Classification of Patients With and Without Syncope by Means of QT Analysis in Hypertrophic Cardiomyopathy: Preliminary Results

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Abstract

In patients with hypertrophic cardiomiopathy a history of syncope is associated with increased risk of sudden death, an important role in its pathophysiology being presumably played by an arrhythmic mechanism.

Aim of the present study was to find out whether several ventricular repolarization parameters are useful to discriminate patients with and without syncope.

The Holter recordings of three groups of subjects (HCM with syncope, HCM without syncope and normal) were analyzed and three sets of variables were measured: six spectral, six QT/RR slope, twelve QT time parameters.

All three sets were submitted to tests (e.g. discriminant analysis) in order to verify the differences among groups. Finally classification of single subjects was carried out.

1. Introduction

Hypertrophic cardiomiopathy (HCM) has a genetic origin [1] . Its main characteristic is the presence of left ventricular hypertrophy, when no other cause can justify the increase of cardiac mass [2].

Several studies have pointed out that a history of syncope may be associated with increased risk of sudden death (SD) in subjects with HCM [3,4]. The identification of subjects at high risk of SD, even in cases where there is not yet clear evidence of syncope, represents an important objective.

An arrhythmic mechanism presumably plays a role in the pathophysiology of SD [5]; however, identifying the presence of an arrhythmic substrate in a specific patient remains an unanswered key issue. Abnormalities in ventricular repolarization may be implicated in the development of these arrhythmias. Indeed, abnormal QT and QTc interval prolongation and increased QT dispersion have been described in patients with HCM [6,7]. However, it has been recently reported that QTc and QT dispersion on the 12-lead electrocardiogram are not reliably useful for predicting sudden death in HCM [8]. In addition to differences in ventricular repolarization, abnormalities in autonomic function have been also reported in HCM [9]. Unfortunately, also heart rate variability analysis is not useful in the assessment of risk in HCM [9]. It is possible that combining ventricular repolarization and autonomic function analysis might improve risk stratification in HCM. Aim of the present study is to find out whether among several re-polarisation parameters , measured from 24h Holter recordings, some can be identified as useful in order to discriminate and classify HCM patients with and without syncope.

2. Methods

The study population consisted of 35 subjects belonging to three groups, whose mean age per group is reported in parenthesis: 1) 8 HCM patients with an history of one or more episodes of syncope (39 ± 14), 2) 13 HCM patients without previous syncope (38 ± 11), 3) 14 normal subjects (35 ± 13).

HCM diagnosis was made according to current criteria including the evidence of left ventricular hypertrophy on 2-dimensional echocardiograms in absence of other cardiac or systemic diseases . Both HCM diagnosis and subsequent Holter recordings from three ECG derivations were done at a special outpatient clinic dedicated to HCM at the Institute of Cardiology, Federico II University of Naples. They were analyzed with a homemade system, whose characteristics were previously reported [10]. Also the automatic interactive algorithm for QRS-T analysis was described before [11] . Out of a large number of time and frequency QT measured variables only some were chosen on the basis of preliminary selective statistical tests. The retained variables were grouped into three sets a, b, c .

a) six spectral domain parameters of QT variability: total power (0-0.35 Hz) in the 24 h and during sleep, ultra low (0-0.0033Hz) in the 24 h, very low (0.0033-0.04Hz) and low (0.04-0.15Hz) and high (0.15–0.35Hz) during sleep.

b) QT_c values and QT/RR slopes measured during 24h, awake and sleep periods.

c) 12 time domain parameters of QT variability: average values of QT_c (1), M and S variables , defined in fig .1, over 24h, awake and sleep periods, minimum value of M, maximum values of S and QT_c over 24h

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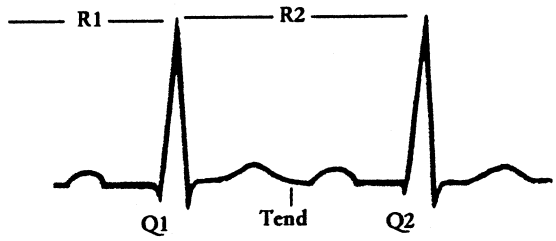
period.

$$QTc\,(msec) = \frac{QT(msec)}{\sqrt{RR(sec)}} \qquad (1)$$



$$M\% = 100\frac{Q2 - Tend}{R2} \qquad (2)$$

$$S\% = 100\frac{Tend - Q1}{R1} \qquad (3)$$

Figure 1 Definitions of variables M and S

Discriminant function analysis allowed the best choice of variables in each set eliminating redundancies and also allowing to find out which set of variables discriminates better among the three groups of subjects listed above. Computations of the centroids of the discriminant functions plots and of the percentage prediction counts per group of subjects enabled the selection of one set of variables as candidate to the successive classification procedure.

