Original Article

Prolonged QT Interval and Reduced Heart Rate Variability in Patients with Uncomplicated Essential Hypertension

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A prolonged QT interval is a risk factor for ischemic heart disease in hypertensive subjects. Heart rate variability (HRV) is both an index of autonomic function and an important prognostic factor in several diseases. The aim of the present study was to evaluate the relation between a prolonged QT interval and autonomic nervous system function in patients with untreated uncomplicated essential hypertension. Two hundred and fifteen untreated patients with essential hypertension underwent a Holter ECG equipped with software dedicated to HRV and QT analyses. Nine percent of the patients showed a corrected QT (QTc) ≥ 440 ms. The HRV indexes in the time domain (SDNN, SDNN index, RMSSD, and pNN50) were significantly reduced in the patients with a prolonged QTc compared to those with a normal QTc (SDNN 24 h: 126.4 ± 29.9 vs. 143.9 ± 35.4 ms, $p=0.02$; SDNN index [nighttime]: 85.9 ± 32.4 vs. 115.5 ± 36.7 ms, $p=0.0006$; RMSSD 24 h: 22.2 ± 7.7 vs. 31.2 ± 13.0 ms, $p=0.0007$; pNN50 24 h: 4.4 ± 4.9 vs. $9.7 \pm 8.4\%$, $p=0.0006$). The linear correlation analysis between QTc length and HRV parameters showed a significant negative correlation with all the time-domain indexes. Such a correlation was maintained for RMSSD 24 h, pNN50 24 h and SDNN index (nighttime) after correction for gender and age. The present study shows that, even prior to the development of cardiac hypertensive disease, a prolongation of the QTc and a reduced HRV, both markers of cardiovascular risk, coexist in a proportion of patients with untreated essential hypertension. Further studies are warranted to evaluate whether the combination of such markers can identify hypertensive patients at risk for life-threatening arrhythmias and sudden death. (*Hypertens Res* 2008; 31: 2003–2010)

Key Words: QT interval, heart rate variability, essential hypertension

Introduction

QT interval prolongation has been associated with an increased risk of ventricular arrhythmias and sudden death in the general population (1), in diabetic patients (2), after myocardial infarction (3), and in chronic heart failure (4). An abnormal ventricular repolarization has been described in patients with hypertensive heart disease (5, 6), and a pro-

longed QT interval is a risk factor for ischemic heart disease in hypertensive subjects (7). Many physiopathological factors influence the duration of the QT interval, including the activity of the autonomic nervous system. Studies evaluating the effect of sympatho-vagal modulation on ventricular repolarization have yielded conflicting results (8–10).

The aim of the present study was to evaluate the relation between a prolonged QT interval and autonomic nervous system function in patients with untreated, uncomplicated essen-

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Table 1. General and Clinical Characteristics of the Study Population

	Total group	Males (<i>n</i> =144)	Females (<i>n</i> =71)	<i>p</i>
Age (years)	39±10	38±10	41±10	0.04
Duration of hypertension (months)	34±45	34±42	35±50	0.76
BMI (kg/m ²)	25±4	25±3	24±4	<0.0001
Systolic BP (mmHg)	146±15	146±14	146±16	0.72
Diastolic BP (mmHg)	94±9	94±9	93±8	0.44
Heart rate (bpm)	77±11	75±11	81±11	0.001
LVMI (g/m ²)	96±24	99±25	86±16	0.05
Glycemia (mg/dL)	92±10	93±10	88±9	0.0006
Creatinine (mg/dL)	0.89±0.16	0.94±0.15	0.77±0.13	<0.0001
Total cholesterol (mg/dL)	207±40	206±40	210±41	0.69
Triglycerides (mg/dL)	125±119	141±136	88±57	<0.001
PRA (ng/mL/h)	1.34±1.33	1.48±1.45	1.06±1.01	0.07
Aldosterone (ng/mL)	146±87	153±90	131±78	0.20
ARR	219±245	210±216	239±295	0.55
QTc (ms)	407±30	400±28	421±29	<0.0001

BMI, body mass index; BP, blood pressure; LVMI, left ventricular mass indexed to body surface area; PRA, plasma renin activity; ARR, aldosterone to PRA ratio; QTc, corrected QT.

tial hypertension. Sympatho-vagal function was measured with heart rate variability (HRV), which is both an index of autonomic nervous system function and an important prognostic factor for cardiovascular disease (11, 12). An abnormal HRV, characterized by a sympathetic predominance, has been shown in patients with essential hypertension, even in the early stages of the disease, as well as in association with left ventricular hypertrophy (13–15).

