RESEARCH ARTICLE

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Received: 03.03.2021
Acceptance: 23.07.2021
DOI: 10.18521/ktd.890622

Konuralp Medical Journal
e-ISSN1309–3878
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Systolic Blood Pressure Variability and Its Relationship with Surrogate Markers of Cardiovascular Risk in Hypertensive Patients

ABSTRACT

Objective: Systolic blood pressure variability (SBPV) is a measure of oscillations in SBP for 24 hours. There are conflicting data about the relationship between SBPV and cardiovascular (CV) diseases. In this study we aim to document relationship between SBPV and surrogate markers of CV damage in a hypertensive patient cohort.

Methods: Previously documented hypertension patients were enrolled. Patients with previous documented CV disease, diabetes mellitus and secondary hypertension were excluded. 24-hour ambulatory blood pressure monitoring (ABPM), echocardiography, electrocardiography and cardio-ankle vascular index (CAVI) measurements were performed. SBPV is defined as standard deviation of mean systolic blood pressure readings from ABMP records. The relationship between SBPV and QTc distance, QT dispersion, presence of fragmented QRS, CAVI results were examined.

Results: 64 patients were enrolled [mean age 50±8, 24(37%) were male]. Mean SBPV was 15.12±4.6 mmHg and there was not a significant correlation between SBPV CAVI, QTc measurements of the study patients but there was a significant positive correlation with QT dispersion values (28.6±15.2 msec, p=0.004, p=0.354). When patients were divided into two categories as high SBPV and low SBPV, QT dispersion was consistently longer in high SBPV group (p=0.006).

Conclusions: In hypertensive patients without documented CV disease and signs of hypertensive CV changes on clinical evaluation, SBPV is positively correlated with QT dispersion but high SBPV is not related with aortic stiffness according to CAVI results. These findings might be a sign of occult left ventricular fibrosis and high risk of arrhythmia in hypertensive patients with high SBPV.

Keywords: Systolic Blood Pressure Variability, Hypertension, Cardiovascular Risk.

Hipertansiyon Hastalarında Sistolik Kan Basıncı Değişkenliği ve Kardiyovasküler Riskin Vekil Belirteçleri Arasındaki İlişki

ÖZET

Amaç: Sistolik kan basıncı değişkenliği (SKBD) 24 saatlik kan basıncı takiplerinde sistolik kan basıncının gösterdiği yükselme ve düşme hareketinin bir ölçüsüdür. SKBD ile kardiyovasküler (KV) hastalıklar arasındaki ilişkiyi gösteren çelişkili bilgiler mevcuttur. Bu çalışmada, hipertansif bir kohortta SKBD ile KV hasarı gösteren vekil belirteçler arasındaki ilişkiyi araştırdık.

Gereç ve Yöntem: Esansiyel hipertansiyon hastalarının dahil edildiği çalışmada; belgelenmiş KV hastalık, diabetes mellitus ve sekonder hipertansiyon öyküsü olan bireyler dışlandı. 24 saat ambulatuar kan basıncı ölçümü (AKBÖ), ekokardiyografi, elektrokardiyografi ve kalp-ayak bileği vaskuler indeks (KAVİ) ölçümleri yapıldı. SKBD, AKBÖ kayıtlarında ortalama sistolik kan basıncı değerinin standart sapması olarak tanımlandı. SKBD ile EKG'de QTc mesafesi, QT dispersiyonu, fragmante QRS varlığı ve KAVİ sonuçları karşılaştırıldı.

Bulgular: 64 hasta çalışmaya dahil edildi [ortalama yaş 50±8 yıl 24(%37) erkek]. SKBD (ortalama 15.12±4.6 mmHg) ile KAVİ ölçümü, QTc mesafesi, fragmante QRS varlığı arasında bir korelasyon bulunamadı ancak QT dispersiyonu ile pozitif bir korelasyon izlendi. Hastalar ortanca SKBD değerine göre ikiye bölünüp yüksek ve düşük SKBD olarak ikiye bölündüğünde QT dispersiyonu yüksek SKBD grubunda tutarlı ve anlamlı olarak daha yüksekti (p=0.006).

