong correlation between inflammation and prehypertension. Consistent with previous studies showing a link between high hsCRP levels and cardiovascular disease, our study highlights the significance of comprehending the pathological alterations in this setting. An important study conducted by Ridker et al. (17) shown that high levels of hsCRP are associated with an increased risk of cardiovascular events and also used hsCRP as a biomarker to predict when such events will occur.This discovery highlights the practical importance of our findings and suggests that those with prehypertensive conditions, defined by high blood pressure and now elevated hsCRP levels, would be more prone to future cardiovascular issues.

Additionally, hsCRP levels are independently linked to the occurrence of hypertension, according to a study done by Sesso et al. in a large cohort of women. This lends credence to the idea that increased hsCRP levels, which denote inflammation, can be directly responsible for the onset of hypertension. Hypertension prevention strategies should prioritize early identification of high-risk patients, especially those with increased hsCRP levels (18).The relationship between prehypertension and elevated hsCRP levels has complex mechanisms. Hypertension is characterized by endothelial dysfunction and arterial stiffness; elevated hsCRP levels suggest chronic low-grade inflammation that may exacerbate these conditions. The ways in which inflammation can lead to increased blood pressure, impaired endothelial function, vasoconstriction, and oxidative stress have been explained in several studies, including those by Guzik and Touyz and Gimbrone and García-Cardeña.

Prehypertensive people had significantly higher hsCRP levels than the control group, highlighting the significance of understanding the link between inflammation and prehypertension. Our results support the need of monitoring and managing CRP levels in prehypertensive individuals to avoid the onset of hypertension and its associated cardiovascular consequences. Several studies have highlighted CRP as a useful marker for predicting cardiovascular risk. These results, when coupled with changes in lifestyle, have the potential to further decrease inflammation and, in the long run, the likelihood of hypertension and its related health problems.

In this study, we examine the relationship between inflammation and cardiovascular health by measuring HRV parameters (LFnu and HFnu) and High Sensitive C-reactive Protein (hsCRP). Our findings may provide insight into possible pathophysiological changes and their correlations. A balanced autonomic nerve system is produced by both LFnu and HFnu, which show moderate values of 0.54 and -0.54, respectively. The direction of the link between hsCRP and HRV measures, however, is the most important component. Possible relationships are indicated by a positive correlation with LFnu and a negative correlation with HFnu. Previous research has highlighted the correlation between high hsCRP levels and an abnormally high LF/HF ratio, suggesting sympathetic dominance and autonomic dysfunction—both of which are frequently linked to cardiovascular diseases (19).On the other hand, the hypothesis that increased inflammation levels are associated with lower parasympathetic activity and a negative correlation with HFnu suggests that cardiovascular health is not good. These results highlight how inflammation affects cardiovascular health and autonomic regulation of the heart. More research, possibly involving hsCRP value-specific analyses, is necessary to fully comprehend these linkages and their effects on cardiac health (20).

Conclusion

Inflammatory pathology is seen in both pre-hypertension and hypertension. Hypertension and its precursor, pre-hypertension, both raise the risk of cardiovascular disease. In persons who do not have a history of hypertension, our study demonstrates a clear correlation between elevated C-reactive protein levels and blood pressure. Prehypertensive individuals were more likely to have a CRP rise than normal blood pressure individuals. It was with blood pressure that the correlation between CRP and prehypertension was most pronounced. In pre-hypertension, our results imply that CRP is dependent on BP; thus, serum CRP estimation can be a good diagnostic and prognostic marker for the diagnosis of prehypertensives; and, by measuring the CRP level, an appropriate treatment module can be framed to prevent the occurrence of hypertension and cardiovascular disorders.

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