QT Intervals and Heart Rate Variability in Hypertensive Patients

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SUMMARY

Low heart rate variability and increased QT dispersion are risk factors for cardiac mortality in various patient populations.

We studied dispersion of QT interval, *i.e.* an index of inhomogeneity of repolarization, and heart rate variability (HRV) *i.e.*, a measure of cardiac autonomic modulation in 76 essential hypertension cases (45 women, 53.0 ± 11.1 years, body mass index: 25.1 ± 1.4 kg/m^2) and 70 healthy cases (42 women, 54.0 ± 10.2 years, body mass index: 25.5 ± 1.6 kg/m^2, $p > 0.05$).

QT-corrected QT intervals and their dispersions were significantly higher in the hypertensive group ($p < 0.0001$), all showing a direct relation with the level of systolic and diastolic blood pressures, ventricular mass index and high Lown grade ventricular rhythm problems. Time domain measures like standard deviation of RR intervals, standard deviation of the means of all corrected RR intervals calculated at 5 min intervals ($p < 0.0001$), proportion of adjacent RR intervals differing by > 50 msec ($p = 0.005$), HRV triangular index ($p = 0.007$), the square root of the mean squared differences of successive RR intervals ($p = 0.011$), and the high frequency (HF, 0.16-0.40 Hz, $p < 0.0001$) part of the frequency domain measure of HRV were all decreased, whereas the low frequency (LF, 0.04-0.15 Hz, $p = 0.013$) part of the frequency domain measures and LF / HF ratio ($p < 0.0001$) were increased in hypertensive cases. Time domain and the HF part of frequency domain measures of heart rate variability showed an inverse relation with the increased levels of both systolic and diastolic blood pressures and Lown grading system of ventricular rhythm problems, whereas LF and LF / HF showed direct relations with high levels of systolic and diastolic blood pressures and high Lown grade ventricular rhythm problems. The measures of heart rate variability apart from LF and LF / HF were inversely related with the QT intervals and dispersions, whereas LF / HF was directly related with them.

Therefore, we conclude that the levels of both systolic and diastolic blood

pressures are related to the generation of ventricular rhythm problems either via increasing left ventricular mass which results in an increase in QT parameter measurements, or by altering heart rate variability measures indicating a disturbance in cardiac autonomic balance in essential hypertension. (Jpn Heart J 2000; 41: 173-182)

Key words: Hypertension, QT intervals, Heart rate variability

EXPERIMENTAL and clinical studies have shown that cardiovascular autonomic regulation plays an important role in cardiac mortality in various patient populations.[1-5] Autonomic cardiac control has been shown to be altered in hypertensive patients compared with their normotensive counterparts.[6] Reduced heart rate variability (HRV), which is an indicator of abnormal cardiac autonomic control, may condition the heart to a spontaneous onset of ventricular arrhythmias.[7] Early clinical studies have shown that untreated systemic hypertension is associated with reduced heart rate variability.[6,8,9]

Multiple risk markers for an arrhythmic substrate, which can be applied to hypertensive heart disease, have been identified in different pathological cardiovascular conditions. These include diminished heart rate variability,[10] QT interval dispersion[11] and ventricular late potentials.[10,12,13] A large QT dispersion (QTd) indicates the presence of a substrate for ventricular tachyarrhythmias, most obviously by a reentery mechanism.[14] In hypertensive cases left ventricular hypertrophy also predisposes the subjects to the risk of ventricular arrhythmias and sudden death.[15-21]

In the present study, we tried to evaluate the relationships among blood pressure, QTd, HRV, left ventricular mass index (LVMI) and ventricular rhythm problems.

METHODS

The study included 76 cases with essential hypertension [45 females, 53.0 ± 11.1 years old, body mass index (BMI): 25.1 ± 1.4 kg/m^2] and 70 healthy normotensive cases (42 females, $54.0 + 10.2$ years old, BMI: 25.5 ± 1.6 kg/m^2) without any known disease. The hypertensive subjects were randomly selected from among patients with essential hypertension. Patients with symptoms, medication or electrocardiographic evidence of coronary artery disease, atrial fibrillation, bundle branch block or technically inadequate Holter recordings because of technical artifacts were excluded. Patients with any disease affecting the autonomic nervous system such as diabetes mellitus, subjects with echocardiographic evidence of valvular heart disease, or those taking any antiarrhythmic medication were also excluded.

