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ENHANCED BLOOD PRESSURE VARIABILITY IN A HIGH CARDIOVASCULAR RISK GROUP OF AFRICAN AMERICANS

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Abstract

Background—High blood pressure (BP) levels in African Americans elicit vascular inflammation resulting in vascular remodeling. BP variability (BPV) correlates with target organ damage. We aimed to investigate the relationship between inflammatory markers and BPV in African Americans.

Methodology—36 African Americans underwent 24-hr ambulatory BP monitoring (ABPM). BPV was calculated using the average real variability (ARV) index. Fasting blood samples were assayed for high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor- α (TNF- α) and white blood cell (WBC) count.

Results—Significant association between hs-CRP and 24-hr systolic variability ($r = 0.50$; $p = 0.012$) and awake systolic variability ($r = 0.45$; $p = 0.02$) was identified after adjusting for age, BMI and 24-hr mean BP. ABPM variables were compared between the hs-CRP tertile groups. In Post-hoc analysis, there was a significant difference in 24-hr and awake periods for both systolic and diastolic variability among the groups. TNF- α and WBC count showed no associations with ABPM variables.

Conclusion—hs-CRP is associated with systolic variability and higher levels of hs-CRP are related with greater BPV. Higher inflammatory status influences wider fluctuations in systolic BP which in turn could facilitate early progression to target organ damage independent of absolute BP levels in African Americans.

Keywords

Blood pressure variability; high sensitivity C-reactive protein; African Americans; tumor necrosis factor- α ; white blood cells; inflammation

Introduction

The prevalence of hypertension is significantly higher among African Americans compared to Whites (1;2). As a precursor to cardiovascular disease (CVD), hypertension is an important contributor to racial disparities in mortality rate (3;4). Most CVD risk factors, including

hypertension, have been recognized to promote a pro-inflammatory state (5;6). Among them, elevated blood pressure (BP) levels in the prehypertensive range have been related to many circulating inflammatory markers, (7;8) independent of other risk factors, which suggests that BP below the hypertension range may potentially be a pro-inflammatory condition (9). It has also been shown that African-Americans have impaired endothelial function as a result of elevated inflammatory and oxidative stress states with a decrease in vascular nitric oxide levels (10;11). Although African American men and women experience the highest rates of morbidity and mortality including target organ damage, the definitive underlying reasons for these statistics are diverse and remain uncertain. The importance of conventional CVD risk factors such as hyperlipidemia, hypertension, diabetes and obesity accounting for some of the racial disparity in these disease states is well established (12;13). Recent evidence highlights the presence of other less studied factors such as variation in BP and low grade systemic inflammation of the vasculature which may also play a role in the development and progression of CVD (14;15).

Variations in BP values are commonly noticed but not well recognized and often underappreciated in the population (16). BP variability (BPV) is the result of a complex interaction between external environmental stimuli and the response to cardiovascular control mechanisms. As a result of the complex interaction between extrinsic and intrinsic factors, BP undergoes continuous fluctuations over a 24-hr period. The development of non-invasive ambulatory BP monitoring (ABPM) has permitted the assessment of BPV as a surrogate marker for the complex interaction between external and internal factors and has revealed the clinical importance of daily fluctuations in BP. Evidence suggests that BPV may be equally as important as the absolute BP value itself (16). Elevated BPV during a 24-hr ABPM session is associated with an increased risk of target organ damage (17;18), early atherosclerosis and cardiovascular events (17).

Previous studies have shown that hypertension and high BPV translates into target organ damage by eliciting a vascular inflammatory remodeling process and that low grade systemic inflammation may be an additive phenomenon contributing to target-organ damage which may contribute to BPV itself (18;19). Yet, data on the association between inflammatory markers and BPV in humans is very limited, especially in African Americans. We chose to study the relationship between inflammatory markers and BPV in a cohort of African Americans with a range of BP values. The purpose of this study was to investigate the relationship between inflammatory markers -high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor- α (TNF- α) and white blood cell count (WBC count) with BPV calculated using the average real variability (ARV) index in African American participants.