Methods

All consecutive hypertensive patients referred to our unit from 1998 to 2001 were considered. All patients went through a clinical examination, including height, weight and blood pressure measurements, laboratory tests, and echocardiography. Patients with secondary hypertension, arrhythmias, bundle branch blocks, left ventricular hypertrophy or valvular diseases, cardiac failure (New York Heart Association [NYHA] class >1), ischemic heart disease, diabetes, or obesity (body mass index [BMI] ≥30) and those taking anti-hypertensive drugs or antiarrhythmic drugs of any class (including digoxin and β-blockers) were excluded.

The patients who qualified for the study underwent an ECG recording by means of a validated computerized Holter system, equipped with software dedicated to HRV and QT analyses. ECG leads *V*₂ and *V*₅ were recorded for 24 h (Premier Holter 4000; Diagnostic Monitoring, Prescott, USA). The recording speed was 2 mm/s and the sampling rate was 300 Hz. The ECG Holter software was used to transfer the patients' data and to identify each QRS complex. Electrical noise, aberrant ECG findings, premature beats and their adjacent RR intervals, and T waves >50 μV were excluded from the analysis. For a recording to be satisfactory for this study,

the number of ectopic beats could not exceed 10% of the total beats.

After application of all the exclusion criteria, 215 patients (144 males, 71 females) were considered. The general and clinical characteristics of the study population are shown in Table 1.

Power spectral analysis, performed by the fast Fourier transformation algorithm, was carried out every 10 min. For each time segment, the power was quantified in total spectrum power (TP) (0.003–1 Hz), ultra- and very low-frequency power (VLF) (<0.04 Hz), low-frequency power (LF) (0.04–0.15 Hz) and high-frequency power (HF) (0.15–0.4 Hz). LF and HF were expressed in normalized units (LF or HF/total power – VLF). VLF power represents a miscellaneous combination of physiological components, LF power is an index of both sympathetic and parasympathetic activity, HF power is an index of parasympathetic activity, and the LF to HF ratio is considered an index of the cardiac sympatho-vagal balance. Time-domain parameters were calculated on the entire recording period and expressed as: mean RR intervals (RR), the standard deviation of all normal-to-normal intervals (SDNN), the standard deviation of the average normal-to-normal intervals calculated over a 5 min period (SDANN), the mean of the 5-min standard deviation of the normal-to-normal intervals calculated over 24 h (SDNN index), the square root of the mean squared differences of successive normal-to-normal intervals (RMSSD), and the number of interval differences of successive normal-to-normal intervals greater than 50 ms divided by the total number of normal-to-normal intervals (pNN50). SDNN and SDANN are considered global indexes of sinus variability; pNN50 and RMSSD are indexes of vagal activity. Daytime and nighttime periods were defined as the intervals between 10 AM and 8