To each variable of each set the Kruskal-Wallis one-way rank test was also applied. This is a non parametric test with a power equal to 95.5% of that of the parametric powerful F test. It is applicable when the number of groups is greater than two (three in our case) and it tests the hypothesis H_0 that the groups belong to the same population. H_0 can be rejected if the test statistics at a given significance level is greater than the values found in the chi-squared probability tables.

The last step is the classification of each subject into one of the three groups on the basis of the values of the variables measured from its Holter recordings. Minimum distance classifiers, Euclidean or Mahalanobis type evaluate the distance of a point, corresponding to a new subject, in the space of the variables from the centroids of the three groups. Euclidean classifiers presuppose that the variables are uncorrelated, Mahalanobis classifiers allow for correlation.

The square of the Mahalanobis distance is given by:

$$d_k^2 = [\mathbf{z} - \mathbf{m}(k)] \cdot C_k^{-1} \cdot [\mathbf{z} - \mathbf{m}(k)] \qquad (4)$$

where the vector z represents a new subject in the space of the variables and the average vector m(k), the centroid of group k (k=1,3). C_k^{-1} is the inverse of the covariance matrix for group k (see Appendix). In the Euclidean distance the covariance matrix is replaced by the identity matrix. A new case is classified as belonging to the group which is closest.

One subject out of the total available of the three groups was selected in turn as candidate to classification (round robin procedure). The remaining subjects were then utilized to evaluate Mahalanobis and Euclidean distances.

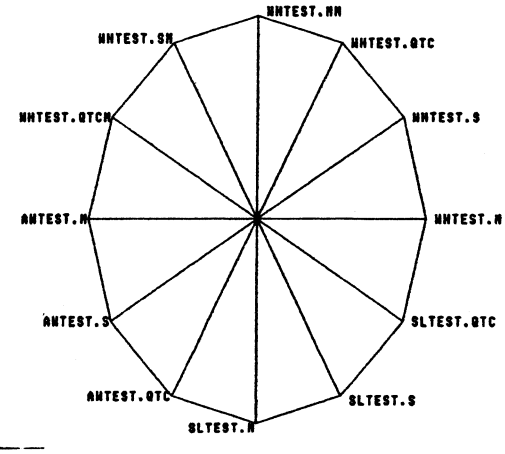


Figure 2 The 12 variables of the third set are reported in a star plot representation with each ray corresponding to a variable.

3. Results

Table 1 Discriminant test results

Set of variables	Actual Group	Centroid co-ordin.	Predicted results 1	2	3
a	1	1.5 , 0.52	62.5	25.0	12.5
	2	0.41, 0.95	14.3	71.4	14.3
	3	-1.5, 0.24	0.0	10.0	90.0
b	1	1.4, 0.13	75.0	12.5	12.5
	2	-0.2, 0.48	0.0	57.1	42.9
	3	-0.98, 0.2	10.0	20.0	70.0
c	1	-3.8, -1.3	100	0.0	0.0
	2	-0.74, 2.2	0.0	100	0.0
	3	3.6, -0.72	0.0	0.0	100

4. Conclusions

From the results obtained it looks as if there exists a clear separation among the three groups of HCM with syncope, HCM without syncope and normal. It would be interesting at this point to verify how are classified HCM patients who incurred sudden death whose preceding Holter recordings are available. As clearly stated in the title, the work presented should be considered a preliminary study on the possibilities of supplying further evidence in order to identify HCM patients at risk of sudden death. It is an evaluation of a methodology based on Holter recordings and we must stress how important in this case is to dispose of good quality recordings, particularly as the QT signal is concerned. The number of available patients in our study was drastically reduced by the number of Holter recordings discarded for totally or partially QT missing or for poor QT morphology.

Appendix

The average vectors **m**(k) and covariance matrices C(k), (one per group of subjects , k =1,3) are :

$$m(k) = \left[\sum_{i=1}^{n(k)} \frac{(x(k,i,1)}{n(k)} \quad \sum_{i=1}^{n(k)} \frac{(x(k,i,2)}{n(k)} \quad \ldots\ldots \sum_{i=1}^{n(k)} \frac{(x(k,i,12}{n(k)} \right]$$

i = 1.....n(k) is the number of subjects per group

j =1,12 is the number of variables , x (k,i,j) is the value of variable j , per subject i, per group k

$$C(k) = \begin{vmatrix} c(k,1,1) & c(k,1,2) & \ldots\ldots & c(k,1,12) \\ c(k,2,1) & c(k,2,2) & \ldots\ldots & c(k,2,12) \\ \ldots\ldots & \ldots\ldots & \ldots\ldots & \ldots\ldots \\ c(k,12,1) & c(k,12,2) & \ldots\ldots & c(k,12,12) \end{vmatrix}$$

the elements of the matrices are given by :

$$c(k,l,j) = \frac{1}{n(k)-1} * \sum_{i=1}^{n(k)} y(k,i,j) * y(k,i,l)$$

l =1,12 is a second index for the number of variables.

and $y(k,i,j) = x(k,i,j) - m(k,j)$

where m(k,j) is an element of vector **m(k)** .

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