Relationship between the elastic properties of aorta and QT dispersion in newly diagnosed arterial adult hypertensives

Yeni tanı almış erişkin arteryel hipertansif hastalarda aortun elastik özellikleri ile QT dispersiyonu arasında ilişki

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ABSTRACT

Objective: Afterload is increased in hypertensive patients and increased afterload associated with both ventricular repolarization inhomogeneity and impaired elastic properties of aorta. Thus, we investigated whether QT dispersion (QTd), which is a reflection of ventricular repolarization inhomogeneity, is related to aortic elastic properties in patients with hypertension.

Methods: Overall 113 patients with newly diagnosed hypertension and 25 normal control subjects were included in this cross-sectional case-controlled study. Aortic strain (AS) and aortic distensibility (AD) were calculated echocardiographically from the derived ascending aorta diameters. Electrocardiograms were recorded in all subjects, and QTd and corrected QTd (cQTd) were then calculated.

Results: Patients as compared with control subjects had lower mean AS and AD ($p<0.001$, for both). The QT interval maximum and corrected QT interval maximum durations, QTd and cQTd were increased in patients compared with control subjects. Multiple linear regression analysis showed that corrected QTd was independently related to age, left ventricular mass index (LVMI), AS and AD ($\beta=0.204$, $p=0.030$, $\beta=0.219$, $p=0.026$, $\beta=-0.238$, $p=0.021$ and $\beta=-0.208$, $p=0.032$ respectively) in hypertensive patients. The QTd was independently related to AS ($p=0.043$) and AD ($p=0.037$), as well as age ($p=0.003$) and LVMI ($p=0.008$).

Conclusion: The QTd and cQTd were increased in hypertensives. Aortic elastic properties may play a role in increased dispersion of QT and cQT intervals. *(Anadolu Kardiyol Derg 2007; 7: 275-80)*

Key words: Hypertension, QT interval, QT dispersion, aortic stiffness, aortic strain, aortic distensibility

ÖZET

Amaç: Hipertansif hastalarda art yük artmıştır ve artmış art yük hem ventriküler repolarizasyon eşitsizliğiyle (inhomogeneity); hem de aortanın bozulmuş elastik özellikleriyle ilişkilidir. Bu yüzden ventriküler repolarizasyon eşitsizliğini yansıtan QT dispersiyonunun (QTd) hipertansif hastalarda aortanın elastik özellikleriyle ilişkili olup olmadığını araştırmayı amaçladık.

Yöntemler: Bu kros-seksiyonel vaka kontrollü çalışmaya hipertansiyon tanısını yeni almış 113 hastayla birlikte 25 sağlıklı kontrol grubu alındı. Aortanın esnekliği ve gerilimi çıkan aorta çaplarından ekokardiyografik olarak hesaplandı. Ekokardiyografi çalışmaya alınan tüm bireylere yapıldı. Ayrıca tüm bireylerin maksimum QT süreleri, minimum QT süreleri, QTd ve düzeltilmiş QTd (cQTd) hesaplandı.

Bulgular: Kontrol grubuyla karşılaştırıldığında; hasta grubunun maksimum QT süresi, minimum QT süresi, QTd ve cQTd artmış olarak bulundu. Hasta grubuna çok değişkenli analiz yapıldığında; cQTd yaş, sol ventrikül kütle indeksi, aortanın gerilimi ve aortanın esnekliğiyle bağımsız olarak ilişkili bulundu (Sırasıyla; $\beta=0.204$, $p=0.030$, $\beta=0.219$, $p=0.026$, $\beta=-0.238$, $p=0.021$ ve $\beta=-0.208$, $p=0.03$). Ayrıca QTd da yaş ($p=0.003$) ve sol ventrikül kütle indeksi ($p=0.008$) yanında aortanın gerilimi ($p=0.043$) ve esnekliğiyle ($p=0.037$) bağımsız olarak ilişkili bulundu.

