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 give more insight into 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, QT interval and QRS width (QRSw) and we proposed other QRS and T wave morphology markers based on the ratios between positive and negative QRS-wave areas and T-wave areas, respectively). ECG markers were computed from representative median beats for each patient in each hour. First, the median marker values in the 24 hours were compared between groups. Second, differences in the 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 months before suffering a cardiac event might reflect anomalies in ventricular conduction. Regarding ECG morphology markers, patients who had already suffered a cardiac event displayed deeper S waves in the QRS complex and more inverted T waves. This work provides new evidence on ECG-based markers and encourages further research on QRS-wave and T-wave morphology 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-defibrillator 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 newly 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 worse prognosis [5]. The relevance of detection in asymptomatic patients 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 Tpe interval, and increased Tpe/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, they have shown conflicting evidence.

Most of so far conducted ECG investigations in HCM have focused on short ECG recordings, while scarce work has been conducted based on Holter recordings, which could be an area of potential interest. Despite extensive efforts, the most recent international guidelines for managing HCM do not incorporate ECG-based markers into clinical practice, suggesting that further research based on different approaches is needed to gain a deeper understanding of the disease and to enhance the detection of high-risk patients.

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

2. Materials and Methods

2.1. Data

The study population consisted of 89 HCM patients attended at Hospital 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 divided into high-risk and low-risk groups, with high-risk including patients who experienced non-sustained ventricular tachycardia and/or syncope during follow-up (symptomatic group), and low-risk consisting 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. Of the total 91 Holter recordings, 63, 8 and 20 corresponded to asymptomatic, at-risk and post-event patients, respectively.

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 based on points taken from the PR segment. Additionally, quality check evaluation was performed to identify low quality segments present in the signal. For this purpose, standard deviation of the signal was computed in windows of 10 seconds and those whose deviation was greater than four times the median of the standard deviation were labelled as noisy signal. Later, low-quality segments were taken into account when selecting appropriate signal 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 within each hour of recording that showed the most stable RR interval was identified. For that purpose, segment candidates (those with greater or equal duration of 15 minutes) were identified within one hour of signal. Stability was evaluated by calculating the standard deviation in every minute of the RR series. The 15-minute window that showed lower standard deviation was selected.

For each 15-minute segment representative of an hour of the Holter signal, an ECG median beat was computed. First, a preliminary median beat was computed from 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 presenting a correlation coefficient lower than 0.95 were discarded and the median beat was subsequently computed from the remaining beats.

2.4. ECG markers

Commonly studied markers such as the RR interval (RR), QT interval (QT) and T-peak-to-T-end interval (Tpe) were computed. QRS width (QRSw) was obtained from the difference between the delineated beginning and end of the QRS complex.

To characterize QRS morphology, a novel marker based on the ratio between the positive (R and Q) and negative (S) areas of the QRS complex was computed and denoted by r_{QRS}. This marker ranged from 1 (predominantly positive waveform) to -1 (predominantly negative waveform). Similarly, a marker was computed to assess the morphology of the T wave by computing the ratio of the positive and negative areas. This T wave marker was denoted by r_T and ranged from 1 (positive T wave) to -1 (inverted T wave), with values around 0 representing biphasic T waves.

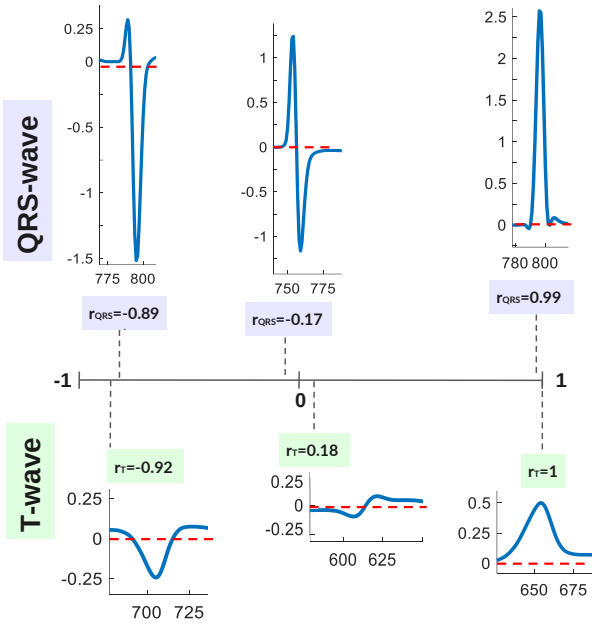

Figure 1. r_{QRS} and r_T markers examples with their correspondent signal.

2.5. Circadian analysis

To evaluate circadian variations, we analyzed day and night periods corresponding to most probably sleeping and

non-sleeping hours, respectively, as reported by [11]. To maximize the number of recordings per hour, the periods from 0am to 6am and from 12pm to 11pm were taken as the sleeping period and non-sleeping period, respectively, thus avoiding the hours around the medical appointment 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 between groups. The Wilcoxon signed rank test was used to test differences in ECG markers between day and night within patients of each group. P-values lower than 0.05 were considered as statistically significant.