Materials and Methods

Participants

This study included 36 African American men (N= 6) and women (N= 30) between the ages 40 – 75 years who were normotensive (N= 14; BP: <120/80 mmHg), prehypertensive (N= 22; BP: 120/80–139/89) mmHg based on office BP measurements taken in accordance with JNC-7 guidelines on three separate occasions. For inclusion in the study, participants were required to be sedentary (regular aerobic exercise $\leq$ 2 day per week), non-smoking, non-morbidly obese (BMI $\leq$ 40 kg/m²), not on lipid-lowering medication. Based on medical history, participants were excluded if they had history of coronary artery disease, congestive heart failure, renal insufficiency, diabetes, hypercholesterolemia, liver disease, lung disease, an intercurrent infection or other inflammatory conditions within the past 3 months. Participants were not on antihypertensive medications or anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs, steroids, etc. at the commencement of the study. All demographic and clinical data were collected prospectively. Participants were recruited via mailed brochures

and local newspaper advertisements. Upon response, the participants were contacted by telephone for screening to assess their initial eligibility. Each participant gave written informed consent following the explanation of study protocol during their first laboratory visit. The protocol was approved by the Temple University Institutional Review Board.

Screening

To ensure the eligibility of all qualified participants, three screening visits were completed prior to inclusion in the study. Screening visit one consisted of a 12-hr overnight fasting blood sample to measure blood chemistry, complete blood count and lipid profile. Any individual who had total cholesterol > 240 mg/dL, fasting blood glucose > 126 mg/dL and BMI > 40 kg/m² was excluded from the study. Screening visits two and three required all qualified participants to undergo a physician administered physical examination and echocardiogram bicycle stress test to confirm that participants displayed no evidence of cardiovascular, pulmonary, or other chronic diseases. Following the successful completion of the physical examination, the eligible participants participated in a 6 week dietary stabilization class.

Dietary Stabilization

Participants underwent dietary stabilization for 6 weeks. They were instructed by a registered dietitian on the American Heart Association (AHA) Dietary Guidelines for Healthy American Adults. This diet consisted of ~ 55% of total daily calories from carbohydrates, 15% from protein, and < 30% from fat, with saturated fat ≤ 10% of total calories, sodium content ≤ 3–4 g/day, and cholesterol intake < 300 mg/day. Participants were required to follow this diet for the duration of the study and maintain within 5% of their study entry body weight for the duration of the program. Compliance to the prescribed diet was monitored by completion of a 3-day food record at the conclusion of dietary stabilization.

24-Hour Ambulatory BP monitoring

Participants underwent 24-hr ABPM using a noninvasive monitor (Space Labs Medical Inc., Model 90219, Redmond, WA) beginning on a morning of each participant's typical day (a routine day at home and work), with the exclusion of Friday through Sunday. BP measurements and heart rate (HR) were obtained at 30-min intervals while awake (06:00–22:00hr) and at 60-min intervals during sleep (22:00–06:00hr). Prior to each session, the monitor was calibrated against a conventional sphygmomanometer. Participants were instructed not to exercise prior to or during the 24-hr ABP period and to pause momentarily during the day and maintain their general body position during each BP measurement. Throughout the 24-hr recording period, participants were required to record their activity and emotional status at the time of each BP measurement. Awake and sleep periods were defined according to self-reported sleep times recorded in participants' diaries. Upon completion of the 24-hr ABP period, data were transferred from the monitor to a laboratory computer for analysis using the Space Labs analysis software. Values outside of the normal physiological range were automatically edited by the analysis software (BP ≥ 260/150 mmHg, pulse pressure > 150 mmHg and heart rate > 200 beats/min). Furthermore, BP values that differed by > 15 mmHg from any other BP readings within a 1-hr time frame were manually edited if they could not be explained by changes in activity or emotional status, as noted in the participant's activity log (< 1 % of all readings). Recordings were not considered valid and were excluded from analyses if > 20% of ABP readings were not obtained.

Analysis of ABPM Data

24-hr, awake, and sleep mean values were calculated for systolic BP (SBP), diastolic BP (DBP), and HR.

The % dip in BP during sleep was calculated as: $(\text{Awake BP} - \text{Sleep BP}) \times (100/\text{awake BP})$.