Sonuç: Hipertansif hastalarda QTd ve cQTd artmıştır. Aortanın elastik özellikleri QTd ve cQTd üzerinde bir rol oynayabilir. *(Anadolu Kardiyol Derg 2007; 7: 275-80)*

Anahtar kelimeler: Hipertansiyon, QT süresi, QT dispersiyonu, aortik sertlik, aortik gerilim, aortik elastisite

Introduction

QT dispersion (QTd) in the surface ECG is a reflection of ventricular repolarization inhomogeneity and has a predictive value in the assessment of the risk for ventricular arrhythmias. An increased QTd is an electrocardiographic measure of ventricular repolarization and also a risk marker for ventricular tachyarrhythmias (1). In patients with hypertension (HTN), QTd has been found to be increased especially in those with left ventricular hypertrophy, and it has been suggested to be a marker for ventricular arrhythmias especially the potentially dangerous ones, including couplet ectopic beats, ventricular tachycardia and fibrillation that can terminate in sudden cardiac death (2, 3).

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Aortic stiffness reflecting impaired elastic properties of aorta (4) was shown to be an independent predictor of all-cause and cardiovascular mortality in patients with essential HTN (5-7).

The QTd, index of ventricular repolarization inhomogeneity, and increased aortic stiffness are important predictors of cardiovascular mortality in patients with essential HTN (2, 3, 5-7). Previous studies (2, 3) have revealed the relationship between QTd and HTN; however the relationship between the elastic properties of the aorta and QTd has not been shown yet.

The aim of the present study is to investigate effect of impaired aortic elastic properties on QTd in patients with newly diagnosed hypertension.

Methods

Patients

One hundred and thirteen consecutive newly diagnosed hypertensive patients and 25 healthy control cases were included in the study. Blood pressure measurements were performed with mercury manometer. Hypertension was defined as ≥140/90 mmHg (8). The mean of three blood pressure recordings taken at 1-week intervals were used to diagnose HTN in the absence of any previous antihypertensive treatment to exclude pharmacologic effects on hemodynamics or ventricular hypertrophy and function. All subjects underwent two-dimensional echocardiography. Those with clinical or Doppler echocardiographic evidence of valvular stenosis or regurgitation were excluded as well as subjects with ischemic heart disease, ischemic ST-T changes on electrocardiogram (ECG), peripheral vascular disease, congestive cardiac failure, diabetes mellitus, alcohol abuse, smoking, hyperlipidemia, abnormal serum electrolyte values, chronic renal failure and patients without appropriate for analysis at least 9 ECG leads recordings. Patients who had evidence of secondary and malignant HTN were also excluded as well as those above 65 years old. Serum creatinine level >1.5 mg/dL and history of diabetes were also exclusion criteria. The control subjects had multiple blood pressure measurements <140/90 mm Hg and were matched for sex and age with the patients. Informed consent for participation in the study was obtained from all individuals.

The study protocol was approved by Ethical Committee of the Harran University.

Study design

The study design was cross-sectional and case-controlled. The sample size for the study was defined with power of the study of 80% and significance level of 5% (2, 5).

Clinical examinations

Blood pressure measurements used in the study were taken with a mercury sphygmomanometer at the time of echocardiography with the patient supine. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken as the first and fifth phases of Korotkoff sounds respectively. Body mass index (BMI) was computed as weight divided by height squared (kg/m^2).

Echocardiography

Echocardiographic examination was performed in all study subjects by using a commercially available system (Aloka Prosound SSD 5000 machine, Japan; 3-MHz transducer). Measurements were made during normal breathing at end-expiration. M-mode echocardiographic measurements were obtained based on the standards of the American Society of Echocardiography (9). Left atrial diameter, left ventricular (LV) end-systolic and end-diastolic diameters (LVIDd), end-diastolic interventricular septal thickness (IVSd), and end-diastolic left ventricular posterior wall thickness (LVPWd) were measured. Left ventricular ejection fraction was determined by Teichholz method (10).

Left ventricular mass (LVM) was calculated using the Devereux formula: LVM = (1.04[(LVIDd + IVSd + LVPWd)^3 - (LVIDd)^3] - 13.6 (11). Then, LV mass index (LVMI) was obtained by the following formula: LVM/body surface area. Relative wall thickness (RWT) was measured at the end of diastole as the ratio of (2xLV posterior wall thickness) / LV internal dimension.

