ECG Morphology-Based Markers for Risk Stratification in Hypertrophic Cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy (HCM) is the leading cause of sudden cardiac death in young adults. Current risk markers for this heterogeneous disease lack performance and, thus, new approaches are needed. This study aims to enhance our understanding of risk assessment in HCM patients analyzing ECG-based markers in 24-hour Holter signals in a retrospective study dividing patients in asymptomatic, at-risk of a cardiac event and after a cardiac event. We studied conventional ECG markers such as RR interval, QRS width (QRSw) and corrected QT and T-peak-to-T-end intervals, which were computed for each patient from representative median beats every hour. First, the median marker values in the 24 hours were compared between groups. Second, variations in these markers between day and night were studied. All patients showed marked circadian variations in RR and QT time series. Patients at risk of suffering cardiac events were found to have wider QRS complexes, with statistically significant differences between day and night. This QRS prolongation in HCM patients, occurring months before suffering a cardiac event, might indicate anomalies in ventricular conduction. Regarding day-night variations, these were slightly greater in patients before an event. This work provides new evidence on ECG-based markers and encourages further research on QRS-wave and T-wave assessment.

1. Introduction

Cardiomyopathies cause 10 to 15% of sudden cardiac death (SCD) events. Among them, hypertrophic cardiomyopathy (HCM) is the leading cause of SCD in young adults and the most common inherited heart disease [1]. While the inclusion of secondary prevention implantable cardioverter-defibrillators in clinical protocols has shown a striking reduction of SCD in HCM, primary prevention remains a challenge since most non-recovered SCD events now occur in not detected at-risk patients.

As new evidence has become available in recent years, risk assessment in North America and Europe has undergone several updates aimed at improving the low performance of current methods [2] [3] [4]. Although SCD is the most fearsome outcome, symptoms like non-sustained ventricular tachycardia (NSVT) and unexplained syncopes are considered as risk factors for a worse prognosis [5]. The growing importance of identifying asymptomatic patients at risk has raised interest in finding risk markers in routine tests like the electrocardiogram (ECG). Although many ECG-based indices such as increased frontal QRST angle, prolonged T-peak-to-T-end (Tpe) interval, increased Tpe/QT corrected (QTc) ratio [6], reduced T-wave amplitude [7], large QRS duration [8], pseudo-STEMI pattern and low QRS voltages [9] have been previously reported as risk indicators using 10-second 12-lead ECG recordings, their efficacy has shown conflicting evidence.

Despite extensive efforts, the most recent international guidelines for managing HCM do not incorporate ECG-based markers into clinical practice. This suggests the need for further research based on different approaches to gain a deeper understanding of the disease and to enhance the identification of high-risk patients. While most of the previous ECG investigations in HCM have focused on short ECG recordings, scarce work has been conducted based on Holter recordings. This presents an area of potential interest as dependency of markers on RR interval, also regarding the time of the day, has been previously related to arrhythmic risk.

This study aims to provide new evidence on risk stratification in an HCM patient cohort from Holter-based markers. ECG markers are quantified from 24-hour Holter recordings and compared between asymptomatic and symptomatic patients. Circadian variations in these ECG markers are also evaluated.

2. Materials and Methods

2.1. Data

The study population consisted of 89 HCM patients from Hospital Clínico Universitario Lozano Blesa (Zaragoza). Two-lead (V5 and aVF) ambulatory Holter signals, ranging from 22 to 24 hours of duration, sampled at a frequency of 200 Hz, were analyzed. Patients were categorized into high-risk and low-risk groups. The high-risk group included patients who did experience non-sustained ventricular tachycardia and/or syncope during follow-up (symptomatic group), while the low-risk group consisted of those who did not (asymptomatic group). Clinical follow-up varied from 2 weeks to 80 months. Within the symptomatic group, patients with the Holter recording acquired before the event were labeled as at-risk, and those with Holter acquired after the event were labeled as post-event. Out of the total 91 Holter recordings, 63 were from asymptomatic, 8 from at-risk and 20 from post-event patients.

2.2. ECG Preprocessing

Due to the noisy nature of the Holter signals, denoising and quality check techniques were implemented. All signals underwent power line interference filtering, low-pass filtering (to remove high-frequency noise) and baseline wander removal, with the baseline being estimated using a cubic spline technique based on fiducial points from the PR segment. Additionally, a quality check evaluation was performed to identify low-quality segments present in the signal. To do so, we computed the standard deviation of the signal within 10-second windows, and those whose deviation exceed four times the median of the standard deviation were labeled as noisy segments. Later, those segments were considered low-quality ones when selecting suitable signals for the analysis.

