Electrocardiographic abnormalities of hypertrophic cardiomyopathy

A. Mincholé[1], R. Ariga[2], S. Neubauer[2], H. Watkins[2], B. Rodríguez[1]

[1] Department of Computer Science, University of Oxford, Oxford, UK
[2] Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, UK

Abstract

Hypertrophic cardiomyopathy (HCM) is a genetic disease characterized by the hypertrophy (thickening) of heart ventricles, and the first cause of sudden cardiac death in the young adults. The ECG is altered in the majority of patients with HCM as a consequence of structural and electrophysiological abnormalities although reliable risk markers are still not available. Fifty four 12-lead Holter recordings (32 HCM patients and 22 controls) have been analyzed in order to obtain specific ECG based biomarkers able to distinguish between both groups. Results showed higher values for HCM in QRS-duration, QT interval (QTc), T peak to T end interval corrected (T_{pe}) and DRest quantifying dispersion of restitution. Also, morphological features such as ST level, T and QRS amplitudes and energies and the first four Karhunen-Loeve transform (KLT) coefficients were analysed. Results showed statistically significant differences between HCM patients and controls (p-value$<$0.02) in the QTc interval, ST level, energies and the first and third KLT coefficients. DRest showed higher values in HCM patients (0.08 versus 0.05 in controls) in agreement with in vivo studies suggesting a correlation between increased dispersion and arrhythmic risk.

1. Introduction

Electrocardiogram (ECG) recordings using Holter monitors provide a noninvasive, not-expensive and widely-used tool to record the electrical activity over 24/48-hour periods. Given the length of the time series obtained, Holter ECG recordings allow for the characterization of the dependency of ECG-based features on heart rate.

Hypertrophic cardiomyopathy (HCM) is a genetic disease characterized by the hypertrophy (thickening) of heart ventricles (usually the left one) and loss of the normal alignment of the muscle cells, referred to as fiber disarray. It affects 1 in 500 people and is the most common cause of sudden cardiac death (SCD) in the under 35's [1]. The majority of patients are asymptomatic, and the accurate prediction of those at risk of such a catastrophic complication is still a challenge [2]. Current risk factor assessments have low sensitivity for predicting SCD and do not achieve the prediction of other disease complications such as heart failure (HF), atrial fibrillation and stroke, in HCM patients [3]. HCM-induced heterogeneities in myocardial structure such as fiber disarray may affect the propagation of electrical excitation through the heart [4], with likely pro-arrhythmic effects. Both activation and repolarization [5,6] properties of the myocardium are likely to be affected by HCM. Therefore, the goal of our study is to quantify QRS, ST and T wave biomarkers from Holter recording of HCM and control patients, in order to investigate their potential for patient classification.

Rate dependent biomarkers such as restitution dispersion, which accounts for the spatial heterogeneity of repolarization when heart rate changes, has been also reported to be an arrhythmogenic substrate and may be affected in HCM patients [7].

2. Methods

2.1. Database

Fifty four 12-lead Holter recordings (32 HCM patients and 22 controls) were analyzed in order to obtain specific ECG based biomarkers able to distinguish between both groups control and pathological HCM. Due to the fact that significant heart rate changes were not obtained in all the Holter recordings, DRest was computed in 19 HCM and 10 controls.

2.2. ECG biomarkers

Temporal features such as QRS-duration, the Bazzet's corrected QT interval (QTc) and T peak to T end interval corrected as for the QT (T_{pe}) were computed using a wavelet-based delineator [8]. Morphological features such as the T wave amplitud, QRS amplitude, STT and QRS waveforms energy (computed as the area under the waveforms), ST level and the correlation of the STT mean waveforms with the four first Karhunen-Loeve (KL) basis func-

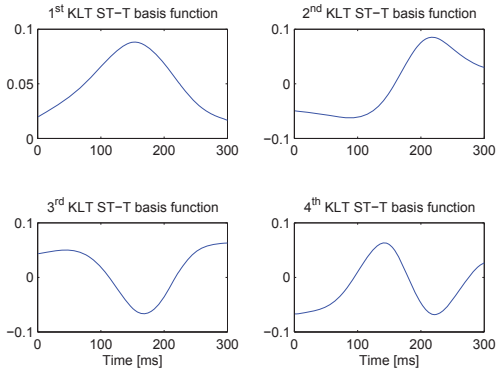

Figure 1. First four KLT basis functions for the ST-T waveform.

tions derived from 200000 preprocessed and selected STT waveforms as described in [9] as shown in Fig.1. The correlations were estimated as the normalised KL coefficients that represent the projections of the mean STT waveforms to the four basis.

DRest, which quantifies dispersion of restitution, was computed in the lead with higher signal-to-noise ratio. Previous studies indicate that the T_{pe} interval reflects spatial heterogeneity in the repolarization time of different ventricular regions [10, 11]. The DRest biomarker (proposed and referred to as $\Delta\alpha$ in [7]) provides an estimation of spatial dispersion in the dynamic APD restitution and is quantified as follows:

$$DRest = \frac{\partial T_{pe}}{\partial RR} \quad (1)$$

with T_{pe} and RR quantified from stable ECG segments at two different RR intervals [7].