Elastic properties of aorta

Ascending aorta diameters were measured from the same view on the M-mode tracing at a level of 3 cm above the aortic valve. The systolic diameter was measured at the maximum anterior motion of the aorta and the diastolic diameter was measured at the peak of the QRS complex on the simultaneously recorded ECG. The following indexes of aortic function were calculated: aortic strain [AS] = 100 x (AoS - AoD) / AoD (12) and aortic distensibility [AD] = 2 x (AoS - AoD) / (AoD x PP) (cm^2 x dyn (-^{1}) x 10$^{(-6)}$) (13). Pulse pressure (PP) was obtained simultaneously by cuff sphygmomanometry of the left brachial artery as SBP minus DBP (14, 15).

Electrocardiographic measurements

All 12 standard ECG leads were recorded by means of a 6-channel ECG recorder (Hewlett-Packard Electrocardiograph Sanborn Series machine, China) at a paper speed of 50 mm/sec. The QT interval of the 113 hypertensives and 25 controls was measured from each lead of the 12-lead ECG, for three consecutive cycles. The QT intervals were measured from the onset of the QRS complex to the end of the T wave. When U waves were present, the QT interval was measured to the nadir of the curve between the T and U waves. Two observers unaware of the patient's clinical data performed the measurements manually. Each QT interval was corrected for the patient's heart rate using Bazett's formula (corrected QT = QT/√RR sec), where corrected QT was the corrected QT interval. The QTd was defined on each electrocardiogram as the difference between the maximal and minimal QT interval in any of the leads measured. Accordingly, corrected QTd (cQTd) was defined as the difference between maximum and minimum heart rate corrected QT interval.

Reproducibility

Interobserver variability of measurements of aortic elasticity measurements were calculated as the difference in two measurements of the same patient by two different observers divided by the mean value. Intraobserver variability was calculated as the difference in two measurements of the same patient by one observer divided by the mean value. Intraobserver and interobserver variability were less than 5% for all aortic elasticity measurements.

Statistical analysis

All analyses were conducted using SPSS for Windows version 11.5 software (Chicago, IL, USA). Results are presented as mean±SD or frequency expressed as a percent. Categorical variables were compared by using Chi-square test. For continuous variables, difference between two groups was assessed by using unpaired t test. Associations of cQTd with

demographical, clinical and echocardiographic parameters were assessed by Pearson correlation test. Independent relationships of QTd with echocardiographic parameters were assessed by multiple linear regression analysis. For multiple regressions, factors showing a significant relationship in bivariate correlation test were selected. Standardized ß regression coefficients and their significance from multiple linear regression analysis were reported. A 2-tailed p value <0.05 was considered statistically significant.

Results

Clinical and echocardiographic characteristics of normal and hypertensive subjects are presented in Table 1. There were no statistical differences in gender, age, body surface area, ejection fraction, left ventricular dimensions and heart rate between the controls and hypertensive subjects (p>0.05 for all). Compared with the control group, the hypertensive patients had significantly higher SBP and DBP and PP (p<0.001 for all). The BMI, left atrial diameter, LVPWd, IVSd, RWT and LVMI were significantly increased in the hypertensive group as compared with control group (p=0.008, p<0.001, p<0.001, p<0.001, p<0.001 and p<0.001 respectively).

Table 1. Demographic, clinical, and echocardiographic characteristics of normal and hypertensive subjects

Parameters	Controls (n=25)	Patients (n=113)	p*
Age, years	50.0±4.4	51.1±7.42	0.49
Gender, M/F	12/13	42/71	0.21
Body surface area, m^2	1.82±0.20	1.87±0.17	0.22
Body mass index, kg/m^2	26.8±3.7	29.6±4.9	0.008
Heart rate, beats/min	78.2±14.1	75.9±12.5	0.42
SBP, mm Hg	113.4±11.8	146.3±21.8	<0.001
DBP, mm Hg	72.2±9.2	91.4±14.2	<0.001
Pulse pressure, mm Hg	41.8±7.2	54.8±13.7	<0.001
Ejection fraction, %	63.9±3.1	64.3±4.7	0.64
Left atrial diameter, mm	30.9±3.8	35.5±4.4	<0.001
PWd, cm	0.85±0.12	1.16±0.17	<0.001
IVSd, cm	0.9±0.09	1.2±0.19	<0.001
LVIDD, cm	4.60±0.41	4.60±0.48	0.45
LVISD, cm	3.04±0.39	3.07±0.43	0.72
RWT, cm	0.37±0.06	0.50±0.08	<0.001
LVMI, g/m^2	87.9±16.0	141.4±33.6	<0.001