BPV was calculated using the average real variability (ARV) index:

$$ARV = \frac{1}{N-1} \sum_{k=1}^{N-1} |BP_{k+1} - BP_k|$$

where, N is the number of valid BP measurements and BP_{k+1} and BP_k represent two successive BP measurements. The ARV index is inspired by the total variability concept of real analysis in mathematics. The rationale for selecting the ARV index for BPV calculations is based on previous studies that have reported that the ARV index is a more reliable index for determining the prognostic significance of BPV. It overcomes the pitfalls of the commonly used standard deviation (SD) which only accounts for the dispersion of values around the mean and not the order of each BP measurement obtained during the 24-hr ABPM period(20).

Blood sampling and Assays

In the morning following a 12-hr overnight fast, blood samples for hs-CRP and TNF- α analyses were drawn into EDTA tubes. Samples were centrifuged at 3000 rpm for 20 min at 4°C, following which plasma samples were transferred to plastic micro tubes and stored at -80°C until assay.

Plasma EDTA samples for hs-CRP were sent to Quest Diagnostics Inc. as per the standard instructions. TNF- α levels were measured using a commercially available Kit (Pierce, Thermo Fisher Scientific, Waltham, MA) according to the manufacturer's instructions. Absorbance was read on an ELISA plate reader (Spectra Max Microplate Reader (Molecular Devices, Sunnyvale, CA), set at 450 nm and 550 nm. The absorbance values obtained at 550 nm values were then subtracted from at 450 nm values to correct for optical imperfections in the microplate. The sensitivity of the assay kit was < 2 pg/ml. Inter and intra-assay coefficients of variation were 5.9% and 7.1%, respectively.

Statistical analysis

All data are expressed as mean $\pm$ the standard error of the mean (SEM). Categorical variables are described in terms of frequencies and percentages. The distribution of all variables was examined using the Shapiro-Wilk test of normality, and homogeneity of variances was determined using Levene's test. Pearson correlation coefficients were used to examine the strengths of relationships between hs-CRP and ABPM BPV indices. Linear regression models were applied to examine whether inflammatory markers were related to BP or BPV after adjusting for age, BMI and 24-hr mean BP. The relationship of each clinical and BP variable were tested using univariate and multivariate regression analyses.

The American Heart Association (AHA) and Centers for Disease Control (CDC) define hs-CRP relative risk categories (low, average, high) as < 1.0, 1.0 to 3.0, and > 3.0 mg/L, respectively based on an aggregation of population studies (21). An additional analysis was performed by categorizing the participants into one of the hs-CRP tertiles to determine their relationship to 24-hr and awake SBP variability. A value of $p < 0.05$ was considered significant. Data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL).

Results

Baseline Demographics, Bio-humoral and ABPM Data

A total of 36 African American participants who met the study criteria were enrolled in the study and formed the study population. The participants' average age was 52 ± 7 yrs with an average BMI of 31.7 ± 5 kg/m² and average total cholesterol of 195 ± 30 mg/dl. The mean office SBP and DBP of the participants was 126 ± 13 mmHg and 80.4 ± 8.7 mmHg, respectively. Other demographic and bio-humoral data are reported in Table 1. Descriptive statistics of ABPM data (systolic, diastolic & HR) and ARV indices for Awake, sleep and 24-hr are reported in Table 2.

The correlation between ABPM variables with inflammatory markers (hs-CRP, TNF- α and WBC) are provided in Table 3. The average hs-CRP for the group was 3.03 mg/L which falls within the high relative risk category. Correlation analysis showed that hs-CRP levels correlated significantly with 24-hr and awake systolic ARV, diastolic ARV and MAP ARV indices. TNF- α levels and WBC count did not significantly correlate with any of the BP variability indices as seen in Table 3.

The relationship between hs-CRP and BPV remained significant after adjusting for the effects of age, gender and BMI. Multiple linear regression showed that there was a significant relationship between hs-CRP and 24-hr systolic ARV ($r = 0.50$; $p = 0.012$) and awake systolic ARV ($r = 0.45$; $p = 0.02$) as seen in Figures 1 and 2.

The values of clinical, laboratory, and hemodynamic characteristics according to the hs-CRP tertile are provided in Table 4. There was a statistical difference in BMI, HDL Cholesterol and Clinical Diastolic BP levels between the three hs-CRP risk groups with p values 0.040, 0.036 and 0.010 respectively. We also noticed 24-hr and awake DBP, 24-hr and sleep MAP, 24-systolic and diastolic ARV, awake and sleep ARV variables ($p = 0.010$ and 0.020 , 0.020 and 0.040 , 0.014 and 0.006 , 0.041 and 0.010) to be different among the groups and that high levels of hs-CRP are associated with greater BPV.