Table 2. HRV Indexes of the Study Population

		Total group	Males (n=144)	Females (n=71)	p
RR (ms)		782±93	800±98	744±71	<0.0001
SDNN (ms)	24 h	142.3±35.3	151.6±35.9	123.4±25.0	<0.0001
SDANN (ms)	24 h	131.0±36.2	140.3±37.7	112.0±23.5	<0.0001
RMSSD (ms)	24 h	30.4±12.8	32.4±13.2	26.1±11.1	<0.0001
pNN50 (%)	24 h	9.2±8.3	10.5±8.3	6.5±7.6	<0.0001
SDNN index (ms)	daytime	108.9±27.3	112.2±28.7	102.2±23.0	0.008
RMSSD (ms)	daytime	26.3±11.5	27.6±12.2	23.5±9.4	0.003
pNN50 (%)	daytime	6.5±7.4	7.4±7.9	4.8±6.1	0.003
SDNN index (ms)	nighttime	112.7±37.5	122.2±36.6	93.5±30.9	<0.001
RMSSD (ms)	nighttime	39.2±19.3	43.0±19.7	31.4±15.7	<0.0001
pNN50 (%)	nighttime	16.7±14.3	19.7±14.2	10.7±12.5	<0.0001
TP (ms ²)	24 h	3,762.5±1,958.5	4,254.2±1,984.4	2,736.5±1,448.1	<0.0001
LF (ms ²)	24 h	1,039.7±845.8	1,126.4±469.6	858.8±1,310.6	<0.0001
HF (ms ²)	24 h	288.8±215.5	308.7±209.7	247.4±223.1	0.002
LF (n.u.)	24 h	83.2±55.1	78.8±7.5	89.6±85.8	0.26
HF (n.u.)	24 h	21.8±14.0	19.5±7.2	25.1±19.9	0.04
LF/HF	24 h	4.58±2.67	4.87±2.54	4.16±2.82	0.12
TP (ms ²)	daytime	3,319.0±1,909.4	3,657.1±2,012.4	2,613.4±1,450.2	<0.0001
LF (n.u.)	daytime	80.2±10.6	80.4±12.9	79.9±6.1	0.11
HF (n.u.)	daytime	17.0±5.9	16.0±5.8	18.6±5.8	0.04
LF/HF	daytime	5.44±2.60	5.83±2.81	4.88±2.15	0.09
TP (ms ²)	nighttime	4,710.7±2,564.6	5,535.4±2,514.2	3,001.4±1,677.4	<0.0001
LF (n.u.)	nighttime	72.7±10.5	73.6±11.3	71.5±9.2	0.33
HF (n.u.)	nighttime	26.2±11.1	24.9±10.9	28.0±11.2	0.24
LF/HF	nighttime	3.56±2.25	3.95±2.65	3.01±1.35	0.24

RR, mean RR intervals; SDNN, standard deviation of all normal-to-normal intervals; SDANN, standard deviation of the average normal-to-normal intervals calculated over a 5 min period; RMSSD, square root of the mean squared differences of successive normal-to-normal intervals; pNN50, number of interval differences of successive normal-to-normal intervals greater than 50 ms divided by the total number of normal-to-normal intervals; SDNN index, mean of the 5-min standard deviation of the normal-to-normal intervals calculated over 24 h; TP, total spectrum power; LF, low-frequency power (0.04–0.15 Hz); HF, high-frequency power (0.15–0.4 Hz); LF/HF, LF to HF ratio; n.u., normalized units.

PM and between 12 PM and 6 AM, respectively.

The QRS signals were detected by a dedicated algorithm. T wave peaks were located, after which the point with the steepest slope along the descending limb of the T wave and the area of least variation were identified. The end of the T wave was defined as the intersection of the isoelectric line of the ECG tracing with the tangent of the inflection point to the descending part of the T wave. The channel with the most suitable T wave amplitude and morphology was selected for analysis; the QT interval was measured in a semi-automated manner, under operator control, to allow for a more accurate identification of the end of the T wave. Time intervals were resolved to 2.5 ms.

By means of the same ECG Holter software, QT intervals were corrected for the previous cardiac cycle length according to Bazett's formula:

$$QTc \text{ (ms)} = QT / \sqrt{RR}.$$

Corrected QT (QTc) was considered prolonged when ≥ 440

ms, in accordance with the criteria commonly used in the literature (1, 3). The choice of Bazett's formula was due to technical reasons (the software of the ECG Holter automatically corrects the QT interval for the previous cycle according to Bazett's formula). Despite the extensive use in literature, the authors are aware that the adequacy of this formula has been questioned because it tends to overcorrect QT at high heart rates and undercorrect it at low heart rates.

All patients gave their fully informed consent and the Hospital Ethical Committee approved the study.

Statistical analysis was performed using the SAS package. Results were expressed as means±SD. The Kruskal-Wallis test for non-parametric samples and the χ^2 test were used to test for group differences of the means and proportions, respectively. The Mann-Whitney test was used to compare subjects with and without prolonged QTc values. Spearman correlation coefficients were calculated to correlate QTc length and HRV parameters. Multiple linear regression analysis was performed using QTc as the dependent variable. A *p*

Table 3. General and Clinical Characteristics of Patients with and without Prolonged QTc Values