Table I.   Clinical and Echocardiographic Characteristics of the Study Groups

Variable	Hypertensives $n = 76$	Normal $n = 70$	p
Female %	59	60	NS
Age Years	53.0 ± 11.1	54.0 ± 10.2	NS
BMI kg / m^2	25.1 ± 1.4	25.5 ± 1.6	NS
Smoker %	20	19	NS
Systolic BP mmHg	165.4 ± 10.4	117.0 ± 7.13	< 0.0001
Diastolic BP mmHg	90.6 ± 5.6	70.0 ± 8.2	< 0.0001
Mean heart rate beats / min	87.2 ± 6.9	76.9 ± 7.7	< 0.0001
LVd mm	49.7 ± 1.7	49.9 ± 2.4	NS
IVS mm	11.9 ± 0.9	8.5 ± 1.0	< 0.0001
LVMI gr/m^2	127.0 ± 7.6	93.9 ± 5.2	< 0.0001
FS %	32.8 ± 2.4	33.6 ± 2.8	NS
LA mm	40.9 ± 2.2	31.2 ± 2.0	< 0.0001

NS = Statistically not significant.

A mercury sphygmomanometer with an arm cuff was used for all blood pressure measurements. After at least 5 minutes rest, blood pressure was measured 3 times at 1 minute intervals from the right arm. The mean of 3 measurements was used in the analysis. All antihypertensive medications were stopped 7 days before the study and all patients were placed on a salt-restricted diet. The demographic variables are summarized in Table I.

A 12-lead surface electrocardiogram (ECG) was performed on each subject. The QT interval was measured at each lead of the 12 lead surface ECG for 3 consecutive cycles. The QT intervals were measured manually from the onset of the T-P baseline. If U waves were present the QT interval was measured to the nadir of the curve between the T and U waves. The corrected QT interval (QTc) was calculated from the 3 cycle mean.[22] QT and QTc dispersions (QTd, QTcd) were defined as the difference between the maximum and minimum QT and QTc intervals, respectively.

All echocardiographic measurements were performed with General Electric-Sonochrome echocardiographic equipment. The M-mode measurements were obtained as recommended by the American Society of Echocardiography.[23] Left ventricular mass was calculated using the Devereux formula.[24] LVMI was calculated by dividing the left ventricular mass by body surface area. Fractional shortening was calculated by dividing the difference between the left ventricular internal diameter in diastole and systole by the diastolic diameter and multiplying by 100.

HRV criteria were obtained from Holter ECG recordings. Each case underwent continuous 24 hour monitoring with two channel recordings (Cardiosis, Biomedical Systemsisty). Temporal analysis of HRV included the

measurement of heart rate (normal to normal RR intervals, resulting from sinus node depolarization), standard deviation of the RR intervals (SDNN-msec), SDNN index (SDNN5, msec), standard deviation of the means of all corrected RR intervals calculated at 5 min intervals (SDANN, msec), the square root of the mean squared differences of successive RR intervals different by > 50 msec (PNN50, %), and HRV triangular index (TRIA, msec).

Spectral analysis was performed by fast fourier transformation including total power (power in the band below 0.40 Hz), the low frequency (LF) (0.04 to 0.15 Hz), and high frequency (HF) (0.16 to 0.40 Hz) components and LF/HF ratio. Normalization of the LF and HF expressed as a ratio was obtained by dividing the LF and HF components by total power and then multiplying the result by 100. Ventricular and supraventricular events which had coupling intervals of 15% and 25% shorter than the mean value of the last 4 normal RR were automatically excluded from HRV analysis. The subsequent interval was also excluded from analysis.

Ventricular rhythm problems were detected and grouped according to the Lown grading system.[25]

Statistics: The Mann-Whitney two independent sample test was used for estimation of the differences in the data between the groups. Linear regression analysis was used to estimate the correlation between variables. A value of $p < 0.05$ was considered significant.

