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Abnormal ventricular repolarization in hypertensive patients: role of sympatho-vagal imbalance and left ventricular hypertrophy ☆

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Abstract

Background: An increased risk for life-threatening arrhythmias and sudden death has been observed in hypertensive patients, associated with either left ventricular hypertrophy (LVH) or prolonged QT interval. To investigate the influence of autonomic imbalance and LVH on QT interval in hypertensive patients, we compared two different models of LVH: hypertension and endurance physical training. *Methods:* Forty-seven untreated subjects affected by essential hypertension and 35 endurance runners, with a similar degree of LVH, were enrolled into the study. All subjects underwent 24-h ambulatory ECG recording and morning blood sampling for catecholamines. Heart rate variability was evaluated by spectral analysis and a computerized algorithm was used to measure the QT interval; QTc was then computed by the Bazett's formula. Left ventricular mass index (LVMI) was assessed by echocardiogram. *Results:* No difference in LVMI was found between hypertensive patients and athletes. Athletes showed lower heart rate (64 ± 1 vs. 75 ± 1 bpm, $p < 0.001$, mean $\pm$ S.E.M.) and shorter QTc (401 ± 3 vs. 434 ± 4 ms, $p < 0.001$) than hypertensive patients throughout the 24-h period. Athletes showed a higher vagal drive compared to hypertensive patients as suggested by bradycardia and higher values of vagal indices, which negatively correlated with QTc. Plasma norepinephrine was significantly lower in athletes than in hypertensive patients ($p < 0.05$) and positively correlated with QTc. *Conclusion:* Despite similar degrees of LVH, hypertensive patients show QTc lengthening, as compared to athletes. Heart rate variability and plasma norepinephrine levels suggest sympathetic predominance in hypertensive patients, which could contribute to abnormal ventricular repolarization, thus identifying patients with an increased arrhythmic risk.

Keywords: Hypertension; QT interval; Autonomic nervous system; Arrhythmia; Hypertrophy; Athletes

1. Introduction

Systemic arterial hypertension increases threefold the risk of death [1], mainly due to arrhythmic events. Hypertension is frequently associated with left ventricular hypertrophy (LVH), which is an independent risk factor for cardiovascular morbidity and mortality, including sudden death; hypertensive patients who present LVH have been shown to have significantly more ventricular ectopic beats than either hypertensive patients without LVH or normotensive subjects [1]. Hypertension is also associated with sympatho-vagal imbalance characterized by vagal withdrawal and relative sympathetic dominance [2,3], which can trigger ventricular arrhythmias [4].

The QT interval is currently considered a marker of ventricular repolarization, and the lengthening of QT interval corrected for heart rate (QTc) has been associated with increased risk for either ventricular arrhythmias or sudden cardiac death [5,6]. Abnormalities in ventricular repolarization have been described in hypertensive patients and associated with left ventricular hypertrophy [7] or nondipper status [3]. Furthermore, prolonged QTc interval has been associated with sympathetic predominance [8] or decreased vagal drive [3,9].

Highly trained endurance athletes show morphologic cardiac changes (i.e., athlete's heart), consequence of several determinants, including type of sport, gender and,

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possibly, inherited genetic factors [10]. The extent of physiologic cardiac remodelling may occasionally be substantial, leading to LVH, reversible with detraining [11].

In order to evaluate the relative influence of LVH and sympatho-vagal drive to the heart on ventricular repolarization, we studied the circadian pattern of QTc and heart rate in moderate hypertensive patients and in endurance athletes, a model of normotensive subjects with LVH.

2. Materials and methods

2.1. Study population

We enrolled into the study 47 untreated patients affected by mild-to-moderate essential hypertension. Hypertension was defined according to the fifth report of the Joint National Committee as office blood pressure $\geq 140/90$ mm Hg (average of three different measurements over a period of 2 months). Secondary causes of hypertension were carefully ruled out, as well as valvular or primary myocardial heart disease and diabetes.

Thirty-five age-, sex- and LVMI-matched endurance runners (on average 55 miles weekly, range 20–65) were also included in the study design.

All subjects had normal cardiac function at the echocardiographic study, normal renal function and no other systemic disease or electrolyte abnormalities at standard laboratory investigations.