	QTc ≥ 440 ms ($n=20$)	QTc < 440 ms ($n=195$)	<i>p</i>
QTc (ms)	468 $\pm$ 30	401 $\pm$ 22	<0.0001
Age (years)	44 $\pm$ 10	39 $\pm$ 25	0.03
Sex (M/F)	7/13	137/58	0.001
Duration of hypertension (months)	25 $\pm$ 17	35 $\pm$ 47	0.81
BMI (kg/m ²)	24 $\pm$ 5	25 $\pm$ 3	0.04
Systolic BP (mmHg)	145 $\pm$ 18	146 $\pm$ 15	0.52
Diastolic BP (mmHg)	93 $\pm$ 10	94 $\pm$ 9	0.48
Heart rate (bpm)	78 $\pm$ 8	77 $\pm$ 12	0.43
LVMI (g/m ²)	97 $\pm$ 17	96 $\pm$ 25	0.63
Glycemia (mg/dL)	88 $\pm$ 8	92 $\pm$ 10	0.04
Creatinine (mg/dL)	0.9 $\pm$ 0.1	0.9 $\pm$ 0.2	0.31
Total cholesterol (mg/dL)	209 $\pm$ 45	207 $\pm$ 40	0.83
Triglycerides (mg/dL)	110 $\pm$ 93	127 $\pm$ 122	0.28
PRA (ng/mL/h)	1.4 $\pm$ 1.0	1.3 $\pm$ 1.4	0.48
Aldosterone (ng/mL)	174 $\pm$ 81	143 $\pm$ 87	0.12
ARR	258 $\pm$ 267	216 $\pm$ 243	0.53

QTc, corrected QT; BMI, body mass index; BP, blood pressure; LVMI, left ventricular mass indexed to body surface area; PRA, plasma renin activity; ARR, aldosterone to PRA ratio.

value <0.05 was considered statistically significant.

Results

The general and clinical characteristics of the study population are shown in Table 1. The QTc interval length was, on average, 407 $\pm$ 30 ms and was higher in females (421 $\pm$ 29 ms) than in males (400 $\pm$ 28 ms) ($p<0.0001$).

Table 2 shows the results of the HRV analysis in the time domain and the frequency domain. All HRV indexes in the time domain were lower in females than in males. The LF index and LF/HF ratio were similar in both sexes, and the HF index was higher in females than in males.

Nine percent of the patients showed a QTc ≥ 440 ms. The two subgroups, with and without prolonged QTc, showed QTc lengths of 468 $\pm$ 30 and 401 $\pm$ 22 ms ($p<0.0001$), respectively. Table 3 shows the general and clinical results of the patients with and without prolonged QTc values.

The HRV indexes in the time domain—SDNN, RMSSD, pNN50, and SDNN index (nighttime)—were significantly reduced in the subgroup of patients with prolonged QTc (Table 4). The HRV indexes in the frequency domain were similar in both subgroups of patients; TP was significantly lower in the patients with QTc ≥ 440 ms (Table 4). Table 5 shows the results of the HRV indexes in the time domain in male and female patients with and without prolonged QTc. In males, pNN50 (24 h, daytime and nighttime) and RMSSD (nighttime) were lower in the group with prolonged QTc. In females, RMSSD (24 h and daytime) and pNN50 (24 h and daytime) were lower in the group with prolonged QTc. All remaining HRV indexes tended to be lower in the group with prolonged QTc, in both sexes.

Linear correlation analysis between QTc length and HRV parameters showed a significant negative correlation with all the time-domain indexes (Table 6, Fig. 1). Such a correlation was maintained for RMSSD, pNN50 and SDNN index (nighttime) after correction for gender and age (Table 5). No significant correlations were found among QTc length and blood pressure, BMI, and laboratory findings.

Multiple linear regression analysis was performed using QTc length as a dependent variable. Age, gender and HRV parameters were introduced into the model as independent factors. The analysis identified SDNN index (nighttime), gender and age as independent factors predicting QTc length (SDNN index: $r^2=0.14$, $p<0.0001$; gender: $r^2=0.20$, $p=0.0006$; age: $r^2=0.22$, $p=0.02$).

Discussion

The present study has shown that, even prior to the development of cardiac hypertensive disease, a prolongation of QT interval and a reduced HRV, both markers of cardiovascular risk, coexist in a percentage of patients with untreated essential hypertension. The reduced HRV, resulting in enhanced sympathetic activity, may play a role in the alteration of ventricular repolarization.