RESULTS

The clinical and echocardiographic data on the subjects in the two study groups are presented in Table I. Age, gender, BMI, left ventricular end diastolic internal diameter, and fractional shortening were similar in both groups. As expected the hypertensive cases had higher systolic / diastolic blood pressure levels ($p < 0.0001$). The hypertensive cases had thicker interventricular septum (IVS) ($p < 0.0001$), higher LVMI ($p < 0.0001$), and larger left atrial (LA) diameter ($p < 0.0001$) than the normotensive group. Mean heart rate (HRm), QT and QTc intervals, and QTd and QTcd were significantly higher ($p < 0.0001$), whereas mean RR interval was shorter ($p < 0.0001$) in the hypertensive group (Table II). Prolonged QT intervals and increased QT dispersions indicate regional differences in action potential duration in myocardium, and in some conditions it represents a risk factor for malignant arrhythmia and is influenced by autonomic modulation.[26-28] The mean values of SDNN ($p < 0.0001$), PNN50 ($p = 0.005$), TRIA ($p = 0.007$), SDANN ($p < 0.0001$), RMSSD ($p = 0.011$), and HF ($p < 0.0001$) were significantly lower, but the mean value of LF ($p = 0.013$) and the LF to HF ratio ($p < 0.0001$) were higher in the hypertensive group (Table III),

Table II. QT Intervals in the Study Groups

Variable	Hypertensives (n=76)	Normals (n=70)	p
QTmax (sec)	0.38 ± 0.02	0.36 ± 0.03	< 0.0001
QTmin (sec)	0.33 ± 0.02	0.33 ± 0.04	NS
QTd (sec)	0.05 ± 0.01	0.02 ± 0.01	< 0.0001
QTcmax (sec)	0.43 ± 0.02	0.39 ± 0.03	< 0.0001
QTcmin (sec)	0.37 ± 0.03	0.36 ± 0.03	NS
QTcd (sec)	0.06 ± 0.04	0.03 ± 0.01	< 0.0001

Table III. Heart Rate Variability Measures and Ventricular Rhythm Problems

Variables	Hypertensives (n=76)	Normals (n=70)	p
Mean RR (msec)	713.2 ± 54.7	790.7 ± 87.5	< 0.0001
SDNN (msec)	104.9 ± 27.6	192.1 ± 42.3	< 0.0001
SDANN (msec)	95.5 ± 27.3	120.2 ± 36.6	< 0.0001
SDNN5 (msec)	53.0 ± 13.6	61.7 ± 29.6	NS
RMSSD (msec)	40.0 ± 16.3	58.5 ± 44.8	0.011
PNN50 (%)	8.0 ± 5.1	14.1 ± 14.7	0.005
TRIA (msec)	464.0 ± 132.7	551.7 ± 132.7	0.007
LF (nu)	68.0 ± 4.1	66.0 ± 4.1	0.013
HF (nu)	15.9 ± 2.0	22.2 ± 4.6	< 0.0001
LF / HF	3.5 ± 0.6	2.5 ± 1.9	< 0.0001
Lown grade	1.5 ± 1.5	0.1 ± 0.3	0.0001

indicating a disturbance in autonomic function. Because HRV is a measure of the cyclic variations of beat to beat RR intervals, this index reflects cardiac autonomic function.[29]