*-p values significance by unpaired t test and Chi-square test
DBP- diastolic blood pressure, IVSd- interventricular septal diameter, LVIDD- left ventricular internal diastolic diameter, LVISD left ventricular internal systolic diameter, LVMI- left ventricular mass index, M/F- male/female, PWd - posterior wall diameter, RWT- relative wall thickness, SBP- systolic blood pressure

QT interval values and aortic elastic properties of normal and hypertensive subjects are presented in Table 2. The QT interval maximum and corrected QT interval maximum values, QTd and cQTd were significantly increased in patient group as compared with control group (p=0.022, p=0.039, p<0.001 and p<0.001, respectively). Aortic systolic and diastolic diameters were significantly higher in the hypertensives than in control subjects (p=0.014 and p=0.001, respectively), while mean AS and AD were lower in patients than in controls (p<0.001 for both).

In bivariate Pearson correlation analysis of the data in the patients' group (n=113), cQTd was only significantly and positively correlated with age, RWT, LVMI, SBP, and significantly inversely related to AD and AS (Table 3). The bivariate relationships between cQTd with AS and AD are illustrated in Figure 1 and Figure 2.

In multiple linear regression analysis, among all variables entered in the analysis cQTd was independently related only with age (ß =0.204, p=0.030), LVMI (ß=0.219, p=0.026), AS (ß=-0.238, p=0.021) and AD (ß=-0.208, p=0.032) (Table 3). In the final multiple regression model, after elimination of variables that did not show significant relationship, QTd was still independently related with AS (ß=-0.201, p=0.043) and AD (ß=-0.209, p=0.037) in presence of significant association with age (ß=0.290, p=0.003) and LVMI (ß=0.268, p=0.008).

Discussion

The main findings of this study are that (1) patients with newly diagnosed hypertension as compared with control group are characterized by both impaired aortic stiffness (AS and AD decreased) and increased QTd and cQTd (2) both QTd and cQTD were independently correlated with AS and AD as well as LVMI and age.

Table 2. Electrocardiographic characteristics and elastic properties of aorta in normal and hypertensive subjects

Parameters	Controls (n=25)	Patients (n=113)	p*
QT max, msec	398.0±38.0	417.4±37.7	0.022
Corrected QT max, msec	450.1±32.2	466.0±34.8	0.039
QT min, msec	373.6±37.7	367.0±32.5	0.37
Corrected QT min, msec	422.5±32.5	409.7±29.1	0.078
QT dispersion, msec	24.4±9.2	50.3±20.2	<0.001
Corrected QT dispersion, msec	27.6±10.4	55.6±22.5	<0.001
Aortic systolic diameter, mm/m^2	16.3±2.0	17.5±2.4	0.014
Aortic diastolic diameter, mm/m^2	15.2±2.1	16.9±2.4	0.001
Aortic strain, %	7.3±2.9	3. 7±1.8	<0.001
Aortic distensibility, $cm^2 \times dyn^{(-1)} \times 10^{(-6)}$	3.7±1.8	1.4±0. 9	<0.001

*-p values significance by unpaired t test

Aortic stiffness is significantly associated with the risk of all-cause and cardiovascular mortality in patients with essential HTN. Measurement of aortic stiffness retains predictive power with respect to all-cause and cardiovascular deaths, even after classic risk factors have been taken into consideration (5-7, 16). Although the mechanism of the increasing of aortic stiffness in hypertension is unclear, the following is one of the possible explanations. In hypertension, stress is caused by high pressure on the arterial walls, with resulting structural changes and atherosclerosis (17).