Sonuç: Belgelenmiş KV hastalıkları ve hipertansif KV değişim belirteçleri görülmeyen hipertansiyon hastalarında SKBD değerleri, QT dispersiyonu ile pozitif korelasyon gösterirken, bir aort sertlik indeksi olan KAVİ ile ilişki görülmedi. Bu bulgular SKBD'si yüksek olan hipertansif hasta grubunda gizli sol ventrikül fibrozis varlığını ve buna bağlı artmış aritmi riskini gösteriyor olabilir.

Anahtar Kelimeler: Sistolik Kan Basıncı Değişkenliği, Hipertansiyon, Kardiyovasküler Risk

INTRODUCTION

Inadequate blood pressure control in hypertensive subjects is documented to be associated with adverse cardiovascular (CV) and cerebrovascular outcomes in numerous studies (1,2). This interaction designated hypertension as the primary target of risk factor modification in CV disease management and prevention. The measurable treatment goal of antihypertensive therapy is generally based on office blood pressure readings, presumed as a hypertensive patient's mean blood pressure for a specific time interval. On the other hand, blood pressure (BP) is not a constant value; instead, it exhibits oscillations through a 24-hour period. This variation in systolic and diastolic BP measurements is studied as an independent risk factor for CV system. Systolic blood pressure variability (SBPV), which is defined as the amount of variation in systolic blood pressure measurements in a certain time period, is documented to be an independent risk factor for end-organ damage and CV outcomes in hypertensive patients in a few studies (3,4). Temporal effects of high systolic blood pressure on the physiologic and histological structure of two main components of CV system, heart and major arterial tree, has been documented with several surrogate markers such as left ventricular mass index (LVMI), pulse wave velocity (PWV) or carotid intima-media thickness (CIMT) (5-7). On the other hand, the relationship between these markers of adverse CV outcomes and SBPV is of interest to answer the question of whether considering SBPV as a goal of treatment in the care of hypertensive patients or not.

In this study, we analyzed the relationship between SBPV and surrogate markers of end-organ damage in the CV system such as cardio ankle vascular index (CAVI), corrected QT distance (QTc), QT dispersion (QTd), and presence of fragmented QRS (fQRS) on ECG in hypertensive patients without CV risk factors and history of CV disease. CAVI is a relatively new marker of arterial stiffness, which differs from PWV as independent from instant blood pressure and heart rate values at the time of measurement (8). Measurements of fQRS, QTc, and QT dispersion are documented as markers of myocardial fibrosis and subsequent abnormalities in depolarization and repolarization in the left ventricle. (9-11)

MATERIAL AND METHODS

Patient Selection: This is a single-center study that had approval from Sakarya University School of Medicine Ethics Committee according to the principles of the Declaration of Helsinki. All the subjects (or their parents or guardians) have given their written informed consent. Sixty-four patients with a history of essential hypertension are selected from our hospital's outpatient cardiology clinic. Patients who have a primary disease leading to hypertension or cardiovascular damage or patients with a history of documented CV disease (coronary artery disease documented with conventional or computed tomography coronary angiography, ischemic or hemorrhagic cerebrovascular disease history), diabetes mellitus, peripheral artery disease, endocrine disorders including thyroid, adrenal and pituitary diseases , neoplastic disease, rheumatologic disease, and vasoactive drug abuse (cocaine etc.) were also excluded. Patients on beta blocker or nondihydropyridine calcium channel blocker therapy were excluded due to possible interaction with QTc measurements. Obesity and smoking status were not exclusion criteria unless they are related with aforementioned diseases because both conditions are common risk factors for essential hypertension. All patients underwent 2D and M-Mode transthoracic echocardiography with appropriate equipment (iE33, Phillips Medical Systems, Andover, Massachusetts). Patients with an ejection fraction lower than 50%, wall motion abnormality, more than mild mitral valve disease and any aortic valve disease, measurements of the aortic root and ascending aorta more than the upper normal limit, left ventricular wall thickness more than 13 mm were excluded.

Ambulatory Blood Pressure Monitoring and Assessment of Blood Pressure Variability: All subjects underwent a 24-hour ambulatory blood pressure monitoring with a validated device. During measurements, subjects were allowed to practice their daily routine except for heavy exercises. BP measurements were obtained every 15 minutes daytime (7 AM-11 PM) and every 30 minutes night time (11 PM-7 AM). SBPV was calculated as the standard deviation (SD) of mean SBP of 24 hours (12). SBPV for daytime and night time were calculated and analyzed separately.