None of the subjects or patients was taking any medication and none was smoker. Alcohol consumption was negligible and comparable in two groups. All subjects were in sinus rhythm; none had baseline or transient ventricular conduction disturbance at 12-lead electrocardiogram (ECG) or at ambulatory ECG recording. Significant coronary artery disease was excluded on the basis of both history and negative effort tolerance ECG test. The investigation was approved by the Institutional Review Board of the C.N.R. Institute of Clinical Physiology, and all participants gave informed consent before the study began.

2.2. Protocol

All subjects underwent an initial evaluation in the morning, including clinical history, physical examination and blood pressure measurement (by means of a conventional sphygmomanometer with the subject sitting). In order to measure plasma epinephrine and norepinephrine, hypertensive subjects underwent a blood sample from the antecubital vein after 20 min of bed rest while fasting (automated high-pressure liquid chromatography, HPLC 725 apparatus, equipped with electrochemical detector, Eurogenetics, Tessenderlo, Belgium).

M-mode echocardiography was used to measure the diastolic thickness of the interventricular septum, the posterior left ventricular wall and the diastolic and systolic left ventricular diameters. Two-dimensional images taken from longitudinal or transverse parasternal views were used to ensure that all measurements were obtained at the same level. Measurements were made accordingly to the American Society of Echocardiography recommendations [12]. Left ventricular mass was calculated according to the Penn convention [13] (using the following formula: $1.04 \cdot [(\text{left ventricular, internal dimension} + \text{posterior wall thickness} + \text{septal wall thickness})^3 - (\text{left ventricular internal dimension})^3] - 14$) and divided by body surface area to obtain left ventricular mass index (LVMI). Due to a significant difference in body mass index a correction for height was also tested with no significant changes in the results, so the common correction for body surface area was used. Left ventricular hypertrophy was defined as a value of LVMI greater than 116 g/m^2 in men and 104 g/m^2 in women [14].

An ambulatory recording of the ECG, using an inferior and a precordial lead, (Remco-Cardioline, Milan, Italy) was obtained in all subjects. Subjects were instructed to carry out their habitual activities and record them on a diary. For the evaluation of the circadian profile of cardiovascular indices, daytime was considered from 6 a.m. to 10 p.m., nighttime 10 p.m. to 6 a.m.

2.3. ECG data processing

The ECG was digitised at 250 Hz. For the QT interval, a computerised algorithm was used to identify the onset of the QRS and the end of the T wave on the precordial lead (with the use of a derivative filter applied to an observation interval on the ECG signal centred on the theoretical trend $0.4 \times RR^{1/2}$, on the basis of threshold-trespassing deflection with reference to the baseline signal) [3,15]. The QT interval was corrected by the heart rate with the Bazett's formula ($QTc = QT/RR^{1/2}$) [16]. Bazett's formula, although presenting the limit of a residual linear association with heart rate, is simple and the most commonly applied: since other correction formulas did not prove to be superior predictors, Bazett's formula is acceptable for correcting QT interval by heart rate [15, 17].

Table 1
General characteristics

	Hypertensives	Athletes
N	47	35
Age (years)	48.5 ± 1.3	50.7 ± 1.6
Sex (M/F)	23/5	17/3
BMI (kg/m^2)	26.1 ± 0.4	23.2 ± 0.4***
SBP (mm Hg)	144 ± 2	116 ± 1***
DBP (mm Hg)	92 ± 1	69 ± 1***
LVMI (g/m^2)	127 ± 3	121 ± 4

Data presented are number of patients or mean value ± S.E.M. BMI = body mass index, F = females, M = males, DBP = diastolic blood pressure, SBP = systolic blood pressure.