In patients with HTN, QTd is increased, and this condition is related to ventricular tachyarrhythmias and cardiac death (1-3). In this patient group, previous studies demonstrated that increased QTd is associated with LVMI (2, 3, and 18). However, Bugra et al. (19) showed that increased LVMI is not the only reason for inhomogenous ventricular repolarization in newly diagnosed HTN. Also, they concluded that there might be other reasons such as effects of increased left ventricular cavity on QTd in newly diagnosed HTN. Our study suggested another influencing factor. In addition to LVMI and

Table 3. Bivariate and multivariate relationships of the cQTD with clinical, and echocardiographic variables in patients with hypertension

	cQTD, msec			
	Pearson correlation coefficient	p	Standardized ß regression coefficients[a]	p
Age, years	0.255	0.006	0.204	0.030
Body mass index,kg/m^2	0.083	0.382		
Body surface area,m^2	0.061	0.524		
RWT	0.317	0.001	0.154	0.104
LVMI,g/m2	0.361	<0.001	0.219	0.026
LVISD,mm	0.101	0.289		
LVIDD,mm	0.011	0.907		
Ejection fraction,%	0.000	0.997		
SBP,mmHg	0.221	0.019	0.123	0.309
DBP,mmHg	0.157	0.097		
Heart rate,beats/min	0.118	0.214		
Aortic strain,%	-0.399	<0.001	-0.238	0.021
Aortic distensibility, cm^2 x dyn ($^{-1}$) x 10($^{-6}$)	-0.364	<0.001	-0.208	0.032

[a] From multiple linear regression.
cQTD - corrected QT interval dispersion, DBP - diastolic blood pressure, IVSd - interventricular septal diameter, LVIDD - left ventricular internal diastolic diameter, LVISD- left ventricular internal systolic diameter, LVMI - left ventricular mass index, M/F - male/female, PWd - posterior wall diameter, RWT - relative wall thickness, SBP - systolic blood pressure