3. Results and discussion

Fig.2 shows the box plots for the different temporal indices T_{pe}, QTc intervals and QRS duration for each of the eight recorded leads. T_{pe} interval as well as QRS duration were slightly longer in HCM patients than in controls but no statistically significant differences were found.

As an example in V3, T_{pe} interval was 99 ± 14 ms in HCM versus 93 ± 8 ms in control, and, QRS duration was 92 ± 13 ms versus 88 ± 13ms. However, QTc interval, also longer in HCM patients (440ms versus 414ms in controls) showed statistically significant differences between HCM patients and controls, p-value$<$0.02.

DRest (see Fig. 3) showed a tendency to higher values in HCM patients (0.08 ± 0.04 versus 0.05 ± 0.03 in controls), in agreement with in vivo studies suggesting a correlation between increased dispersion and arrhythmic

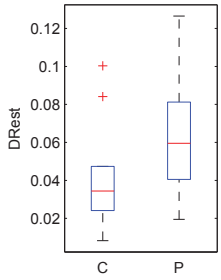

Figure 3. Boxplot representing DRest values for control (C) and HCM (P).

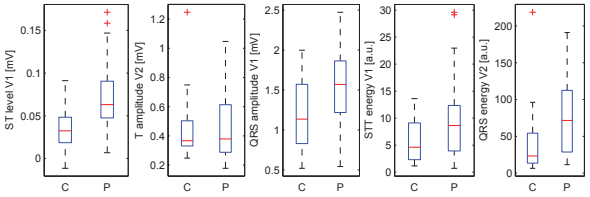

Figure 4. Boxplot representing different morphological features ST level, T wave and QRS complex amplitudes and T wave and QRS complex energies for control (C) and HCM (P).

risk. However, no statistically significant differences were found.

Regarding the analysed morphological features (see Fig.5), ST level showed statistically significant differences (< 0.02) just in V1 showing a higher mean value of 97 ± 15 μV in HCM versus 36 ± 27 μV in control. This is in agreement with some studies that have found non ischemic ST elevation in apical HCM patients in the precordial leads [12].

The amplitude of the T wave did not show statistically significant differences in this database, although negative giant T waves in precordial leads have been observed in HCM patients [13]. However, the energy of the STT waveforms showed significant differences between both groups in V1. Higher values were found in HCM (11 ± 12) than in controls (6 ± 4).

Regarding the QRS amplitude, slightly higher QRS complexes were found in HCM as reported in other cohorts [13]. In the same line, mean QRS energy in HCM (77 ± 50 in arbitrary units) was about two fold the value in control (42 ± 47). Statistically significant differences (p-value< 0.01) were found in leads V2 and V3.

With respect to the STT KLT coefficients, most of the STT waveforms showed the highest correlations with the first STT KL basis, obtaining a higher value in the first STT KLT coefficient than in the remaining three. Moreover,

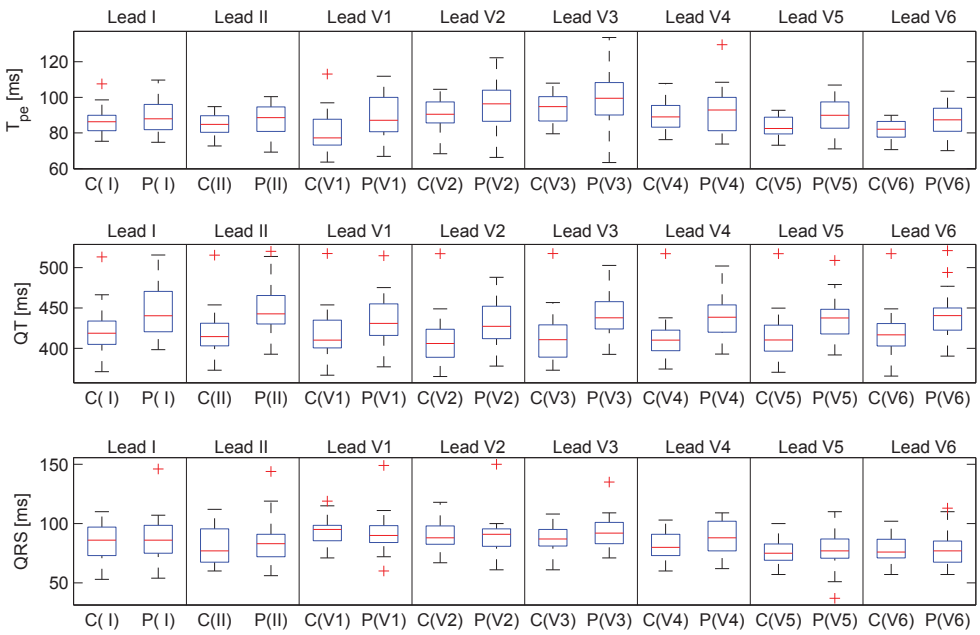

Figure 2. Boxplots showing the different temporal indices T_{pe}, QTc intervals and QRS duration for each of the eight recorded leads for control (C) and pathological HCM (P).