In hypertensive subjects higher Lown grade ventricular rhythm problems were observed ($p = 0.001$) (Table III). QT interval ($r = 0.21$, $p = 0.02$), QTc interval ($r = 0.16$, $p = 0.03$), QTd ($r = 0.21$, $p = 0.006$), QTcd ($r = 0.20$, $p = 0.01$), LF / HF ($r = 0.18$, $p < = 0.01$), HRm ($r = 0.17$, $p = 0.02$), LVMI ($r = 0.76$, $p < 0.0001$), and LA ($r = 0.80$, $p < 0.0001$) were directly related with diastolic blood pressure (BP). They were all directly related with systolic blood pressure: QT ($r = 0.17$, $p = 0.02$), QTc ($r = 0.20$, $p = 0.01$), QTd ($r = 0.31$, $p = 0.0001$), QTcd ($r = 0.28$, $p = 0.0004$), LF/HF ($r = 0.17$, $p = 0.02$), HRm ($r = 0.21$, $p = 0.006$), LVMI ($r = 0.76$, $p < 0.0001$), LA ($r = 0.76$, $p < 0.0001$). Mean RR interval ($r = -0.16$, $p = 0.04$), RMSSD ($r = -0.19$, $p = 0.01$), SDANN ($r = -0.18$, $p = 0.04$), SDNN ($r = -0.20$, $p = 0.01$), TRIA ($r = -0.24$, $p = 0.004$), PNN50 ($r = -0.16$, $p = 0.03$), and HF ($r = -0.30$, $p = 0.001$) were inversely related with diastolic pressure and they all had an inverse relation with systolic BP: mean RR interval ($r = -0.16$, $p = 0.04$), RMSSD ($r = -0.19$, $p = 0.03$), SDANN ($r = -0.17$, $p = $

0.02), SDNN ($r = -0.19$, $p = 0.02$), PNN50 ($r = -0.18$, $p = 0.02$), TRIA ($r = -0.22$, $p = 0.02$), HF ($r = -0.28$, $p = 0.002$) (Table IV). QT ($r = 0.18$, $p = 0.029$, QTc ($r = 0.30$, $p = 0.0001$), QTd ($r = 0.30$, $p = 0.0001$), QTcd ($r = 0.22$, $p = 0.001$), LF / HF ($r = 0.38$, $p = 0.001$), LVMI ($r = 0.24$, $p = 0.002$), and HR ($r = 0.28$, $p = 0.001$) showed direct relations with the ventricular rhythm problems according to the Lown grading system, but RR interval ($r = -0.19$, $p = 0.02$), SDANN ($r = -0.23$, $p = 0.002$), SDNN ($r = -0.17$, $p = 0.03$), TRIA ($r = -0.19$, $p = 0.02$), and HF ($r = -0.36$, $p = 0.001$) showed inverse relations with the Lown grading system (Table IV). Only the QT ($r = 0.33$, $p = 0.001$), QTc ($r = 0.50$, $p < 0.00001$), QTd ($r = 0.61$, $p < 0.00001$), and QTcd ($r = 0.45$, $p < 0.00001$) showed

Table IV. Correlations between QT Intervals, HRV Measures and Echocardiographic Variables and Systolic and Diastolic Blood Pressure and the Ventricular Rhythm Problems

Variable		Systolic BP	Diastolic BP	Lown Grade
Qtmax:	r	0.17	0.21	0.18
	p	0.02	0.02	0.02
QTcmax:	r	0.20	0.16	0.30
	p	0.01	0.03	0.0001
QTd:	r	0.31	0.21	0.30
	p	< 0.0001	0.006	0.0001
QTcd:	r	0.28	0.20	0.22
	p	0.0004	0.01	0.001
Mean HR:	r	0.21	0.17	0.28
	p	0.006	0.02	0.001
LF:	r	0.17		
	p	0.02	NS	NS
LF / HF:	r	0.17	0.18	0.30
	p	0.02	0.01	0.001
HF:	r	− 0.30	− 0.28	− 0.36
	p	0.001	0.02	0.001
LVMI:	r	0.76	0.76	0.24
	p	< 0.00001	< 0.00001	0.002
LA:	r	0.76	0.80	
	p	< 0.00001	< 0.00001	NS
Mean RR:	r	− 0.16	− 0.16	− 0.19
	p	0.04	0.04	0.02
RMSSD:	r	− 0.19	− 0.19	
	p	0.03	0.01	NS
SDANN:	r	− 0.17	− 0.18	− 0.23
	p	0.02	0.04	0.02
SDNN:	r	− 0.19	− 0.20	− 0.17
	p	0.02	0.01	0.03
TRIA:	r	− 0.22	− 0.24	− 0.19
	p	0.02	0.01	0.02
PNN50:	r	− 0.18	− 0.16	
	p	0.02	0.03	NS

Table V.   Correlations between QT Intervals and the Spectral Measures of HRV and LVMI