2.3. Computation of Median Beats along Time

The RR interval was first computed along the complete Holter signal as the difference between consecutive QRS fiducial points detected using a wavelet-based approach [10]. Next, the 15-minute segment that showed the most stable RR interval within each hour of recording was identified. For that purpose, the standard deviation was calculated for the RR interval series within a 1-minute window, and then the segment with a duration of 15 minutes, having the lowest standard deviation of the RR series within one hour of the signal, was selected.

For each 15-minute segment, representative of an hour of the Holter signal, a median ECG beat was computed. First, a preliminary median beat was computed using all the beats in the segment. Next, the individual beats of the segment were aligned with the preliminary median beat and the Pearson correlation coefficient was computed. Beats with a correlation coefficient lower than 0.95 were discarded and the median beat was subsequently recomputed from the remaining beats.

2.4. ECG markers

ECG markers such as the RR interval (RR), QRS width (QRSw), QT interval [11] (QT), T peak-to-peak amplitude (Ta), and T-peak-to-T-end interval [12] (Tpe) were computed. QRSw was computed as the difference between the delineated beginning and end of the QRS complex. QT was computed as the difference between the onset of the Q wave and end of T wave and Tpe as the difference between the detected peak and end of the T wave.

QT and Tpe dependency on RR were evaluated by individually adjusting a parabolic model for each patient using the QT (or Tpe) and RR values obtained from all Holter hours as in [13] (Fig.1). Then, QT and Tpe were corrected for the effects of RR using the parabolic regression model with the value of its slope, α_{QT}, individually fitted for each patient.

Those patients who had few data along the 24 hours due to very noisy signals were not included in the analysis.

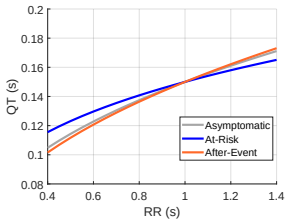

Figure 1. Examples of QT vs RR parabolic models obtained from the QT and RR data of three patients from each group of study.

2.5. Circadian analysis

To evaluate circadian variations, we analyzed day and night periods corresponding to the most probable sleeping and non-sleeping hours, respectively, as defined by [14]. We defined the hours from 0am to 6am as the sleeping period and from 12am to 11pm as the non-sleeping period, excluding the hours around typical medical appointments when Holter recordings started and ended.

2.6. Statistical analysis

The Mann–Whitney U test was used to assess differences between groups when comparing the ECG markers

calculated over 24 hours and when comparing the differences in the markers during day and night periods between groups. The Wilcoxon signed-rank test was used to test differences in ECG markers between day and night periods within patients of each group. P-values lower than 0.05 were considered to be statistically significant.

3. Results and discussion

3.1. Analysis of RR and QT intervals

Marked circadian patterns were found in RR interval on each group (Fig.2), with significant differences between day and night (p=1.49e^{-5}, p=0.015, p=0.0001 for asymptomatic, at-risk and post-event groups, respectively). Nevertheless, the day-night variation in RR intervals did not display statistically significant differences when comparing different groups, nor did the comparisons of the RR intervals calculated from the 24 hours. This indicates that the three groups showed similar RR interval variations between day and night, with similar 24-hour mean RR interval.

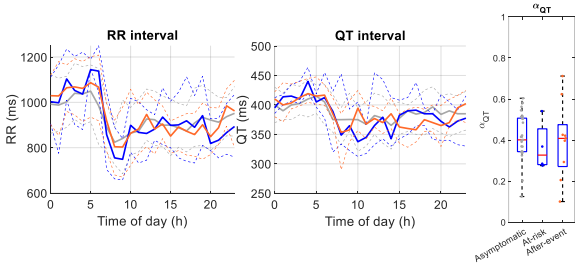

Figure 2. RR and QT variations over 24 hours and boxplots of the slope α_{QT} obtained from individually fitting a parabolic regression model to the QT and RR data of each patient.

The QT interval variations over time followed the RR interval variations, with both QT and RR showing similar interquartile ranges in the groups and no significant differences between them (Fig.2). The slope (α_{QT}) of the parabolic regression model fitted to the QT and RR values for each patient was observed to be lower in at-risk patients than in asymptomatic and after-event patients. This suggests that the dependency of the QT on RR is less pronounced in at-risk patients.

