Inflammation is related to unbalanced cardiac autonomic functions in hypertension: an observational study

Hipertansiyonda enflamasyon kardiyak otonomik fonksiyonlarda dengesizlik ile ilişkilidir: Gözlemsel bir çalışma

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ABSTRACT

Objective: Inflammation plays a role both in the mechanisms leading to hypertension alone and in the mechanisms leading to atherosclerosis with hypertension. Previous studies have shown the relationship between the autonomic functions and inflammatory system activation. The aim of the study was to evaluate the relationship between inflammation and cardiac autonomic functions in hypertensive patients.

Methods: One hundred twenty one hypertensive patients (mean age 59±11 years, 60 male) and 34 healthy volunteers (mean age 58±11 years, 18 male) were included in the present cross-sectional observational study. The 24-hour ambulatory electrocardiogram recordings were taken using Pathfinder Software. The heart rate variability (HRV) analysis was performed using time domain parameters using the same software. Heart rate turbulence (HRT) parameters, turbulence onset and turbulence slope were calculated with HRT software. Statistical analysis was performed using unpaired t-test or Mann-Whitney U test, one-way ANOVA or Kruskal-Wallis analysis of variance, Chi-square test, and Spearman rank order correlation analysis. The association of hypertension with high sensitivity C-reactive protein (hs-CRP), HRV and HRT was analyzed after adjustment for confounding variables as age and creatinine levels.

Results: The mean hs-CRP was higher, HRV was slightly reduced while HRT was markedly blunted in hypertensive patients in comparison with control group [SDNN; 132±28 vs. 112±34 msec, RMSSD; 27 (23-35) vs. 22 (16-28) msec, TO; -2.80±2.15 vs. -0.96±2.36%, TS; 7.56 (5.24-10.60) vs. 4.65 (2.44-7.26) msec/RR, p<0.01 for all]. All of the HRV and HRT parameters were more deteriorated in the highest tertile hs-CRP group [SDNN; 93±34 msec, RMSSD; 17 (13-22) msec, TO; 0.03±2.22%, TS; 2.43 (1.84-3.89) msec/RR, p<0.05 for all]. There were correlations between hs-CRP and HRV and HRT parameters (SDNN; r=-0.690, RMSSD; r=-0.277, TS; r:-0.417, TO; r=0.267, p<0.05 for all).

Conclusion: There is an inflammatory process in hypertensive patients and inflammation is related with unbalanced cardiac autonomic functions. *(Anadolu Kardiyol Derg 2012; 12: 233-40)*

Key words: Hypertension, inflammation, autonomic nervous system, atherosclerosis, heart rate variability, heart rate turbulence

ÖZET

Amaç: Enflamasyonun, hem hipertansiyona sebep olan mekanizmalarda, hem de hipertansiyonla birlikte ateroskleroza sebep olan mekanizmalar içerisinde role sahip olduğu bilinmektedir. Birçok çalışmada otonom sinir sistemi ile enflamatuvar sistem aktivasyonunun ilişkisi gösterilmiştir. Çalışmanın amacı hipertansif hastalarda enflamasyon ile kardiyak otonomik fonksiyonlar arasındaki ilişkiyi değerlendirmektir.

Yöntemler: Hipertansiyon tanısı almış 121 hasta (ortalama yaş 59±11 yıl, 60 erkek) ile 34 sağlıklı gönüllü (ortalama yaş 58±11 yıl, 18 erkek) eninekesitli gözlemsel çalışmaya alındı. Tüm katılımcılardan 24 saatlik ambulatuvar elektrokardiyogram kayıtları alınarak analizleri Pathfinder programı ile yapıldı. Kalp hızı değişkenliğinin (KHD) zaman bağımlı parametreleri aynı program kullanılarak hesaplandı. Kalp hızı türbülansı (KHT) parametreleri olan türbülans başlangıcı (TO) ve türbülans eğimi (TR) otomatik olarak HRT programı ile hesaplandı. İstatistiksel analiz eşleştirilmemiş t-testi, Mann-Whitney U testi, tek-yönlü ANOVA, Kruskal-Wallis varyans analizi, Ki-kare testi ve Spearman korelasyon katsayısı analizi ile yapıldı. Hipertansiyon ile yüksek duyarlıklı C-reaktif protein (hs-CRP), KHD ve KHT arasındaki ilişki yaş ve kreatinin seviyesi gibi karıştırıcı değişkenler için düzeltildikten sonra analiz edildi.