*** $P < 0.001$ vs hypertensives.

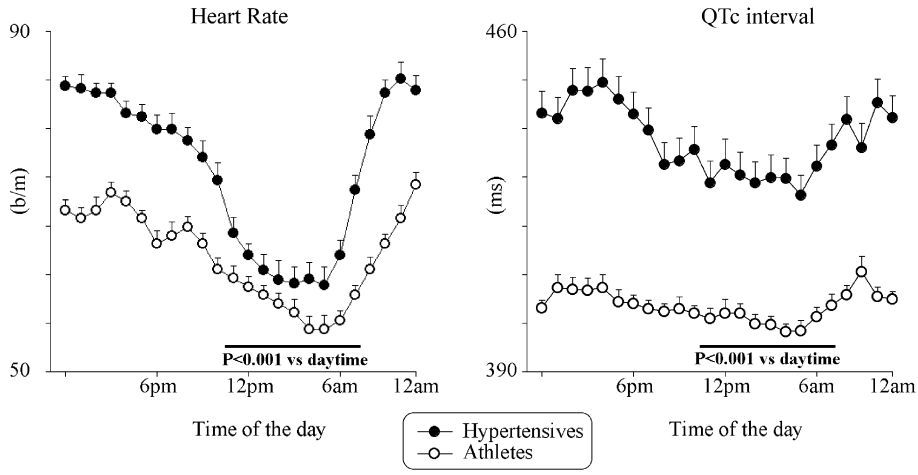

Fig. 1. Circadian variation of heart rate and QTc interval in hypertensive patients and athletes (mean ± S.E.M.), showing a maintained modulation of heart rate and QTc in both groups of subjects.

Time domain heart rate variability was computed by means of commercial software (Remco-Cardioline). The following parameters have been calculated: standard deviation of all NN intervals (SD); standard deviation of the averages of NN intervals in all 5-min segments of the entire recording (SDANN); the square root of the mean of the sum of the squares of differences between adjacent NN intervals (rMSSD); mean of the standard deviations of all RR intervals for all 5-min segments of the entire recording (sdRR); number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording divided by the total number of all NN intervals (pNN50). SD is a general marker of total (beat-to-beat and circadian) heart rate variability, SDANN is a marker of the circadian variability; rMSSD, sdRR and pNN50 are markers of beat-to-beat heart rate variability, reflecting mainly vagal modulation of sinus node.

In order to obtain a spectral representation of the RR interval variability, an autoregressive model was applied to consecutive intervals of 256 data points throughout the 24-h period, as previously described [18]. Two orders of spontaneous oscillations were considered in the RR power spectrum: low-frequency rhythm (LF, from 0.03 to 0.15 Hz) and respiratory sinus arrhythmia (high frequency component, HF, from 0.15 to 0.40 Hz). The LF component of the RR interval variability is sensitive to both vagal and sympathetic influences, whereas the HF power is sensitive to vagal influence only; the LF/HF ratio is regarded as an index of sympatho-vagal balance [19].

2.4. Statistical analysis

The results are given as mean ± SEM. Conventional statistical methods were used to calculate the individual mean values of heart rate, QTc interval and spectral parameters for the 24-h period, the day and the night. Due to their skew distribution, spectral values were analysed statistically only after natural logarithmic transformation. Due to the known relation between spectral indexes and heart rate, comparisons of spectral variables between hypertensive patients and athletes were performed after statistical adjustment for heart rate. Comparison between groups were performed using unpaired *t*-test, for parametric variables and chi-square test, followed by the Fisher exact test, for

Table 2
Heart rate, QTc interval and spectral parameters of heart rate variability

	Hypertensives			Athletes		
	24 h	Day	Night	24 h	Day	Night
Heart rate (bpm)	75 ± 1	81 ± 1	65 ± 2***	64 ± 1†††	68 ± 1†††	55 ± 1***,†††
QT interval (ms)	388 ± 4	373 ± 3	408 ± 5***	391 ± 3	379 ± 3	416 ± 4***
QTc interval (ms)	434 ± 4	437 ± 4	425 ± 5***	401 ± 3†††	405 ± 2†††	400 ± 1***,†††
Total power ($lnms^2$)	6.6 ± 0.1	6.4 ± 0.1	6.8 ± 0.1***	6.9 ± 0.1†	6.9 ± 0.1††	7.2 ± 0.1***,†
LF power ($lnms^2$)	6.0 ± 0.1	6.0 ± 0.1	6.2 ± 0.1	6.6 ± 0.1†	6.5 ± 0.1††	6.6 ± 0.2††
HF power ($lnms^2$)	5.0 ± 0.2	4.6 ± 0.2	5.6 ± 0.1***	5.4 ± 0.1†	5.2 ± 0.1††	5.9 ± 0.2***
LF/HF ratio	7.69 ± 0.96	9.18 ± 1.19	3.61 ± 0.37***	6.58 ± 0.59	7.55 ± 0.70	4.04 ± 0.44***

LF = low frequency, HF = high frequency.
*** $P < 0.001$ vs daytime values.
† $P < 0.05$.
†† $P < 0.01$.
††† $P < 0.001$ vs hypertensives.