Discussion

In the present study, we investigated the relationship between inflammatory markers (hs-CRP, TNF- α and WBC count) and BPV in African American participants. We showed that there was a significant relationship between hs-CRP levels and ARV, a novel BPV index. Here we report that hs-CRP level significantly correlates with 24-hr and awake systolic variability after accounting for age, BMI and absolute BP parameters in African American participants. hs-CRP accounted for 25% of 24-hr systolic ARV variance as opposed to accounting for only 9% of variance of 24-hr SBP. hs-CRP accounted for 20% of awake systolic ARV variance as opposed to accounting for only 9% of awake SBP. We also showed that the highest hs-CRP tertile group had the greatest 24-hr systolic ARV, 24-hr diastolic ARV, awake systolic ARV, awake diastolic ARV compared to the other tertile groups indicating that the high risk group have a greater variability compared to the other two groups. Together, these results suggest that hs-CRP may be a better predictor of CVD risk through BPV than absolute BP values in African Americans.

Although hypertension has been clearly established as a predictor of target-organ damage and a determinant of prognosis, the notion that daily variability in BP levels may also impact prognosis is somewhat a novel concept. BPV, which is the result of a complex interaction between external environmental stimuli and the response of cardiovascular control mechanisms, is enhanced in hypertension and increases with increased severity of hypertension (22). However, the prognostic significance of BPV has been evaluated only in different cohorts

of initially untreated or treated hypertensive participants (23) and in general population (24), but not in African Americans. The influence of BPV, measured by noninvasive monitoring and its association with inflammatory markers is not yet clear (25). Measured BP varies due to a large number of factors such as measurement technique, accuracy of equipment, and multiple subject factors such as stress and anxiety. Even if these factors are controlled, BP is subject to biological variation from beat to beat, minute to minute and day to day. Each BP value is therefore analogous to a single sample from a population of BP values (16). However, it is a person's mean BP over months and years that is thought to determine his or her risk of CVD. In order to increase the precision of the estimated BP, clinical diagnosis is based on the average of 2 or 3 measurements taken after resting for 5 minutes in a non-stimulating environment according to JNC 7 (26). Despite such standardized procedures, BP remains highly variable, both within and between individuals of similar demographics.

BPV has been shown to increase with increasing BP values and correlates with target-organ damage, independent of absolute BP values (27). The appropriateness of SD as an index of BPV has been recently questioned (28). Indeed, the SD only reflects the dispersion of values around the mean and does not account for the order in which BP measurements are obtained. As an alternative, a new index has been proposed, ARV, which was inspired by the total variability concept of real analysis in mathematics and is sensitive to the individual BP measurement order (20). Using SD and ARV as indices of BPV, Mancia et al showed that ARV, but not SD may predict CVD risk (29).

CRP is a 115-kDa pentamer expressed almost exclusively by hepatocytes as part of the non-specific acute-phase response to tissue damage, infection and inflammatory conditions (30). hs-CRP is a marker and a mediator of vascular inflammation. It is associated with the future development of hypertensive disease and can predict mortality and major adverse cardiac events both in the healthy and in hypertensive participants (31;32). Experimental data suggest that elevated BP may stimulate a pro-inflammatory response and that endothelial inflammation may also lead to changes in the arterial wall that characterize the hypertensive state (33). Both hs-CRP and BP are independent determinants of CVD risk, and in combination, these parameters have been reported to have additive predictive value (34).

Some reports have shown a significant association between inflammatory markers and elevated BP in apparently healthy participants (35;36). However, there is little evidence to demonstrate an association between inflammation and BPV in humans. Recently, Abramson et al. demonstrated positive associations between markers of inflammation and BPV in healthy and normotensive adults (37). To our knowledge, this is the first report on the relationship between hs-CRP and 24-hr and awake systolic variability in African Americans. In the present study, we observed an association between BPV index and hs-CRP, which is a key marker and a mediator in the inflammatory process in African Americans and there was no association between TNF- α levels and WBC with either BP or BPV index. Reasons for this are admittedly unclear yet. Although it is possible that some inflammatory markers are better related to BPV than to absolute BP levels, as reported in another recent study (38), such speculations would need additional confirmation.