Electrocardiographic Indices and CAVI Measurement: All patients underwent electrocardiographic (ECG) testing after medical history checking. The paper speed of ECG is set to 50 mm/sec, and the voltage amplitude grid is set to 2 mm as 1mV for more sensitive measurements of intervals and wave morphologies. QTc is measured according to Bazett's formula, and dispersion of QTc is defined as the difference between the longest and shortest QTc interval on a 12 lead ECG record. Patients with QRS duration longer than 120 milliseconds were excluded. fQRS is defined as the presence of additional R' waves or a notch in the nadir of the R or S wave (fragmentation) in two contiguous leads corresponding to a coronary territory in a routine 12-lead ECG. All measurements on ECG recordings are made by a single observer to eliminate interobserver variability. We did not have access to computer-based detailed ECG measurement and digital processing systems. CAVI measurements was done with VaSera VS-1000 device (Fukuda-Denshi Company, LTD, Tokyo, Japan).

Statistical Analysis: Data are expressed as mean ± standard deviation (SD) for normally distributed continuous variables, as median and interquartile ranges for skew-distributed continuous variables, and as frequencies for categorical variables. The means for normally distributed continuous variables were compared by independent-samples t-test. Skew-distributed continuous variables were compared using a Mann–Whitney U-test. Patients were divided further into two groups according to the median of the dependent variable SBPV as over-median (High SBPV) and below-median (Low SBPV) groups and were compared with each other for the independent variables again. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed with the SPSS software (version 15.0 for Windows; SPSS Inc., Chicago, IL, USA)

RESULTS

We studied 64 patients (mean age 50 ± 8 years); 24 were male (37%). Mean eGFR was 100.2 ± 8.7 mg/dL, and mean BMI was 29.9±4.6 kg/cm^2 (Table 1).

Table 1. Baseline demographics of study patients and mean values derived from tests in the study protocol.

Age (years)	50 ± 8
Male (%)	24 (37)
eGFR (mg/dL)	100.2±8..7
BMI	29.9 ± 4.6
Smokers (%)	34 (53)
CAVI	7.9±1.2
ABI	1.1±0.1
SBPV	15.2±4.5
QTc (msec)	420.5±29.5
QTd (msec)	28.6±15.2

(SBPV=systolic blood pressure variability, BMI=basal metabolic index, eGFR=estimated glomerular filtration rate, QTc=corrected QT distance according to Bazzett's formula, QTd=QT dispersion, CAVI=cardio-ankle vascular index, ABI=ankle-brachial index)

Mean SBPV was 15.12±4.6 mmHg (14.9±5.1mmHg for daytime and 11.9±5.1mmHg for night time), and there was not a significant correlation between SBPV and glomerular filtration rate (GFR), CAVI, ABI, QTc measurements of the study patients (100.2 ± 8.7, 7.9 ±1.2, 1.1 ± 0.1 and 420.5±29.5 msec, respectively), but there was a significant positive correlation with QT dispersion values (28.6±15.2, p=0.004, ρ=0.354) (Figure 1).