Bulgular: Sağlıklı gönüllüler ile karşılaştırıldığında, hastaların hs-CRP değerlerinde artış, KHD parametrelerinde hafif, KHT parametrelerinde ise belirgin bozulma tespit edildi [SDNN; 132±28 karşın 112±34 msn, RMSSD; 27 (23-35) karşın 22 (16-28) msn, TO; -2.80±2.15 karşın %-0.96±2.36, TS; 7.56 (5.24-10.60) karşın 4.65 (2.44-7.26) msn/RR, hepsi için p<0.01]. Hastaların hs-CRP değerlerine göre en yüksek tertilde olanların, orta ve düşük

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tertilde olanlara göre tüm KHD ve KHT değerleri daha çok bozulmuş olarak gözlendi [SDNN; 93±34 msn, RMSSD; 17 (13-22) msn, TO; %0.03±2.22, TS; 2.43 (1.84-3.89) msn/RR, hepsi için p<0.05]. Korelasyon analizine göre hs-CRP ile KHD ve KHT parametreleri arasında güçlü bir ilişki saptandı (SDNN; r=-0.690, RMSSD; r=-0.277, TS; r:-0.417, TO; r=0.267, hepsi için p<0.05).
Sonuç: Hipertansif hasta popülasyonunda kardiyak otonomik fonksiyonlardaki dengesizlik enflamasyon ile ilişkilidir.
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Anahtar kelimeler: Hipertansiyon, enflamasyon, otonomik sinir sistemi, ateroskleroz, kalp hızı değişkenliği, kalp hızı türbülansı

Introduction

Inflammation has shown to play a crucial role in the pathogenesis of atherosclerosis (1). Several large-scale epidemiological studies have concluded that plasma levels of high-sensitivity C-reactive protein (hs-CRP), which reflect inflammatory process even in small values, are a strong independent predictor of risk of future myocardial infarction, stroke, peripheral arterial disease, and vascular death among individuals with or without known cardiovascular disease (2, 3).

Heart rate variability (HRV) analysis has been used as a predictor of sudden cardiac death and as a useful tool for assessing autonomic cardiac functions (4, 5). It has been shown to be the strongest independent predictor of the progression of focal coronary atherosclerosis (6). An association of decreased HRV with inflammation has been shown in general population, coronary artery disease, and heart failure; however, no such relationship was reported for hypertension (7-15).

Heart rate turbulence (HRT), which reflects the response of heart rate to a premature ventricular beat (PVB), has been introduced as a new noninvasive tool for cardiac risk stratification. HRT is one of the strongest independent cardiac risk predictors after myocardial infarction (16).

Hypertension is one of the major risk factors of atherosclerosis (17). Recent studies have shown that basic inflammatory biomarkers, such as C-reactive protein, are involved in mechanisms that lead to hypertension (18). Chronic activation of sympathetic nervous system is a key component in the development of hypertension (19). Several studies have suggested a relationship between the imbalance of the autonomic nervous system and the activation of the inflammatory system (20).

However, the underlying mechanisms and the relationship between blood pressure, inflammation, and the autonomic nervous system are complex and still controversial.

The aim of the study was to evaluate the relationship between cardiac autonomic functions and inflammation in patients with hypertension.

Methods

Study design and population

This observational cross-sectional study was carried out in our Cardiology Department of the Faculty of Medicine, Tokat Gaziosmanpaşa University.

Patients with previously diagnosed and treated essential hypertension were evaluated. Patients were selected among those referred to our outpatient clinic between January 2009 and August 2010.

Of 641 hypertensive patients, only 121 of them met the inclusion criteria and were included in the study (reasons for exclusion- coronary artery disease, n=95; hemodynamically unstable valvular heart disease, n=20; atrial fibrillation, n=35; diabetes mellitus, n=89; smoker, n=101, absence of suitable PVBs for HRT analysis, n=105; other reasons, n=75).

The control group was recruited from healthy volunteers seen at the cardiology outpatient clinic.

Patients with coronary artery disease, hemodynamically unstable valvular heart disease, congenital heart disease, atrial fibrillation, heart conduction disorders, branch block, an implanted pacemaker, diabetes mellitus, prior cerebrovascular accident, chronic obstructive pulmonary disease, severe liver or renal insufficiency, acute or chronic inflammatory disease, and malignancy were excluded from the study. Smokers were also excluded from both groups. As per recommendations reported elsewhere, blood spot concentrations of high sensitivity C-reactive protein (hs-CRP) exceeding 8.6 mg/L were considered indicative of acute inflammation and these values were removed from analyses (21). Patients were treated according to the current guidelines (22).