QT interval prolongation has been associated with an increased risk of ventricular arrhythmias and sudden death in the general population (1), in diabetic patients (2, 16), after myocardial infarction (3) and in chronic heart failure (4). Furthermore, even the longest QT values still within the normal range have been associated with a higher risk of coronary heart disease in healthy middle-aged and elderly male populations (17). QT interval prolongation is one of the risk factors

Table 4. HRV Indexes of Patients with and without Prolonged QTc Values

		QTc ≥ 440 ms ($n=20$)	QTc < 440 ms ($n=195$)	<i>p</i>
RR (ms)		747 $\pm$ 82	786 $\pm$ 94	0.06
SDNN (ms)	24 h	126.4 $\pm$ 29.9	143.9 $\pm$ 35.4	0.02
SDANN (ms)	24 h	117.8 $\pm$ 30.7	132.3 $\pm$ 36.5	0.06
RMSSD (ms)	24 h	22.2 $\pm$ 7.7	31.2 $\pm$ 13.0	0.0007
pNN50 (%)	24 h	4.4 $\pm$ 4.9	9.7 $\pm$ 8.4	0.0006
SDNN index (ms)	daytime	98.7 $\pm$ 21.5	110.0 $\pm$ 27.7	0.10
RMSSD (ms)	daytime	19.5 $\pm$ 6.1	27.0 $\pm$ 11.7	0.0009
pNN50 (%)	daytime	2.2 $\pm$ 3.0	7.0 $\pm$ 7.6	0.0004
SDNN index (ms)	nighttime	85.9 $\pm$ 32.4	115.5 $\pm$ 36.7	0.0006
RMSSD (ms)	nighttime	26.4 $\pm$ 13.1	40.5 $\pm$ 19.3	0.0007
pNN50 (%)	nighttime	7.2 $\pm$ 9.7	17.7 $\pm$ 14.3	0.0001
TP (ms ²)	24 h	2,292.9 $\pm$ 1,173.8	3,914.8 $\pm$ 1,962.2	<0.0001
LF (ms ²)	24 h	568.9 $\pm$ 308.4	1,088.5 $\pm$ 868.9	<0.0001
HF (ms ²)	24 h	180.1 $\pm$ 201.6	300.0 $\pm$ 214.2	0.0002
LF (n.u.)	24 h	76.4 $\pm$ 9.2	84.0 $\pm$ 57.8	0.66
HF (n.u.)	24 h	21.9 $\pm$ 9.0	21.8 $\pm$ 14.5	0.79
LF/HF	24 h	4.4 $\pm$ 3.0	4.6 $\pm$ 2.7	0.73
TP (ms ²)	daytime	2,085.25 $\pm$ 1,070.6	3,446.8 $\pm$ 1,933.1	0.0004
LF (n.u.)	daytime	80.3 $\pm$ 6.9	80.2 $\pm$ 11.0	0.60
HF (n.u.)	daytime	18.0 $\pm$ 6.7	16.9 $\pm$ 5.8	0.65
LF/HF	daytime	5.36 $\pm$ 3.18	5.45 $\pm$ 2.55	0.71
TP (ms ²)	nighttime	2,714.4 $\pm$ 1,506.2	4,907.1 $\pm$ 2,565.5	<0.0001
LF (n.u.)	nighttime	71.9 $\pm$ 11.3	72.8 $\pm$ 10.5	0.81
HF (n.u.)	nighttime	31.0 $\pm$ 18.3	25.6 $\pm$ 10.7	0.54
LF/HF	nighttime	3.38 $\pm$ 2.82	3.58 $\pm$ 2.20	0.57

QTc, corrected QT; RR, mean RR intervals; SDNN, standard deviation of all normal-to-normal intervals; SDANN, standard deviation of the average normal-to-normal intervals calculated over a 5 min period; RMSSD, square root of the mean squared differences of successive normal-to-normal intervals; pNN50, number of interval differences of successive normal-to-normal intervals greater than 50 ms divided by the total number of normal-to-normal intervals; SDNN index, mean of the 5-min standard deviation of the normal-to-normal intervals calculated over 24 h; TP, total spectrum power; LF, low-frequency power (0.04–0.15 Hz); HF, high-frequency power (0.15–0.4 Hz); LF/HF, LF to HF ratio; n.u., normalized units.