3. Results and discussion

3.1. Analysis of RR and QT intervals

Marked circadian patterns were found for the RR interval in each of the groups, with significant differences between day and night (p=1.49e^{-5}, p=0.015, p=0.0001 for asymptomatic, at-risk and post-event group). 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.

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. The slope of a linear polynomial fitted to the QT/RR relationship was higher in post-event patients than in asymptomatic and at-risk patients, suggesting that the dependency of the QT on RR is more pronounced in these patients.

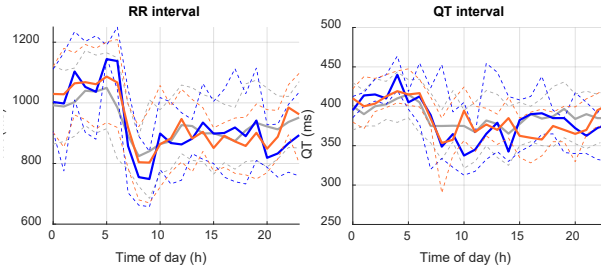

Figure 2. RR and QT variations over 24 hours.

3.2. All-day analysis of QRS and T wave

QRS width, evaluated over 24 hours in any of the two leads (V5 or aVF), was significantly larger in the at-risk group than in the asymptomatic group (p=0.02). This significant difference was also observed when restricting the analysis to the nighttime (p=0.002) and to the daytime (p=0.03). This suggests that an increase in QRS width, accounting for slow ventricular conduction, could possibly 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]. No significant differences in QRS width were observed between asymptomatic and post-event patients (Figure 4.a), suggesting that the treatment given after suffering an event may have an effect on QRS.

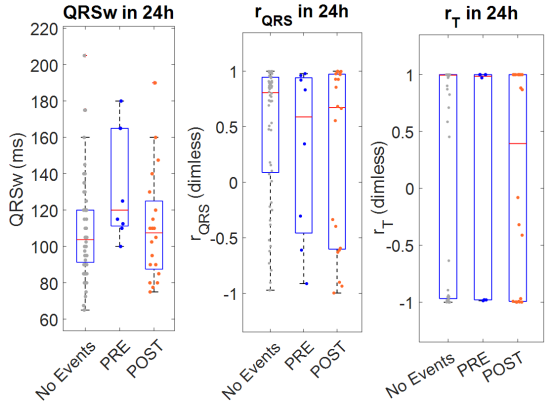

Figure 3. From left to right: a) QRS width, b)r_{QRS}, c)r_T median for each group in whole day.

Regarding the ratio r_{QRS}, asymptomatic patients showed predominant R waves compared to at-risk and post-event patients, who displayed deeper S waves (Figure 4.b).

The ratio r_T showed no significant variations between groups (Figure 4.c). However, while inverted T waves were present in 35% and 37,5% of cases in asymptomatic and at-risk patients, post-event patients showed a larger predominance of inverted T waves (50%).

3.3. Variations between day and night

Differences in the ECG markers between day and night were obtained for each of the patients. In at-risk patients, differences in QRS width between day and night were of borderline statistical significance. No significant differences were found in the other groups. The differences in the at-risk group could not be attributed to RR, which presented RR differences between day and night of lower magnitude in this group than in the others (p=0.02 versus p=1.04e^{-5} and 1.9e^{-}4).

The ratio r_{QRS} showed minor changes between day and night, with those changes being slightly larger in asymptomatic patients compared to at-risk or post-event patients.

Finally, although there were no significant changes in the day-to-night variations of T wave morphology either between groups or within groups, more prominent differences in at-risk patients and post-event patients were observed when compared to asymptomatic ones (with p values p=0.1875, p=0.1272 and p=0.353, respectively).

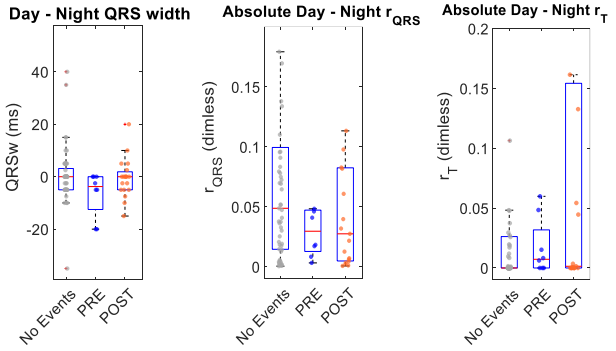

Figure 4. From left to right: QRS width, absolute r_{QRS} and r_T day-night differences in the analyzed groups.

4. Conclusion

ECG-based markers were analyzed in HCM patients. The group of patients who developed an event after the Holter recording displayed wider QRS complexes. Additionally, changes in QRS width between day and night in these patients seemed to be more pronounced when compared with asymptomatic patients and at-risk patients. ECG morphology analysis showed that at-risk patients had deeper S waves and more inverted T waves. They also showed larger T wave changes between day and night. 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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