The exact mechanisms explaining the clinical significance of BPV are, as yet, unclear. However, various mechanisms may be involved in the association between BPV and CVD in African Americans. One of the putative mechanisms is hemodynamic stress on the vessel wall. Steeper BP variations may produce a greater stress on the vessel wall and in turn trigger an inflammatory vascular response leading to vasoconstriction and a further increase in vascular shear stress on the endothelial cells which may result in endothelial dysfunction and vascular damage. Thus, BPV may induce subclinical inflammatory vascular response which in turn may lead to impairment of endothelial function and vascular remodeling. Shear stress-induced

platelet activation and subsequent hypercoagulability may lead to cardiovascular events. Neurohumoral activation, which is increased in those with increased BPV (39), may also increase the risk for CVD.

It must be noted that there are some limitations to our study. First, our sample size is small but this was due to the exclusion of diabetics, smokers, participants on anti-hypertensive and lipid lowering medication, with cardiovascular disease. This was done to create as homogenous group as possible and to ensure lack of confounding variables that may influence BP measures or inflammatory marker levels. It must be noted that even with a relatively small sample size, due to heightened inherent systemic inflammatory status in this cohort, we observed significant associations between inflammatory markers and BPV. Second, it may seem that the high levels of hs-CRP in this cohort may be consequential to the high BMI and influence BPV, however, in our analyses we accounted for BMI along with the other potential confounding factors. Third, only associations are reported. These associations potentially point to areas for investigating mechanisms. Despite these limitations, we believe that the study provides new scientific information.

In conclusion, we show that BPV is more strongly associated with low grade systemic inflammation than absolute BP values. hs-CRP is associated with systolic variability and higher levels of hs-CRP are related with greater BPV. These results suggest that in our cohort of putatively normal African Americans with BP levels below the hypertensive range, a subclinical impairment of endothelial function due to heightened inherent systemic inflammatory status places them at a higher cardiovascular risk and influences wider fluctuations in systolic BP which in turn could facilitate early progression to hypertensive target organ damage and related cardiovascular events independent of absolute BP levels. Of course, this speculation requires confirmation by mechanistic studies.

The clinical implications of these relationships are presently unclear in the absence of longitudinal studies. However, an interesting speculation is that an evaluation of hs-CRP and BPV might contribute to risk stratification in African Americans. Understanding the mechanisms and the extent to which BP is variable is crucial since the large variability of BP impacts diagnosis and progression of hypertension and a wide variety of its complications through vascular inflammation.

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Figure 1. The relationship of 24-hr systolic BP, 24-hr systolic BP variability with hs-CRP
 24-hr SBP, 24-hr Ambulatory Systolic Blood Pressure; 24-hr ARV, 24-hr Ambulatory Blood Pressure Average Real Variability.

Figure 2. The relationship of Awake systolic BP, Awake systolic BP variability hs-CRP
 Awake SBP, Awake Ambulatory Systolic Blood Pressure; Awake ARV, 24-hr Ambulatory
 Blood Pressure Average Real Variability.

Table 1

Descriptive statistics for study population (n = 36)

Variable	Mean $\pm$ SEM
Age years	52 $\pm$ 7
Male (%) / Female (%)	6(20%) / 30(80%)
BMI (kg/m ²)	31.70 $\pm$ 5.00
Total Cholesterol (mg/dL)	195.00 $\pm$ 30.00
Triglycerides (mg/dL)	86.80 $\pm$ 40.00
LDL-C (mg/dL)	115.00 $\pm$ 30.00
HDL-C (mg/dL)	63.00 $\pm$ 19.00
Serum Creatinine(mg/dL)	0.83 $\pm$ 0.11
Office Systolic BP (mmHg)	126.00 $\pm$ 13.00
Office Diastolic BP (mmHg)	80.40 $\pm$ 8.70
Hemoglobin (g/dL)	13.50 $\pm$ 0.36
WBC (10 ³ / μ L)	6.78 $\pm$ 0.46
hs-CRP (mg/L)	3.03 $\pm$ 2.30
TNF- α (pg/ml)	46.20 $\pm$ 22.00

Data are expressed as mean $\pm$ SEM unless otherwise indicated. BMI, body mass index; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; BP, blood pressure; HR, heart rate; hs-CRP, high sensitivity C-reactive protein; TNF- α , tumor necrosis factor-alpha; WBC count, white blood cell count.