The present study was a single-center study. All examinations were performed at the cardiology clinic.

All subjects gave their informed consent and the study protocol was approved by the ethics committee at our institution.

Study variables

Baseline characteristics were recorded during the direct interview with the patient.

Hypertension was defined as the active use of antihypertensive drugs or documentation of blood pressure more than 140/90 mmHg. Blood pressure measurements were performed twice; during the initial examination and at the time of Holter device attachment. The mean of the two measurements were used for the analysis. All of the measurements were taken from the left arm in sitting position after a 5-minute rest in a quiet room. Smoking was defined as current smoking.

Patients with hs-CRP levels <1 mg/L were categorized as having lower relative risk for cardiovascular events. Those with levels of 1 to 3 mg/L were at intermediate risk, and those with levels >3 mg/L were at higher relative risk (23). The patient group was divided into three subgroups according to the interquartile ranges of their hs-CRP levels. The first quartile (<25%) and the last quartile (>75%) formed lowest and highest tertile groups respectively, while remained (25-75%) formed mid tertile group.

Demographic properties included age and gender, and biochemical parameters included fasting plasma glucose, serum creatinine, lipid profile, thyroid status, erythrocyte sedimentation rate, and white blood cell and hemoglobin levels. Baseline characteristics, systolic and diastolic blood pressures, predictor variables-presence of hypertension and hs-CRP, outcome vari-

ables - HRV and HRT parameters, confounding variables-age and creatinine levels were included the analyses.

Heart rate variability analysis

The 24-hour Holter recordings taken from the patient and control groups were downloaded onto a computer and analyzed with a Reynolds Medical Pathfinder Software, Version V8.255 (Reynolds Medical Hedford, England). All recordings were also examined visually and artifacts were deleted manually. All of the recordings had at least 22 hours of data once the artifacts were deleted. The HRV parameters were calculated by a computer and statistically analyzed. The time-domain HRV parameters used in this study were chosen according to the guidelines of the European Society of Cardiology and North American Society of Pacemaker and Electrophysiology (24), and included mean RR intervals (RR), percentage of differences between adjacent NN intervals that are >50 msec (pNN50), standard deviation of all normal RR intervals (SDNN), standard deviation of the mean of normal RR intervals at each 5-minute segment (SDANN), and root mean squared differences of successive RR intervals (RMSSD). Frequency-domain parameters of HRV were not performed on our 24-hour Holter data due to problems of nonstationarity (24).

Heart rate turbulence analysis

Heart rate turbulence parameters, turbulence onset (TO) and turbulence slope (TS) were calculated automatically by a computer program (HRT View, Version 0.60-0.1 Software Program, Munich, Germany). Abnormal data found between 5 sinus beats before and 15 sinus beats after a PVB as well as visually identified artifacts that the program accepted as a normal PVB were excluded from analysis. TO, an indicator of early sinus acceleration after PVB, was defined as the difference between the mean duration of the first two sinus beats following a PVB and the mean duration of the last two sinus beats preceding a PVB, divided by the mean duration of the last two sinus beats preceding the PVB (25). TS is an indicator of late sinus deceleration after PVB and is defined as the maximum positive slope of a regression line assessed over any sequence of five subsequent RR intervals within the first 20 sinus rhythm intervals after PVB (26).

Blood sampling and biochemical measurements

Blood samples were obtained during admission for routine chemistry including hs-CRP following an overnight fast. The hs-CRP analyses were made using the immunonephelometry method (Dade Behring, Inc., BN Prospect, Marburg, Germany) in our hospital laboratory.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 15.0 (SPSS Inc, Chicago, Illinois). Normally distributed variables presented as mean and SD, otherwise, median and interquartile range values are given. Between-group comparisons of means were performed using unpaired *t* test or Mann-Whitney U test (as indicated), whereas proportions were compared using Chi-square test. Multivariate analysis of covariance (MANCOVA) was used to identify the association of hs-CRP, HRV and HRT parameters with hypertension after adjustment for confounding variables as age and serum creatinine levels. Correlations were assessed using Spearman's test. Differences in variables among hs-CRP tertile groups were assessed using either one-way ANOVA or Kruskal-Wallis analysis of variance, with multiple comparisons performed using Bonferroni's test in case of global statistical significance. P values below 0.05 were considered statistically significant.