Variable		LF	HF	LF / HF	LVMI
QT:	r		− 0.19	0.19	0.33
	p	NS	0.01	0.01	0.0004
QTc:	r		− 0.22	0.20	0.5
	p	NS	0.005	0.01	< 0.00001
QTd:	r		− 0.30	0.28	0.61
	p	NS	0.001	0.001	< 0.00001
QTcd:	r		− 0.31	0.29	0.45
	p	NS	0.001	0.002	< 0.00001
LVMI	r	0.17	− 0.14	0.16	
	p	0.07	0.08	0.08	

a direct relation with the LVMI, and measures of HRV had no relation with LVMI (Table V). There was a direct relation between QT intervals and the LF / HF ratio: QT ($r = 0.19$, $p = 0.01$), QTc ($r = 0.20$, $p = 0.01$), QTd ($r = 0.28$, $p = 0.001$), QTcd ($r = 0.29$, $p = 0.002$), but an inverse relation with the HF ; QT ($r = − 0.19$, $p = 0.01$), QTc ($r = − 0.22$, $p = 0.005$), QTd ($r = − 0.30$, $p = 0.001$), QTcd ($r = − 0.31$, $p = 0.001$) (Table V). These changes indicate a shift of sympathovagal balance toward a sympathetic predominance and reduced vagal tone. The relation between QT intervals and the HF component of HRV represents parasympathetic modulation and the relation between QT intervals and the LF / HF ratio represents sympathetic modulation predisposing them to ventricular rhythm problems.

DISCUSSION

Experimental studies provide powerful evidence for the significance of the dispersion of myocardial recovery times for the occurrence of ventricular arrhythmias.[30-33] There has been limited information on the presence of abnormalities in the autonomic regulation of heart rate in patients with systemic hypertension.[34] The present study shows that the measures of HRV are reduced in hypertensive patients taking no medication relative to their age matched normotensive counterparts. Our results are in accordance with the results of Guzzetti, et al.[35] and Dassi[9] and coworkers. They also showed the LF component of HRV and LF / HF to be higher and the HF component to be lower in hypertensive cases. Chakko, et al.[6] reported that all of the power spectrum components were significantly reduced in hypertensive subjects with evidence of left ventricular hypertrophy in comparison to age matched controls. The relation between QT intervals and the high frequency component of HRV represents parasympathetic modulation, and the relation between QT intervals and low to

high frequency ratio represents sympathetic modulation. The negative relation between the QT intervals and the HF component of HRV and the positive relation with the LF / HF in our hypertensive cases indicated the sympathetic predominance in hypertensive patients predisposing them to ventricular rhythm problems.

QTd has been shown to be a useful noninvasive method for the detection of inhomogeneity of ventricular recovery times.[26,36-41] This study of hypertensive subjects showed that QT and QTc dispersions increased in hypertensive patients, showed a tendency to increase more with increasing LVMI, and had a direct relation with the occurrence of high Lown grade ventricular rhythm problems. The same was shown by Galinier, et al.[42] In our study increased QTd and QTcd correlated with measures of HRV suggesting that abnormal cardiac control is related to repolarization abnormalities in hypertension. There is also increasing evidence to suggest that impaired cardiovascular autonomic regulation may predict mortality and adverse events in patients without documented ischemic heart disease.[5,43] High blood pressure itself deteriorates cardiovascular autonomic control and a blood pressure reduction itself could improve HRV.[44-46] We found a relation between systolic and diastolic blood pressure levels and QT intervals, HRV, LVMI , and also between LVMI and QT intervals. The relation with high blood pressure existed for the measures of HRV, especially for the HF power, showing impaired sympathovagal balance, but increased QT intervals and dispersions were related both with increased blood pressures and the presence of left ventricular hypertrophy, showing a closer relation with the latter.

It is concluded that hypertension may alter autonomic modulation of heart rate and also cause left ventricular hypertrophy, both predisposing to ventricular arrhythmias. Accordingly medications which reduce blood pressure and alleviate left ventricular hypertrophy could improve abnormal cardiac autonomic function and repolarization inhomogeneity.

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