Table 2

Descriptive Statistics for Ambulatory BP

	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)
Awake	128 ± 12	80 ± 9	97 ± 9	76.1 ± 10.2
Sleep	117 ± 9	69 ± 7	86 ± 9	68.4 ± 10.1
24-hr	127 ± 11	79 ± 8	95 ± 9	74.3 ± 9.8
Awake ARV	8.03 ± 1.3	7.0 ± 1.4	7.2 ± 1.6	7.4 ± 2.6
Sleep ARV	8.5 ± 3.03	7.2 ± 3.6	7.9 ± 4.6	5.5 ± 3.2
24-hr ARV	8.4 ± 1.2	7.1 ± 1.5	7.5 ± 2.0	7.1 ± 2.1

Data are expressed as mean ± SEM unless otherwise indicated.

SBP: Systolic BP DBP: Diastolic BP; MAP: Mean Arterial Pressure; HR: Heart rate; ARV: Average real variability.

Table 3

Correlation table of ABPM variables with inflammatory markers

<i>ABPM parameters</i>	<i>hs-CRP(mg/L)</i>	<i>TNF-α(pg/ml)</i>	<i>WBC($10^3/\mu$L)</i>
24-hr SBP(mmHg)	0.314 [†]	0.191	-0.183
24-hr DBP(mmHg)	0.275	0.232	-0.318
24-hr MAP(mmHg)	0.317	0.211	-0.239
24-hr HR(bpm)	0.276	0.248	0.025
Awake SBP(mmHg)	0.314	0.189	-0.139
Awake DBP(mmHg)	0.460 [†]	0.118	-0.358
Awake MAP(mmHg)	0.277	0.226	-0.234
Awake HR(bpm)	0.446 [*]	0.142	-0.562
Sleep SBP(mmHg)	0.323	0.208	-0.172
Sleep DBP(mmHg)	0.487 [†]	0.100	-0.459
Sleep MAP(mmHg)	0.258	0.230	0.026
Sleep HR(bpm)	0.312	0.343	0.019
<i>Average Real Variability</i>			
24-hr systolic ARV (mmHg)	0.472 [†]	0.164	-0.17
24-hr diastolic ARV(mmHg)	0.368 [*]	0.319	10.029
24-hr MAP ARV(mmHg)	0.500 [†]	0.309	-0.069
24-hr HR ARV(bpm)	-0.154	-0.026	0.206
Awake systolic ARV(mmHg)	0.410 [*]	0.014	-0.039
Awake diastolic ARV(mmHg)	0.376 [*]	0.303	-0.047
Awake MAP ARV (mmHg)	0.500 [†]	0.263	-0.023
AwakeHR ARV(bpm)	-0.114	0.039	0.205
Sleep systolic ARV(mmHg)	-0.34	0.309	-0.109
Sleep diastolicARV(mmHg)	-0.137	0.087	0.055
Sleep MAP ARV(mmHg)	0.087	0.256	0.016
Sleep HR ARV(bpm)	-0.132	-0.139	0.211

Abbreviations as given in Tables 1–3.

*, p < 0.05;

†, p < 0.01

Table 4

Clinical, Laboratory, and Hemodynamic Characteristics According to hs-CRP Tertile