Table 3
Heart rate variability/time domain

	Hypertensives	Athletes
SD (ms)	144 ± 6	164 ± 7*
pNN50 (%)	6.2 ± 0.8	9.6 ± 1.5*
RMSSD (ms)	20.0 ± 1.0	24.1 ± 1.6*
SDANN (ms)	138 ± 6	149 ± 7
sdRR (ms)	54.5 ± 2.4	67.0 ± 3.3**

SD: standard deviation of all NN intervals, SDANN: standard deviation of the averages of NN intervals in all 5-min segments of the entire recording, rMSSD: the square root of the mean of the sum of the squares of differences between adjacent NN intervals, sdRR: mean of the standard deviations of all RR intervals for all 5-min segments of the entire recording, pNN50: number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording divided by the total number of all NN intervals.

* $P<0.05$.

** $P<0.01$ vs hypertensives.

nonparametric variables. Paired *t*-test was used to assess differences within the groups between day- and nighttime mean values. Linear regression analysis was used to assess the relationship among QTc interval and other variables. A *P*-value <0.05 was considered statistically significant.

3. Results

The general characteristics of the subjects are presented in Table 1. A significant difference was observed in body mass index, athletes showing lower values: therefore adjustment for body mass index was performed prior to make comparisons between groups. None of the subjects showed conduction disturbances or transient myocardial ischemia at ambulatory recording. Out of 47 hypertensive patients, 9 had multifocal ventricular ectopics and none had ventricular tachycardia. None of the athletes showed significant arrhythmias.

Blood pressure values, measured by conventional sphygmomanometer, were significantly higher in hypertensive subjects than in athletes (144 ± 2 vs. 116 ± 1 mm Hg, for systolic, and 92 ± 1 vs. 69 ± 1 mm Hg, for diastolic blood pressure, both $P<0.001$).

A similar circadian pattern of heart rate, with a nocturnal decrease, was present in hypertensive patients or athletes (Fig. 1). Athletes were significantly bradycardic with respect to hypertensive patients over the 24-h period, at day- or nighttime (all $P<0.001$) (Table 2).

3.1. Circadian pattern of QTc interval in hypertensive patients compared to athletes (Table 2)

Compared to athletes, hypertensive patients showed a longer QTc interval throughout the 24-h period ($P<0.001$). A preserved circadian pattern was evident either in hypertensive patients or in athletes with a significant nocturnal decrease in QTc interval ($P<0.001$) (Fig. 1). No significant differences were observed in absolute QT values between the two groups.

3.2. QTc interval and sympatho-vagal drive

Plasma norepinephrine was significantly higher, though within the laboratory reference range, in hypertensive patients compared to athletes (385 ± 24 vs. 308 ± 23 pg/ml, $P=0.023$), while epinephrine presented similar values in both groups (30 ± 4 vs. 35 ± 4 pg/ml, NS). A significant positive correlation ($R=0.32$, $P=0.011$) was found among plasma norepinephrine and duration of QTc over the 24-h period. Conversely, no correlation was found between catecholamine plasma levels and degree of left ventricular hypertrophy.

As far as heart rate variability concerns, lower values either in time or frequency domain indices were observed in hypertensive patients compared to athletes (Tables 2 and 3). Specifically, indices derived from time domain analysis known to reflect mainly vagal modulation, such as pNN50, rMSSD and sdRR, were significantly lower in hypertensive patients. The same difference was present for absolute LF and, more markedly, for HF power values throughout the 24-h period. Although circadian variation of the spectral values was preserved in both groups, the difference in LF and HF power was particularly evident during the day. A significant negative correlation was found among duration of QTc over the 24-h period and sdRR ($R=-0.28$, $P=0.015$) or total power ($R=-0.24$, $P=0.039$) or LF power ($R=-0.24$, $P=0.033$) or HF power