Results

Clinical characteristics

One hundred-twenty-one patients (59±11 years, 60 males) and 34 control subjects (58±11 years, 18 males) were included to the study. The mean duration of history of arterial hypertension was 4.2±3.2 years.

There were no significant differences between the patient and control groups with regard to age, sex, systolic and diastolic blood pressures, fasting blood glucose, serum creatinine, lipid profile, thyroid status, erythrocyte sedimentation rate, and white blood cell and hemoglobin levels (Table 1). The patient group had higher hs-CRP levels than controls (p<0.05) (Table 1).

Table 1. Demographic characteristics between the patient and the control groups

Variables	Control group (n=34)	Patient group (n=121)	*p
Sex, male, n (%)	18 (53)	60 (50)	0.730
Age, years	58±11	59±11	0.815
Systolic blood pressure, mmHg	130 (120-140)	130 (120-150)	0.239
Diastolic blood pressure, mmHg	80 (75-85)	80 (73-90)	0.068
Glucose, mg/dL	93±9	97±13	0.168
Creatinine, mg/dL	0.74±0.20	0.83±0.24	0.053
Total cholesterol, mg/dL	199±42	195±39	0.556
LDL-cholesterol, mg/dL	126±34	126±34	0.920
HDL-cholesterol, mg/dL	46±11	49±13	0.252
Triglyceride, mg/dL	172 (100-246)	132 (107-195)	0.430
TSH, µIU/mL	1.67 (1.00-2.40)	1.30 (0.75-2.10)	0.378
Hemoglobin, gr/dL	13.0±0.6	13.2±1.5	0.483
White blood cell, x10^3/µL	6.5 (5.7-7.4)	6.7 (5.9-8.1)	0.403
Erythrocyte sedimentation rate, mm/h	11 (8-16)	12 (8-20)	0.275
hs-CRP, mg/L	1.77±1.53	2.99±2.72	0.003** 0.029**,***

Data are shown as number (percentage), mean±SD, and median (interquartile range) values
*unpaired t-test, Mann-Whitney U test, and Chi-square test
-calculated by log transformed data, *-result of MANCOVA (Age and serum creatinine level were included as covariates)
HDL - high-density lipoprotein, hs-CRP - high sensitivity C - reactive protein, LDL - low-density lipoprotein, TSH - thyroid stimulating hormone

There were also no significant differences between the groups divided according to hs-CRP tertiles with regard to sex, systolic and diastolic blood pressures, fasting blood glucose, lipid profile, thyroid status, and white blood cell and hemoglobin levels (Table 2). Highest tertile group was significantly younger than mid tertile group (p=0.014). Mid tertile group had higher creatinine values than lowest tertile group (p=0.010). Erythrocyte sedimentation rate was significantly higher in highest tertile group than lowest and mid tertile group (p<0.001 for both) (Tables 2 and 5).

None of the patients presented any sustained or non-sustained ventricular tachyarrhythmias as observed with 24-hour ambulatory ECG monitoring. The amount of PVB was not significantly different between the two groups [Control group 7 (3-26); patient group 9 (2-193), p=0.496].

Heart rate variability and heart rate turbulence findings

There were no significant differences between the patient and control groups with regard to RR, pNN50, and SDANN (Table 3). SDNN, RMSSD, and TS were significantly lower and TO were significantly higher in the patient group (Table 3).

All of the HRV parameters were significantly lower in the highest tertile group (p<0.05 for all) (Table 4 and 5). TO was significantly higher and TS was lower in the highest tertile group (p<0.05 for all) (Table 4 and 5).

Correlation analysis

The hs-CRP was negatively correlated with SDNN (r=-0.690, p<0.001), RMSSD (r=-0.277, p<0.001), and TS (r:-0.417, p<0.001) and positively correlated with TO (r=0.267, p=0.001).

Discussion

The major finding of this study was that there is an inflammatory process in hypertensive patients and that inflammation is related to altered cardiac autonomic functions in this population.