<i>Demographics</i>	hs-CRP tertiles			P value
	<i>Low risk (<1 mg/L)</i>	<i>Avg risk (1–3)mg/L</i>	<i>High risk (> 3mg/L)</i>	
Age, years	52.90± 7.30	54.30± 6.00	51.30± 5.40	0.520
BMI(kg/m ²)	28.60± 3.40	31.60± 6.50	34.20 ± 4.00	0.040
Total Cholesterol(mg/dL)	203.00 ± 24.60	182.00± 25.20	191.50 ±27.60	0.239
Triglycerides(mg/dL)	80.50± 24.00	91.70± 47.00	85.50± 27.00	0.779
LDL-C(mg/dL)	110.00 ± 33.50	105.00± 21.20	114.70 ±25.70	0.696
HDL-C(mg/dL)	76.90± 26.00	58.70 ± 10.70	59.60± 10.60	0.036
Serum Creatinine(mg/dL)	0.79 ±0.12	0.81 ± 0.09	0.87 ± 0.17.00	0.541
Clinic Systolic BP (mmHg)	116.70 ±10.6	124.80 ± 5.90	127.7±13.30	0.077
Clinic Diastolic BP(mmHg)	72.40± 6.20	79.90± 5.30	80.30 ± 6.70	0.010
HR(bpm)	78.00± 3.40	79.30± 8.20	86.8 ± 5.10	0.138
Hemoglobin(g/dL)	13.10± 0.14	13.20 ± 0.11	13.40± 13.00	0.482
WBC (10 ³ /μL)	5.90± 2.20	4.50± 0.74	5.30± 1.40	0.359
hs-CRP(mg/L)	0.71 ± 0.25	1.95± 0.48	5.57 ± 1.70	0.000
TNF-α(pg/ml)	27.10± 20.6	44.70 ± 17.30	59.70± 23.50	0.276
<i>ABP parameters</i>				
24-hr SBP(mmHg)	118.80± 9.50	129.60 ±10.30	127.80 ±12.30	0.089
24-hr DBP(mmHg)	71.80± 5.90	83.70± 7.10	77.70± 9.50	0.010
24-hr MAP(mmHg)	88.40± 6.50	99.24 ± 7.50	95.20± 9.70	0.020
24-hr HR(bpm)	71.50± 10.50	74.80± 11.50	77.20± 8.10	0.434
Awake SBP(mmHg)	120.80 ±10.50	131.00± 11.30	130.10 ±13.30	0.144
Awake DBP(mmHg)	73.80 ± 6.90	85.80± 8.00	79.60± 9.70	0.020
Awake MAP(mmHg)	90.50± 7.70	100.90± 8.00	97.30± 10.10	0.059
Awake HR(bpm)	73.40± 10.90	77.60± 12.50	78.80± 8.20	0.486
Sleep SBP(mmHg)	110.40± 8.60	118.80± 7.50	119.70± 10.00	0.057
Sleep DBP(mmHg)	63.60± 5.00	71.20± 5.30	71.10± 10.10	0.062
Sleep MAP(mmHg)	79.80± 5.20	87.20± 5.70	88.30± 9.60	0.040
Sleep HR(bpm)	64.20± 9.60	68.30± 11.30	71.60± 9.30	0.251
<i>Average Real Variability</i>				
24-hr systolic ARV(mmHg)	7.20± 0.67	8.30± 1.40	8.80± 1.10	0.014
24-hr diastolic ARV(mmHg)	5.90± 0.93	7.40± 1.50	7.50± 0.77	0.006
24-hr MAP AR (mmHg)	6.10± 1.00	7.50± 1.70	8.00± 1.00	0.007
24-hr HR ARV(bpm)	7.40 ± 1.70	7.50 ± 2.00	6.50± 2.20	0.477
Awake systolicARV (mmHg)	7.20± 0.94	7.90± 1.30	8.50± 1.20	0.041
Awake diastolic ARV(mmHg)	5.60± 0.81	7.20± 1.60	7.40± 1.00	0.010
Awake MAP ARV(mmHg)	6.05 ± 1.20	7.20± 1.50	7.80± 0.90	0.010
Awake HR ARV(bpm)	7.60± 1.80	7.70± 2.40	6.80 ± 2.40	0.560
Sleep systolic ARV(mmHg)	7.30± 2.00	8.40± 3.80	9.50± 2.70	0.241
Sleep diastolic ARV(mmHg)	6.80± 2.20	7.60± 4.40	6.60± 2.80	0.768
Sleep MAP ARV(mmHg)	6.00± 2.40	8.30± 4.80	7.50± 2.00	0.302

<i>Demographics</i>	hs-CRP tertiles			P value
	<i>Low risk (<1 mg/L)</i>	<i>Avg risk (1–3)mg/L</i>	<i>High risk (> 3mg/L)</i>	
Sleep HR ARV(bpm)	6.00± 3.80	6.10± 4.20	7.50± 2.00	0.766

Data are expressed as mean ± SEM unless otherwise indicated;

*, p < 0.05

hs-CRP, high sensitivity C-reactive Protein; ARV, Average Real Variability; Avg, Average; SBP, systolic BP, DBP, diastolic BP; HR, heart rate.