

Increased QT Variability in Patients with Hypertrophic Cardiomyopathy

ML Migaux, F Marciano, S Cuomo*

Institute of Cybernetics, CNR, Pozzuoli, Napoli; *Division of Cardiology, A. Cardarelli Hospital, Napoli, Italia

Abstract

The purpose of this study was to examine QT interval variability in hypertrophic cardiomyopathy (HCM) by using frequency domain indices.

Twenty-six subjects participated to the study: 16 had HCM (5 females, 9 males; mean age 39 ± 13 years), 10 were healthy volunteers (5 females, 5 males; mean age 35 ± 13 years), who served as controls. Twenty-four-hour Holter recordings of each subject were analysed on a homemade Holter analyser. The following spectral domain measures of QT interval variability were computed: ultra low (ULF), very low (VLF), low (LF) high frequency (HF) and total power.

Spectral domain measures of QT interval variability were significantly higher in subjects with HCM than in controls. Further studies are required to evaluate whether analysis of QT variability on Holter recordings might have prognostic implications.

1. Introduction

Patients with hypertrophic cardiomyopathy (HCM) are at increased risk of sudden cardiac death [1]. Ventricular arrhythmias are a common finding in these patients. Non-sustained ventricular tachycardia occurs in about 25% of adult patients with HCM during Holter electrocardiographic monitoring [2]. Abnormalities in repolarization of ventricular myocardium may be implicated in the development of these arrhythmias. Previous works have indeed shown that QT and QTc intervals are often prolonged in patients with HCM [3,4]. However, it has been recently shown that QTc and QT dispersion are not reliable predictor of HCM-related sudden death [5]. Moreover, the presence of autonomic dysfunction has been documented in patients with HCM [6,7], even if it seems of limited usefulness in the assessment of risk.

This study was designed to quantify beat-to-beat fluctuations in the QT interval of patients with HCM using an algorithm developed by us. We compared frequency domain indices of QT interval variability in HCM patients with control subjects.

2. Methods

2.1. Subjects.

Sixteen patients with HCM (5 females, 11 males; mean age 39 ± 13 years) and 10 healthy volunteers (5 females, 5 males; mean age 35 ± 13), who served as controls, were included in the study. HCM was diagnosed on the basis of current diagnostic criteria including the evidence of left ventricular hypertrophy on 2-dimensional echocardiograms in the absence of other cardiac or systemic diseases that cause left ventricular hypertrophy [8]. All study subjects were ambulatory and had a 24-hour Holter monitoring ECG, showing sinus rhythm, normal QRS duration and clear end point of the T wave in at least one lead. None of the study patients received antiarrhythmic drugs at the time of the Holter recordings. All the study subjects were asked to maintain their normal activities and their normal asleep-awake rhythm during the recording.

2.2 Holter recordings and QT measurements

Three-channel 24-hour Holter monitoring was performed in all subjects with a Del Mar Avionics (Irvine, California) model 459 recorder. Holter recordings were analyzed on a homemade analyser built around a Motorola 68030-50 Mhz microprocessor (Motorola Inc. Libertyville, IL, USA). Operating characteristics of this analyser have been previously reported [9]. Briefly, 3 recorded ECG analog channels were read via a modified Teac-Tascam 234 Syncaset tape deck (Teac Co., Tokyo, Japan) and digitised at 200 samples/sec. Besides evaluation of the usual ECG parameters, including identification of QRS widths and shapes and of RR interval abnormalities, QT intervals at each beat were evaluated as follows.

The interval between the peak of the R wave (R_a) and the end of the T wave (T_e) was found in a 2 steps process. Firstly, a table relating the values of the intervals between R_a and the peak of the T wave T_a to RR intervals is built into the program.

The T_a point was then searched within a moving window centered around the value given by the table. Then the interval $T_a T_e$ was measured. The maximum slope value was found computing slopes after T_a as

moving averages of the slopes measured at four consecutive sample points, reducing in so doing the influence of artifacts and noise. It was, then, possible to derive a threshold as a fraction of this maximum value. Several consecutive slopes after the maximum were then compared with this threshold. The first point where the slope was smaller than the threshold was taken as T_e . Finally $Q R_a$ value \underline{is} was added to $R_a T_e$ to form the QT interval. The sequences of all RR and QT intervals were stored with a code number identifying its normality or their class of abnormality. Premature ventricular complexes and their adjacent beats, used only for time keeping purposes, were rejected just as noise and other aberrant ECG signals. Data losses did not exceed 15% of the total recordings..

Human supervision was performed before and during analysis of each Holter recording.

At the beginning, portions of the tapes are analysed, the results are verified, beat by beat, on the computer monitor and eventually, if necessary, the displacements of the windows for the detection of the peak and of the end of the T waves are adjusted. Also the amplitude threshold of the T wave might be adjusted. Similarly, at the end of the analysis, human intervention is recalled, when long periods of missing T waves or T wave ends are displayed on the monitor. After readjusting, as described earlier, analysis is resumed from the beginning of the tape. Whenever several attempts of readjustment fail, the recording is definitively discarded.

The sequences of all normal RR (NN) and their corresponding QT intervals were analysed in order to compute frequency domain measures of variability for the entire 24 h recordings.