Table 5. HRV Indexes of Patients with and without Prolonged QTc Values, Categorized by Gender

		Male		Female	
		QTc ≥ 440 ($n=7$)	QTc < 440 ($n=137$)	QTc ≥ 440 ($n=13$)	QTc < 440 ($n=58$)
RR (ms)		780 $\pm$ 124	801 $\pm$ 97	729 $\pm$ 44	748 $\pm$ 75
SDNN (ms)	24 h	138 $\pm$ 40	152 $\pm$ 36	120 $\pm$ 22	124 $\pm$ 26
SDANN (ms)	24 h	129 $\pm$ 42	141 $\pm$ 38	112 $\pm$ 22	112 $\pm$ 24
RMSSD (ms)	24 h	25 $\pm$ 6	33 $\pm$ 13	21 $\pm$ 9	27 $\pm$ 11*
pNN50 (%)	24 h	5 $\pm$ 4	11 $\pm$ 8*	4 $\pm$ 6	7 $\pm$ 8*
SDNN index (ms)	daytime	109 $\pm$ 26	112 $\pm$ 29	93 $\pm$ 18	104 $\pm$ 24
RMSSD (ms)	daytime	22 $\pm$ 4	28 $\pm$ 12	18 $\pm$ 7	25 $\pm$ 10*
pNN50 (%)	daytime	2 $\pm$ 2	8 $\pm$ 8*	2 $\pm$ 4	5 $\pm$ 6*
SDNN index (ms)	nighttime	89 $\pm$ 51	124 $\pm$ 35	84 $\pm$ 19	96 $\pm$ 33
RMSSD (ms)	nighttime	26 $\pm$ 15	44 $\pm$ 20*	26 $\pm$ 13	33 $\pm$ 16
pNN50 (%)	nighttime	6 $\pm$ 8	20 $\pm$ 14*	8 $\pm$ 11	11 $\pm$ 13

* $p<0.05$ between normal and prolonged QTc values. QTc, corrected QT; RR, mean RR intervals; SDNN, standard deviation of all normal-to-normal intervals; SDANN, standard deviation of the average normal-to-normal intervals calculated over a 5 min period; RMSSD, square root of the mean squared differences of successive normal-to-normal intervals; pNN50, number of interval differences of successive normal-to-normal intervals greater than 50 ms divided by the total number of normal-to-normal intervals; SDNN index, mean of the 5-min standard deviation of the normal-to-normal intervals calculated over 24 h.

Table 6. Linear Correlation between the Heart Rate Variability Indexes and the QTc Interval Length

			Total group	Male (<i>n</i> =144)	Female (<i>n</i> =71)
SDNN (ms)	24 h	Coefficient	−0.32	−0.13	−0.16
		<i>p</i>	<0.0001	0.10	0.16
SDANN (ms)	24 h	Coefficient	−0.26	−0.09	−0.10
		<i>p</i>	<0.0001	0.28	0.39
SDNN index (ms)	daytime	Coefficient	−0.24	−0.15	−0.21
		<i>p</i>	0.0004	0.07	0.08
SDNN index (ms)	nighttime	Coefficient	−0.42	−0.20	−0.34
		<i>p</i>	<0.0001	0.02	0.04
RMSSD (ms)	24 h	Coefficient	−0.37	−0.21	−0.37
		<i>p</i>	<0.0001	0.01	0.001
pNN50 (%)	24 h	Coefficient	−0.37	−0.22	−0.37
		<i>p</i>	<0.0001	0.007	0.001

SDNN, standard deviation of all normal-to-normal intervals; SDANN, standard deviation of the average normal-to-normal intervals calculated over a 5 min period; SDNN index, mean of the 5-min standard deviation of the normal-to-normal intervals calculated over 24 h; RMSSD, square root of the mean squared differences of successive normal-to-normal intervals; pNN50, number of interval differences of successive normal-to-normal intervals greater than 50 ms divided by the total number of normal-to-normal intervals.

Fig. 1. Linear correlation between the QTc interval length and the RMSSD index of heart rate variability in the total group of patients (*n*=215): Spearman correlation coefficient −0.37, *p*<0.0001.

for cardiovascular events in patients with essential hypertension, with (5) and without (7) left ventricular hypertrophy, even after effective antihypertensive treatment (5).