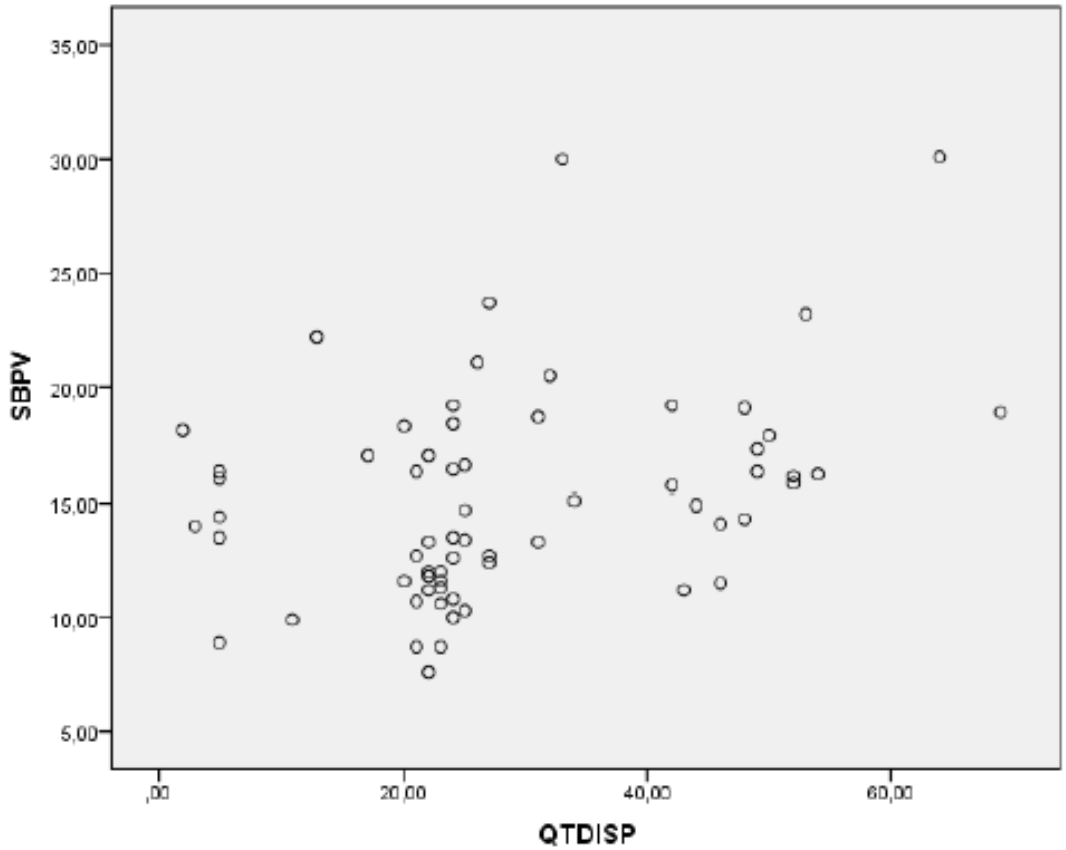

Figure1. SBPV and QTdisp correlation (SBPV=systolic blood pressure variability, QTDISP=QT dispersion)

The mean blood pressure of the study cohort was 131.9±14.9/ 86.1±10.9 mmHg for systolic/diastolic readings. When patients were divided into two categories as high SBPV and low SBPV, there was no statistically significant difference between the two groups in terms of GFR, CAVI, ABI, fQRS, and QTc values (Table 2), but high SBPV group patients had higher QT

dispersion comparing to low SBPV patients (21/23/25, 22/31/49, p=0.006, low and high SBPV values, respectively) (Table 2).

Table 2. Comparison of low and high SBPV patient groups according to laboratory and other test results representative of end organ damage. (Median SBPV=14,55 , Low SBPV is for values < 14,55 , High SBPV is for values > 14,55)

	Low SBPV (n=32)	High SBPV (n=32)	p value
SBPV (mmHg)	11,7±1,8	18,6±3,8	<0.001
Age (years) (mean ± SD)	49±9	51±8	0.261
Smoking status (n, %)	21 (65)	21 (65)	1.000
BMI	29,7±4,1	30,1±5,1	0.908
GFR (ml/min/1.73m$^{2)}$	100±9,3	100,3±8	0.373
QTc (msec)	419,6±25,7	421,3±33,3	0.158
QT d* (25th/50th/75th percentiles)	21/23/25	22/31/49	**0.006**
CAVI	8±1,4	7,8±1,1	0.247
ABI	1,1±0,1	1,1±0,1	0.495
fQRS (n, %)	16 (50)	20 (62)	0.313

*Skew distributed continuous variables are expressed in median and 25th-75th percentiles
(SBPV=systolic blood pressure variability, BMI=basal metabolic index, GFR=glomerular filtration rate, QTc=corrected QT distance according to Bazzett's formula, QTd=QT dispersion, CAVI=cardio-ankle vascular index, ABI=ankle-brachial index, fQRS=fragmented QRS)

DISCUSSION

Our main findings from the study are that SBPV was not associated with GFR, CAVI, ABI, fQRS, and QTc measurements of the study patients, but there was a positive correlation between SBPV and QT dispersion. This correlation was still significant when patients were divided into two groups according to the mean SBPV value of the whole study group as low and high SBPV subgroups. Patients in the high SBPV subgroup had significantly higher QT dispersion comparing to patients in the low SBPV subgroup.