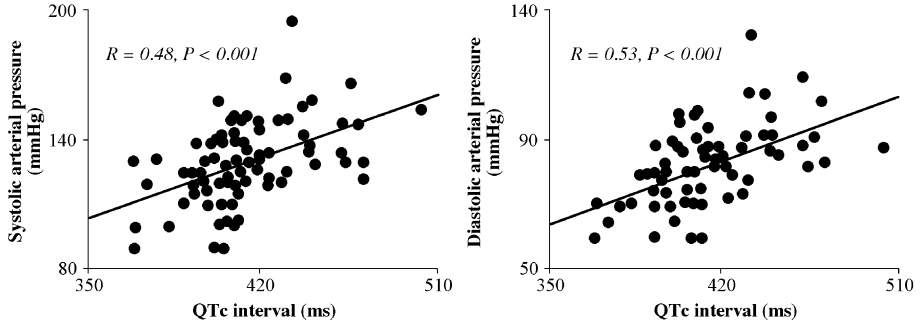

Fig. 2. Linear regression between 24-h QTc interval and systolic and diastolic blood pressures.

($R = -0.24$, $P = 0.034$). No correlation was found among LVMI and heart rate variability indices.

3.3. Left ventricular hypertrophy and blood pressure values: relation with QTc interval

Left ventricular hypertrophy was found in 31 hypertensive patients and 18 athletes. A slight though significant correlation was found between LVMI and averaged 24-h QTc interval ($R = 0.22$, $P = 0.045$), daytime QTc ($R = 0.23$, $P = 0.033$) and nighttime QTc ($R = 0.34$, $P = 0.002$). Conversely, a stronger correlation was found between QTc and systolic and diastolic blood pressure values ($R = 0.48$, $P < 0.001$ and $R = 0.53$, $P < 0.001$, respectively) (Fig. 2).

4. Discussion

The main finding of this study is that QTc interval is prolonged in hypertensive patients as compared to normotensive athletes showing a similar degree of LVH, with a preserved circadian rhythm. Sympathetic predominance found in hypertensive patients would indicate a role of autonomic dysfunction in determining abnormal ventricular repolarization, independently of LVH.

A central role of left ventricular hypertrophy in altering ventricular repolarization has been proposed to explain either QTc lengthening or higher QTc dispersion in hypertensive patients [20], possibly related to structural changes in the hypertrophied myocardium, altering the ion channels operating during the early repolarization phase, and to fibrotic changes in the myocardium leading to electrophysiological heterogeneity [21–23].

In the studied population, LVH per se was not apparently able to induce abnormalities of QTc duration, since normotensive healthy subjects with similar degree of LVH did not present QTc lengthening: additional factors are therefore acting in the pathogenesis of prolongation of ventricular repolarization in hypertensive patients. A possible explanation for the low relevance of LVH in the process that leads to QTc lengthening could be the relatively short duration of the disease and the moderate degree of hypertension in the present subset of patients: in the early stages of hypertension, LVH is probably not accompanied to the marked structural changes and fibrosis described in advanced stages of the disease.

QTc interval duration is influenced even by the autonomic nervous system [3,24,25]: abnormal sympathetic modulation [8] or vagal withdrawal [3,9] may directly alter ventricular repolarization, leading to prolongation of the QT interval. Differences in the autonomic drive to the heart between groups might explain the difference in QTc duration, despite similar degrees of LVH. In the present study, hypertensive subjects showed a sympathetic predominance associated with signs of adrenergic overactivity, as pointed out by higher norepinephrine plasma levels, and vagal withdrawal, indicated by lower vagal indices derived from heart rate variability, namely pNN50, sdRR, and HF power, and even LF power, of mixed sympatho-vagal origin. This autonomic imbalance with an overall sympathetic shift may predispose hypertensive patients to prolongation of QTc interval, as confirmed by the significant correlation among QTc interval and plasma norepinephrine levels or heart variability indices.

In conclusion, sympatho-vagal imbalance in hypertensive patients with LVH could contribute to abnormal ventricular repolarization process leading to prolongation of QTc. The association of two markers of arrhythmogenic risk, as QTc lengthening and LVH, may identify a subset of patients in whom enhanced and specific therapeutical efforts are required, aimed to regression of both LVH and sympatho-vagal imbalance.

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