A prolonged QT interval was found in 9% of the patients (5% of males and 18% of females) in the present study. Such a prevalence is lower than that (27%) in a previous study (18), in which hypertensive patients were older and mostly complicated by left ventricular hypertrophy, and similar to that (10%) in the wide hypertensive population of the PIUMA study (7).

The hypertensive patients with a prolonged QT interval were older and most were females. This finding confirms the association, frequently reported in the literature, among QT

prolongation, increasing age and female gender. The possible causes of prolonged QT interval in untreated, uncomplicated essential hypertensive patients may include abnormalities of potassium channels of the myocytes (19), foci of subclinical local myocardial ischemia, and local ventricular denervation (abnormalities of autonomic cardiac control) (14, 20, 21).

By increasing vulnerability to ventricular arrhythmias, a reduced HRV after myocardial infarction is an important negative prognostic factor (22). In hypertensive patients, an alteration of HRV resulting in enhanced sympathetic activity has been described both prior to the onset of hypertension (13) and in relation to the development of hypertensive heart damage (23).

The HRV indexes in the time domain (SDNN, RMSSD, pNN50 and SDNN index) and the total power (TP) in the frequency domain were significantly reduced in our hypertensive patients with a prolonged QT interval. The correlation analysis showed a significant negative correlation between QT length and all HRV indexes in the time domain. Such a correlation was maintained for RMSSD, pNN50 and SDNN index (nighttime) after correction for age and gender.

The definition of the role of autonomic control in ventricular repolarization is complex, due to the differences in sympatho-vagal regulation between the sinus node and ventricular muscle, variation in the vagal modulation of sympathetic tone at different heart rates, and the rate-dependent characteristic of the QT interval (9).

Sympathetic modulation and/or vagal impairment have been proposed to alter ventricular repolarization (24–26). In dogs, sympathetic and parasympathetic tones physiologically regulate the QT interval through the action of myocardial autonomic nerves *via* both the sinus node and ventricular muscle (27). A reduced vagal tone with a relative enhanced sympathetic activity may favour a prolongation of the QT

interval in canine hearts (28).

In healthy subjects, QT dispersion increases with increasing sympathetic activity or with decreasing parasympathetic activity (29). In diabetic patients with mild parasympathetic neuropathy, QT heart rate dependence is impaired and this is associated with an impaired sympatho-vagal balance (30).

Passino *et al.* (26) found a prolonged QT interval in hypertensive patients compared to normotensive athletes showing a similar degree of left ventricular hypertrophy but with a preserved sympatho-vagal balance. According to the authors, sympathetic predominance would therefore play a role in determining the abnormal ventricular repolarization in hypertensive patients, independently of left ventricular hypertrophy. Other authors postulate that chronic anxiety, found in over 50% of hypertensive patients, causes a persistent sympathetic predominance, which could favour the development of left ventricular hypertrophy and the subsequent increased QT dispersion (31).

The present study is compatible with the above results and shows, for the first time, the coexistence of a prolonged QT interval and reduced HRV in a percentage of untreated hypertensive patients, even prior to the development of left ventricular hypertrophy.

Other factors traditionally responsible for altered ventricular repolarization, such as drugs, renal diseases and electrolyte abnormalities, may be ruled out in the present study, due to the accurate selection of the population.

Limitations of the study include the single examination, which does not allow consideration of the spontaneous variability of the QT interval over time; the semi-automatic analysis of the 24 h Holter ECG, which may still be affected by artefacts and sinus arrhythmia; and the correction of QT length by means of the controversial Bazett's formula. Despite the correction for gender in the linear correlation analysis, another limitation of the study is the predominance of females in the prolonged QTc group, which may reduce the significance of the finding of lower time-domain HRV indexes in that group. The lack of a control group further limits the interpretation of the results.

The present data suggest the possibility of a higher risk of life-threatening arrhythmias and sudden death in a percentage of hypertensive patients with coexistence of a prolonged QT interval and reduced HRV, prior to the development of cardiac hypertensive disease. Follow-up studies are warranted to evaluate the potential role of the association of abnormal ventricular repolarization and reduced HRV in predicting cardiac autonomic dysfunction and mortality rates.

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