Hypertension is one of the leading factors that cause atherosclerosis (17). Several large-scale studies showed that higher blood pressure leads to more severe atherosclerosis (27, 28). McGill et al. (28) concluded that the effect of hypertension on atherosclerosis is principally to accelerate the formation of raised lesions rather than fatty streaks. By the beginning of the fourth decade, hypertensive subjects have approximately double the extent of raised lesions in their coronary arteries as do normotensive subjects. The exact mechanisms that lead to atherosclerosis remain unknown, but endothelial dysfunction caused by the shear stress of high blood pressure might be the one of them. Moreover, inflammatory processes and endothelial dysfunction play a fundamental role in the pathogenesis and progression of arterial hypertension (29).

Table 2. Demographic characteristics between the groups according to hs-CRP tertiles

Variables	Lowest tertile (n=38)	Mid tertile (n=43)	Highest tertile (n=40)	*F/ Chi-square	*p
Sex, male, n (%)	18 (47)	22 (51)	20 (50)	-	0.942
Age, years	57±10	63±10	56±12	4.747	0.010
β blocker	19 (50)	24 (56)	17 (43)	-	0.479
RAS inhibitor	24 (63)	28 (65)	24 (60)	-	0.889
Diuretic	9 (24)	10 (23)	9 (23)	-	0.992
Calcium channel blocker	8 (21)	5 (12)	12 (30)	-	0.118
Acetylsalicylic acid	13 (34)	25 (58)	18 (45)	-	0.096
Statin	9 (24)	12 (28)	6 (15)		0.359
Systolic blood pressure, mmHg	140 (120-145)	130 (120-150)	130 (120-150)	0.936	0.626
Diastolic blood pressure, mmHg	80 (70-90)	80 (70-90)	80 (80-90)	0.445	0.800
Glucose, mg/dL	96±14	95±14	98±12	0.678	0.510
Creatinine, mg/dL	0.75±0.17	0.90±0.26	0.81±0.24	4.470	0.014
Total cholesterol, mg/dL	188±34	195±41	201±36	1.082	0.343
LDL-cholesterol, mg/dL	119±34	125±32	132±35	1.234	0.295
HDL-cholesterol, mg/dL	51±13	49±13	47±12	0.891	0.413
Triglyceride, mg/dL	125 (100-171)	149 (105-195)	136 (115-222)	2.017	0.365
TSH, μIU/mL	1.44 (0.87-2.08)	1.29 (0.70-1.81)	1.28 (0.72-2.15)	0.799	0.671
Hemoglobin, gr/dL	12.8±1.6	13.3±1.3	13.4±1.5	2.011	0.139
White blood cell, $x10^3/\mu L$	6.7 (5.6-8.2)	6.7 (6.0-7.3)	7.1 (6.1-8.6)	1.674	0.433
Erythrocyte sedimentation rate, mm/h	8 (5-12)	12 (9-18)	19 (12-33)	26.615	<0.001

Data are shown as number (percentage), mean±SD, and median (interquartile range) values
*-One-way ANOVA, Kruskal-Wallis analysis of variance, and Chi-square tests
HDL-high - density lipoprotein, hs-CRP - high sensitivity C - reactive protein, LDL - low-density lipoprotein, TSH - thyroid stimulating hormone

Hypertension is also closely related to inflammation. We have already known that basic inflammatory biomarkers are involved in mechanisms that lead to hypertension (18). Pathophysiologically, inflammation has been implicated in both endothelial dysfunction and arterial stiffness in hypertension, with reduced availability of nitric oxide being integral to this process (18). It can be speculated that every mechanism leading to inflammation will accelerate the atherosclerotic process. Our results are compatible with these findings but insufficient to reveal the underlying mechanism.

It has been proposed that the primary abnormality in essential arterial hypertension may be related to sympathetic nervous activation (30). Several studies have reported decreased HRV among hypertensives (31, 32). However, limited data exist about HRT in hypertension. Poreba et al. (33) showed that TO was significantly higher and TS was significantly lower in patients with left ventricular hypertrophy. To our knowledge, this is the first study comparing the HRT parameters between hypertensive and healthy subjects.