QT dispersion is regarded as a measure of heterogeneity in left ventricular (LV) repolarization and refractoriness. Many factors, including sympathetic activity, history of previous CV diseases, circadian changes in hormonal and humoral elements, may also alter QT interval length and QT dispersion. Cardoso et al. (13) showed that QT dispersion is a predictor of CV events in diabetic patients. In a systematic review from Yitzchok et al. (14) it is suggested that QT dispersion might have a prognostic role in predicting mortality in stroke. These studies have documented that in patients with known cardiovascular risk factors such as diabetes and cerebrovascular event history, QTd might predict future CV events and prognosis. Therefore, the positive correlation of QTd and SBPV from our study results might be indicating a subclinical fibrosis and/or repolarization anomaly in LV and, therefore, an increased risk of CV events, including sudden cardiac death in the high SBPV group. Conversely, this difference might be related to any other factor that causes high SBPV and high QTd values simultaneously (decreased autonomic balance, dysfunctional baroreflex mechanism, etc.) since this is a cross-sectional study, and we cannot document a causal relationship (15). The absence of a relationship between other ECG marker of left ventricular fibrosis (fQRS) and SBPV in our cohort might be indicating that repolarization anomalies in LV appear, before alterations in LV afterload and high SPBV leads to LV hypertrophy (LVH) and fibrosis, as patients with documented LVH on echocardiography were excluded from this study (Table 1 and 2).

CAVI is a novel marker for arterial stiffness and increased CV risk (16,17). In this study, we could not document a relationship between CAVI measurements and SBPV. SBPV is documented to be associated with increased aortic stiffness but not carotid artery stiffness, according to previously published data from Zhou et al. (18). The patient cohort in this study was based on the Maastricht Study, which consists of type 2 diabetes mellitus patients, and PWV was measured to document aortic stiffness. Shin et al. also reported an association between daytime SBPV and arterial stiffness, which was also documented with PWV (19). PWV measurement has several limitations, such as estimation of the length of the arterial system, estimation of a unidirectional pathway for pulse pressure to travel and close relation with instant BP and heart rate at the time of measurement (20). We used CAVI instead of PWV to measure arterial stiffness, which is not affected by the instant BP or heart rate and, we have excluded all patients with documented CV risk factors, including diabetes, from the study. These two factors might have resulted in this conflicting result with the previous data. On the other hand, although statistically not significant, the mean CAVI measurement in the high SBPV subgroup was lower than the low SBPV subgroup. Nevertheless, our patient cohort is extremely small to draw a definite conclusion in this manner.

The significance of fQRS on routine ECG was first studied as a sign of myocardial scar in patients undergoing nuclear stress test (21). In this study, fQRS was documented as a marker of prior myocardial infarction (MI) and left ventricular scar with a higher sensitivity and negative predictive value comparing to the presence of q waves. Later, the prognostic value of fQRS in patients with different aspects of coronary artery disease, including ST-elevation MI and non-ST elevation MI, were studied separately (22,23). In both of these studies, fQRS on ECG was reported as associated with poor prognosis. A small study from Kadı et al. (24) has documented that in hypertensive patients with normal coronary arteries,

left ventricular mass (LVM) and LVMI of patients who had fQRS on their ECG was significantly higher than patients who did not have. This study proved that hypertension-related myocardial fibrosis is associated with fQRS independent of coronary artery disease. Furthermore, Eyuboglu et al. reported an association between fQRS presence and increased blood pressure in the absence of LVH (25). In our study, despite the higher frequency of fQRS among patients in the high SBPV group comparing to the low SPBV group, this difference did not reach statistical significance. This was an unexpected finding considering the aforementioned studies and reports. In the absence of LVH and CAD, with more patients enrolled in the study, we might have documented similar results with previous studies, or it might be postulated that in this selected group of patients, SBPV is not as a powerful predictor of myocardial fibrosis as mean SBP is.

We had planned a larger patient group initially, but due to the SARS-CoV-2 virus pandemic, we had to stop our patient recruitment process earlier than planned, so the low number of patients included in the study is the primary weakness of our study. CAD is excluded based on patients' medical history in this study, and it is impossible to be entirely sure about the absence of CAD in the study patients without a coronary angiography. This weakness might have an effect on study results. Moreover, this is a cross-sectional study, and we cannot derive a causal relationship between SBPV and other markers of CV system disorders.

CONCLUSION

In hypertensive patients without documented CV disease and in the absence of LVH, SBPV is positively correlated with QT dispersion, which might signify an increased risk of ventricular arrhythmia. High SBPV was neither related to increased arterial stiffness nor the presence of fQRS. Further studies are needed to understand the consequences of blood pressure variability on the cardiovascular system and help physicians refine their treatment protocols in patients with hypertension.

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