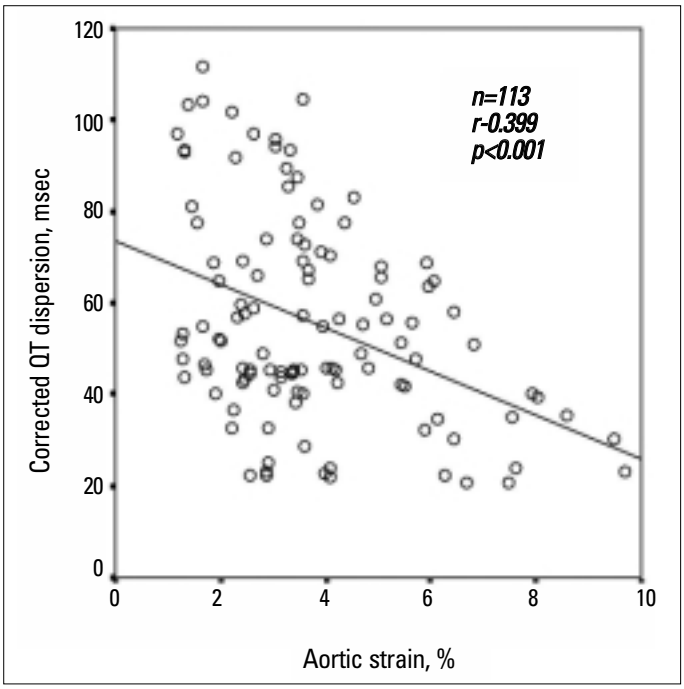

Figure 1. Relationship between corrected QT dispersion and aortic strain

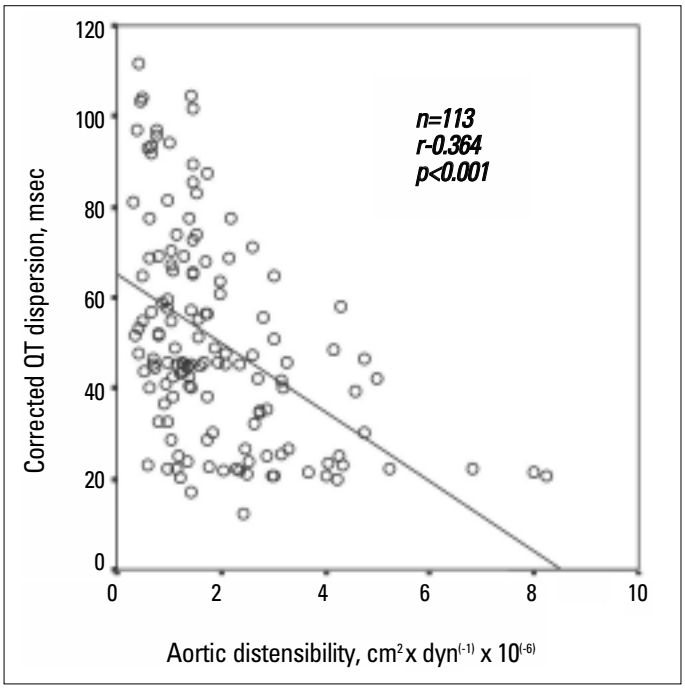

Figure 2. Graph demonstrating significant relationship between corrected QT dispersion and aortic distensibility

age, impaired elastic properties were found to be influencing on QTd and cQTd, which reflects inhomogenous ventricular repolarization.

Ural et al. (20) suggested that not only increased left ventricular mass but also increased afterload is a reason for electrical inhomogeneity in hypertensives. Increased aortic stiffness raises left ventricular afterload (21, 22). The significant correlation of cQTd with impaired aortic elastic properties, namely increased aortic stiffness, indicates that not only increased LVMI but also increased afterload is a reason for ventricular inhomogeneity in our study. Arterial stiffness causes premature return of reflected waves in late systole, increases central PP and the load on the ventricle, reduces ejection fraction, and increases myocardial oxygen demand (21). In this case there might also be the relative ischemia due to increased muscle mass and impaired coronary microvascular perfusion, being more significant in HTN, and therefore causing the impairment of repolarization features, namely the increase in QTd and cQTd.

Impaired aortic elastic properties play a role in impaired left ventricle diastolic function (4). Association between impaired left ventricle diastolic function with QTd was demonstrated in a previous study (23). Aortic stiffness is associated with left ventricular hypertrophy in normotensive and hypertensive patients (2, 3, 18, 24, 25). Furthermore, left ventricular hypertrophy, which is reflected with increased LVMI, is a known reason for increased QTd. Because of above reasons, presence of effect of impaired aortic elastic properties on ventricular repolarization may be plausible.

Limitations of the study

Several limitations of this study should be concerned. In translating our results into clinical practice, two limitations of this study must be kept in mind. Firstly, manual measurement of QTd may be subject to errors. However, automatic techniques are less likely to be able to cope with morphological and noise factors in practice. Before methodological problems are resolved, many previous studies have to rely on the classical ECG intervals measured manually with all its limitations. Secondly, PP was measured by cuff sphygmomanometry of the brachial artery. However, several reports have demonstrated the excellent correlation of the noninvasively calculated aortic function indexes with indexes derived by invasive measurement (14, 15). Additionally, in our study, subjects with pre-hypertension were included in control group. This might lead to bias since pre-hypertension leads to several hemodynamic and morphological alterations. As a last limitation, coronary artery disease can not be strictly excluded since coronary angiography was not performed in the study population.

Clinical implications

Improvement of aortic elastic properties by medical treatment such as angiotensin-converting enzyme inhibitors, or angiotensin type 1 receptor blockers (26), calcium channel blockers (27) may be an important therapeutic goal in patients with newly diagnosed HTN in order to improve ventricular repolarization inhomogeneity, and, consequently, improve prognosis in these patients (14, 16).

Conclusion

The present study demonstrated that aortic stiffness increased and QTd (QTd and cQTd) increased in patients with newly diagnosed HTN. Furthermore, impaired aortic elastic properties (aortic stiffness and aortic distensibility) -namely increased aortic stiffness, had independent effects on QT dispersion.

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