Table 3. Comparison of heart rate variability and turbulence parameters between the patient and the control groups

Variables	Control group (n=34)	Patient group (n=121)	*p
RR, msec	807±105	848±126	0.086
pNN50, %	4.3 (1.7-11.2)	2.9 (1.1-7.9)	0.094
SDNN, msec	132±28	112±34	0.002 0.021***
SDANN, msec	111±34	99±33	0.058
RMSSD, msec	32±14	24±11	<0.001** 0.005**,***
TO, %	-2.80±2.15	-0.96±2.36	<0.001 0.001***
TS, msec/RR	9.12±5.50	5.70±4.27	<0.001** <0.001**,***

Data are shown as mean±SD and median (interquartile range) values
*-unpaired t-test and Mann-Whitney U test, **-calculated by log transformed data, ***-result of MANCOVA (Age and serum creatinine level were included as covariates)
pNN50-percentage of differences between adjacent NN intervals that are >50 msec, RMSSD-root mean squared differences of successive RR intervals, RR RR-interval, SDANN-standard deviation of mean of normal RR intervals at each 5-minute segment, SDNN - standard deviation of all normal RR intervals, TO - turbulence onset, TS - turbulence slope

In laboratory experiments, it has been shown that alterations in autonomic nervous system activate proinflammatory cytokines (34, 35). Tracey et al. (36) have shown that both electrical and pharmacological stimulation of the efferent vagal nerve decreases levels of circulating cytokines. It has also been shown that cardiac parasympathetic tone may increase over time as a result of higher circulating CRP (37). A relationship between HRV and inflammation has been demonstrated in patients with congestive heart failure and coronary artery disease (11, 12). Studies of populations free of overt cardiac disease have suggested similar relationships (13-15). Sajadieh et al. (13) have reported recently that several types of HRV parameters assessed by 24-hour ambulatory ECG recording were associated with subclinical inflammation in a middle-aged to elderly healthy white population. They suggested that an imbalance of the autonomic nerve system may be involved in the inflammatory reaction and the interaction might play an important role in the process of atherosclerosis.

Despite to various studies regarding to HRV, there are only two studies evaluating the relationship between inflammation and HRT. Lanza et al. (38) showed a relation between CRP and HRT in patients with unstable angina pectoris. Kop et al. (39) concluded that autonomic dysfunction and inflammation contribute to the increased cardiovascular mortality risk associated with depression. In our study, both HRV and HRT parameters strongly correlated with hs-CRP and were found to be more blunted in hypertensive patients with higher hs-CRP levels. To our knowledge, this is the first study investigating the relation between inflammation and heart rate turbulence in hypertensive population.

There is a complicated relation between hypertension, inflammation, and cardiac autonomic functions. It is very hard to understand the underlying mechanism between these parameters. In our study, blood pressures were not statistically different between controls and hypertensives. There were also no differences in blood pressures between the three tertiles of the patient group and no correlation between blood pressure and hs-CRP levels.

Table 4. Heart rate variability and turbulence parameters between the groups according to hs-CRP tertiles

Variables	Lowest tertile (n=38)	Mid tertile (n=43)	Highest tertile (n=40)	*F/ Chi-square	*p
RR, msec	855±109	909±112	774±118	14.872	<0.001
pNN50, %	4.2 (1.9-9.4)	4.1 (1.6-8.5)	1.6 (0.5-5.0)	7.054	0.029
SDNN, msec	125±35	118±28	93±34	10.857	<0.001
SDANN, msec	112±35	102±25	82±33	9.043	<0.001
RMSSD, msec	25 (19-32)	24 (20-32)	17 (13-22)	14.453	0.001
TO, %	-1.76±2.47	-1.19±2.09	0.03±2.22	6.362	0.002
TS, msec/RR	6.15 (4.13-11.69)	5.30 (4.30-7.92)	2.43 (1.84-3.89)	25.324	<0.001

Data are shown as mean±SD and median (interquartile range) values
*-one-way ANOVA and Kruskal-Wallis analysis of variance tests
pNN50-percentage of differences between adjacent NN intervals that are >50 msec, RMSSD - root mean squared differences of successive RR intervals, RR - RR interval, SDANN-standard deviation of mean of normal RR intervals at each 5 -minute segment, SDNN - standard deviation of all normal RR intervals, TO - turbulence onset, TS - turbulence slope

Table 5. The results of ANOVA posthoc Bonferroni's test and posttests of Kruskal-Wallis test