The 24h power spectrum estimates were computed by means of the fast Fourier transforms and by averaging a sufficient number of spectra so as to reduce the estimation error. Time functions samples were obtained from the QT sequences by linear interpolation with time steps of 100 ms; this is a low-pass filtering operation which attenuates any variability above the chosen value of the sampling frequency. The power (ms^2) of QT variability was calculated within the frequency bandwidth shown in Table 1.

Table 1. Frequency domain measures of QT variability.

Power (ms^2)	Hz
Ultra low frequency	0.00066 to 0.0033
Very low frequency	0.0033 to 0.04
Low frequency	0.04 to 0.15
High frequency	0.15 to 0.34
Total	0.00066 to 0.34

2.3 Statistical analysis

All data are expressed as mean \pm SD. An unpaired t test

was used to compare variables between groups. Statistical significance for all tests was accepted at the $P<.05$ level.

3. Results

No differences were found in the age between patients and controls.

Spectral domain analysis of QT variability evidenced the presence of rhythmical modulation of QT.

Table 2 shows the data for QT variability analysis in HCM patients compared with controls.

Table 2. QT variability in HCM patients and in controls.

	HCM patients (ms^2)	Controls (ms^2)
ULF	6.9 \pm .32	6.4 \pm .22*
VLF	5.6 \pm .41	5.1 \pm .15¶
LF	5.2 \pm .43	4.7 \pm .18¶
HF	5.1 \pm .42	4.6 \pm .20¶
TP	7.4 \pm .34	6.9 \pm .16*

ULF = ultra-low frequency power; VLF = very-low frequency power; LF = low-frequency power; HF = high-frequency power; TP = total power.

* $p<0.001$ vs HCM patients; ¶ $p<0.005$ vs HCM patients.

All parameters of QT variability were significantly higher in patients with HCM than they were in controls.

4. Discussion

The developed software enables fully automatic quantification of QT variability in the frequency-domain. The main finding of the present study is that QT variability, as assessed by frequency-domain analysis, is significantly increased in patients with HCM in comparison to healthy subjects.

Non-sustained ventricular tachycardia is frequently detected during Holter monitoring in adult patients with HCM [2] and is associated with an increased incidence of sudden death. However, the factors that increase the risk for malignant arrhythmias in HCM are incompletely understood and identification of patients at risk for sudden death remains difficult. Abnormalities in autonomic control have been described in patients with HCM [6,7,10] and may be associated with a propensity to electrical instability and ventricular tachyarrhythmias, even though the underlying mechanisms are unclear. To date, various techniques different from QT variability have been used in the evaluation of autonomic tone in different clinical conditions, including short and long-term recordings measuring time domain or frequency domain heart rate variability [11], assessment of baroreceptor sensitivity [12], measurements of respiratory sinus arrhythmias [13]. Among these, heart rate

variability has become an increasingly accepted prognostic tool, because Holter monitoring enables to collect easily a large amount of patient data. Combining QT variability and heart rate variability analysis might improve the ability to detect autonomic dysfunction.

Increased QT variability may predispose patients with HCM to the development of ventricular arrhythmias, even if the present study did not directly evaluate the incidence of ventricular arrhythmias in these patients. Regarding the not prognostic nature of the present study, caution is warranted in estimating the clinical significance of the observed increase in QT variability. Indeed, the physiological basis and the clinical significance of beat-to-beat QT variability have not been yet extensively investigated.

Consistent with our findings, abnormal temporal fluctuations in ventricular repolarization have been previously reported in HCM patients with higher susceptibility to ventricular arrhythmias [14]. Whatever the explanation for this phenomenon may be, our findings indirectly support the potential clinical importance of temporal repolarization instability in patients with HCM. Besides QT variability, several different methods of evaluating ventricular repolarization have been more frequently employed, such as QT and QTc interval duration, QT dispersion, circadian rhythmicity of QTc, T wave alternans. It is not known if all of these measures are equivalent with respect to risk prediction. Although there are very few head-to-head comparisons, it is likely that these measures are not equivalent, because they provide independent pieces of information regarding ventricular repolarization.

Another unresolved issue is whether antiarrhythmic strategies should be guided by quantification of ventricular repolarization. Although this is suggestive, more data are needed on this issue.

Based on our findings we propose that future studies should be conducted to extend the evaluation of QT variability to a larger population of HCM patients, in order to determine its value in detecting and management of high risk patients.

At present, measurement of QT variability needs to be better defined and standardized before it might be used in individuals patients. In fact, a major limitation of QT variability for risk stratification is the lack of standardization of automatic QT measurement. From a methodological point of view, precise determination of the end of the T wave is the most difficult point. It has been suggested that differences between different computer algorithms in determining the end of the T wave may have important consequences with respect to diagnostic performance [15].

Finally, the range of normal values of QT variability is another unsettled issue.

In conclusion, patients with HCM show increased QT variability, which may predispose them to life-

threatening arrhythmias.

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Address for correspondence.

Sergio Cuomo,
Piazzetta Mondragone, 9
80132 Napoli, Italy

srgcuomo@yahoo.it