3.2. All-day analysis of QRS and T wave

QRSw (Fig.3a), evaluated over 24 hours in any of the two leads (V5 or aVF), was significantly larger in the at-risk group when compared to the asymptomatic group (p=0.02). This significant difference was also observed when the analysis was limited to the nighttime (p=0.002) and daytime (p=0.03). This suggests that an increase in QRSw, accounting for slow ventricular conduction, might be observed months before the event. This is in agreement with previous works identifying a wider QRS complex as a risk factor in HCM patients [9]. However, there were no significant differences in QRSw observed between asymptomatic and post-event patients (Fig.3a), suggesting that the treatment given after suffering an event could influence QRSw.

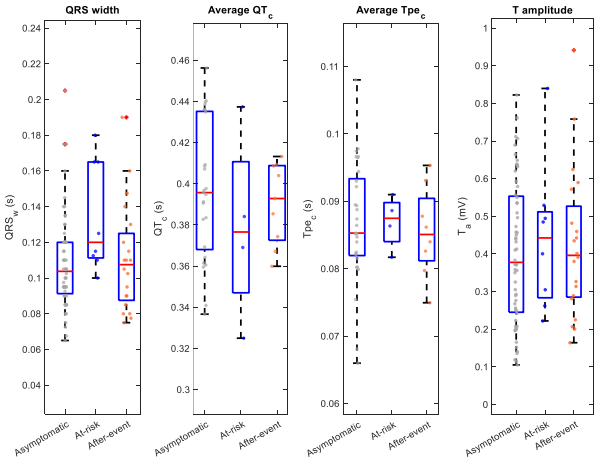

Figure 3. From left to right: a) QRSw, b) Average QTc, c) Average Tpec, and d) Ta, for each group in the 24 hours.

Regarding QTc (Fig.3b), the at-risk group displayed lower QTc compared to the asymptomatic and after-event groups. However, the at-risk group displayed slightly increased Tpec values (Fig.3c).

The amplitude of the T wave (Fig.3d) was slightly higher in patients who were about to suffer a cardiac event although large variability was observed in all groups.

3.3. Variations between day and night

In at-risk patients, small differences between day and night were found in QRSw whereas no consistent differences were found in the other groups (Fig.4a). These QRSw differences in the at-risk group could not be attributed to RR intervals, as their RR differences between day and night were of smaller magnitude compared to the other groups (p=0.02 versus p=1.04e^{-5} and 1.9e^{-4}).

Day-to-night variations in QTc were greater in symptomatic patients compared to asymptomatic ones (Fig.4b). The at-risk group displayed larger consistent changes between day and night in Tpec when compared to asymptomatic or after-event patients (Fig.4c).

Although there were no significant changes in the day-to-night variations of Ta, slight differences were observed in the after-event group when compared to the asymptomatic and at-risk groups (Fig.4d).

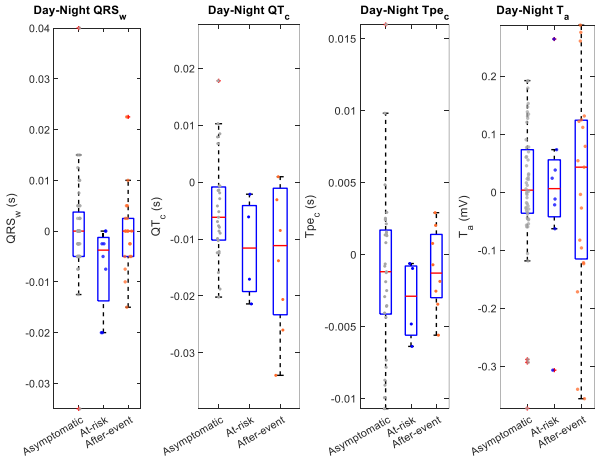

Figure 4. From left to right, day-to-night differences in: a) QRSw, b) Average QTc, c) Average Tpec, d) Ta, for all the three groups.

4. Conclusion

ECG-based markers were analyzed in HCM patients. The group of patients who suffered an event after the Holter recording displayed lower QT dependency on RR and wider QRS complexes. Additionally, these patients displayed larger day-to-night variations in QTc and Tpec when compared to asymptomatic and after-event patients.

This work provides preliminary evidence on ECG-based markers for HCM risk evaluation, but further research on QRS and T wave morphology is warranted.

5. Acknowledgments

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