Variables		Lowest tertile	Mid tertile	Highest tertile
Age, years	Lowest tertile	-	0.064	1.000
	Mid tertile	0.064	-	0.014
	Highest tertile	1.000	0.014	-
Creatinine, mg/dL	Lowest tertile	-	0.010	0.407
	Mid tertile	0.010	-	0.427
	Highest tertile	0.407	0.427	-
Erythrocyte sedimentation rate, mm/h	Lowest tertile	-	0.138	<0.001
	Mid tertile	0.138	-	<0.001
	Highest tertile	<0.001	<0.001	-
RR, msec	Lowest tertile	-	0.102	0.006
	Mid tertile	0.102	-	<0.001
	Highest tertile	0.006	<0.001	-
pNN50, %	Lowest tertile	-	1.000	0.042
	Mid tertile	1.000	-	0.129
	Highest tertile	0.042	0.129	-
SDNN, msec	Lowest tertile	-	1.000	<0.001
	Mid tertile	1.000	-	0.002
	Highest tertile	<0.001	0.002	-
SDANN, msec	Lowest tertile	-	0.545	<0.001
	Mid tertile	0.545	-	0.013
	Highest tertile	<0.001	0.013	-
RMSSD, msec	Lowest tertile	-	1.000	0.003
	Mid tertile	1.000	-	0.006
	Highest tertile	0.003	0.006	-
TO, %	Lowest tertile	-	0.842	0.002
	Mid tertile	0.842	-	0.044
	Highest tertile	0.002	0.044	-
TS, msec/RR	Lowest tertile	-	1.000	<0.001
	Mid tertile	1.000	-	<0.001
	Highest tertile	<0.001	<0.001	-

pNN50-percentage of differences between adjacent NN intervals that are >50 msec, RMSSD-root mean squared differences of successive RR intervals, RR - RR interval, SDANN - standard deviation of mean of normal RR intervals at each 5- minute segment, SDNN - standard deviation of all normal RR intervals, TO - turbulence onset, TS - turbulence slope

According to our results, we can speculate that hypertension itself is rather more important than the level of blood pressure. Gupta et al. (40) found that hs-CRP levels were not correlated with blood pressure levels in subjects with stage-1 and stage-2 hypertension. Tycinska et al. (41) showed that hs-CRP levels were correlated with blood pressures in both optimal treated and suboptimal treated hypertensive patients. Large-scale studies are needed in order to clarify these conflicting results.

Although the serum hs-CRP level has been reported to be reduced by antihyperlipidemic agents (specifically statins) in our study, hypertensive patients had higher hs-CRP levels than controls (42). Moreover, there was an insignificant difference in statin therapy between the groups divided according to hs-CRP tertiles.

Heart rate variability level is significantly affected by beta-adrenergic receptor blockers, but in patients without structural heart disease, HRT was reportedly unaffected by recently initiated beta-blockade (43). In our study we studied HRV and HRT together in order to minimize this effect.

Despite the significant differences in TO and TS compared to controls, the mean of TO and TS values from hypertensive patients were still within normal ranges. In the patient group, TO was abnormal in 37 patients (30%) and TS was abnormal in 29 patients (24%). The relatively middle-aged population of our study may explain the relatively normal TO and TS values because it is known that TO increases and TS decreases with age (44).

Study limitations

The lack of a reference method for studying autonomic dysfunction that could be used as a validation of the method in this study is an important limitation. However, it is already known that HRV and HRT are useful tools for assessing autonomic cardiac functions (4, 44). Unfortunately, this type of data recruited from 24-hour Holter recordings may not be the correct methodology for studying cardiac autonomic responses in a clinically defined group (45). Absence of a power spectral analysis of heart rate to a tightly controlled provocative test instead of long-term recordings obtained in circumstances, which are always difficult to control is one of the other limitations of this study. Antihypertensive agents such as beta- blockers and calcium channel blockers may affect the autonomic nervous system and this may alter HRV and HRT. This potential effect must be taken into account during the interpretation of the results between patients and controls. Waist circumference and body mass index are closely related to serum CRP levels and HRV parameters. Unfortunately, we did not measure these parameters. Finding suitable PVBs for analysis is a common limitation of any HRT study. This will cause some patients to remain excluded from the study. Thus, the study sample will not represent the entire patient population. We did not perform ambulatory blood pressure monitoring which is another limitation of our study. Noninvasive risk predictors of arrhythmias such as HRV and HRT can cause false positive results especially in a middle-aged healthy population (-37% for SDNN, 19% for TO, 5% for TS) (46). The false positive results of our control group are 3% for SDNN, 3% for TO, and 0% for TS. The incidence of these false positive results is lower than previous findings.

Conclusion

There is an inflammatory state in hypertension and higher degrees of inflammation are related to increased deterioration of the cardiac autonomic functions. Hypertension itself may be playing a more important role than the level of blood pressure in respect to inflammation and cardiac autonomic dysfunction.

Conflict of interest: None declared.

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