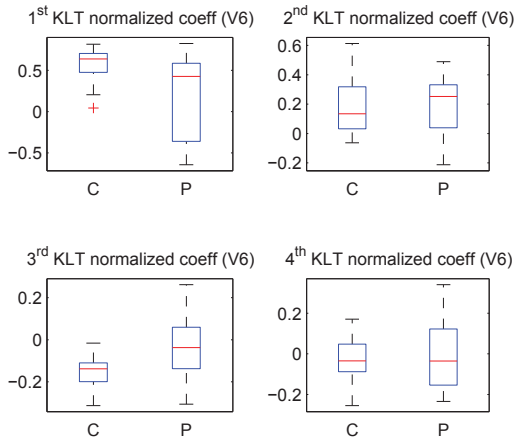

Figure 5. Boxplot representing the normalised projections of the mean STT waveform of lead V6 to the four STT KLT basis functions for control (C) and HCM (P).

first KL basis accounts for most of the STT complex in control but not in HCM in which lower value in the first STT KLT coefficients and a higher variability was found (0.6 ± 0.2 in V6 in control versus 0.2 ± 0.5 in HCM). Statistically significant differences (p-value< 0.01) were found in the first STT KLT coefficient in leads I, II, V2, V5 and V6. Also, statistically significant differences (p-value< 0.01) between control and HCM were found in the third STT KLT coefficient in leads I, II, V3-6. These third coefficients were negative for the control subjects and close to zero for HCM patients.

4. Conclusions

Holter recordings obtained from 32 HCM and 22 control subjects were analyzed to quantify temporal and morphological activation and repolarization features. DRest showed higher values in HCM than in controls, although no significant differences were found. Morphological features such as the STT KLT coefficients achieve statistically significant differences between HCM and control. Repolarization or conduction abnormalities represented by the T_{pe} , QTc interval and QRS duration do not appear to be specific to characterize HCM patients.

Acknowledgements

AM is supported by a Marie Curie Intra-European fellowship (FP7-PEOPLE-2011-IEF). AM acknowledge sup-

port of grant TEC2010-19410 from MINECO, Spain. BR holds a Wellcome Trust Senior Research Fellow in Basic Biomedical Science.

References

[1] Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. echocardiographic analysis of 4111 subjects in the cardia study. coronary artery risk development in (young) adults. Circulation Aug 1995;92(4):785–9.

[2] Gyllenhammar T, Fernlund E, Jablonowski R, Jögi J, Engblom H, Liuba P, Arheden H, Carlsson M. Young patients with hypertrophic cardiomyopathy, but not subjects at risk, show decreased myocardial perfusion reserve quantified with cmr. Eur Heart J Cardiovasc Imaging Aug 2014; .

[3] Cahill TJ, Ashrafian H, Watkins H. Genetic cardiomyopathies causing heart failure. Circ Res Aug 2013; 113(6):660–75.

[4] Tseng WYI, Dou J, Reese TG, Wedeen VJ. Imaging myocardial fiber disarray and intramural strain hypokinesis in hypertrophic cardiomyopathy with mri. J Magn Reson Imaging Jan 2006;23(1):1–8.

[5] Kirschner SE, Becker E, Antognozzi M, Kubis HP, Francino A, Navarro-López F, Bit-Avragim N, Perrot A, Mirrakhimov MM, Osterziel KJ, McKenna WJ, Brenner B, Kraft T. Hypertrophic cardiomyopathy-related beta-myosin mutations cause highly variable calcium sensitivity with functional imbalances among individual muscle cells. Am J Physiol Heart Circ Physiol Mar 2005;288(3):H1242–51.

[6] Coppini R, Ferrantini C, Yao L, Fan P, Del Lungo M, Stillitano F, Sartiani L, Tosi B, Suffredini S, Tesi C, Yacoub M, Olivotto I, Belardinelli L, Poggesi C, Cerbai E, Mugelli A. Late sodium current inhibition reverses electromechanical dysfunction in human hypertrophic cardiomyopathy. Circulation Feb 2013;127(5):575–84.

[7] Mincholé A, Pueyo E, Rodríguez JF, Zacur E, Doblaré M, Laguna P. Quantification of restitution dispersion from the dynamic changes of the t-wave peak to end, measured at the surface ecg. IEEE Trans Biomed Eng May 2011; 58(5):1172–82.

[8] Martínez JP, Almeida R, Olmos S, Rocha AP, Laguna P. A wavelet-based ecg delineator: evaluation on standard databases. IEEE Trans Biomed Eng Apr 2004;51(4):570–81.

[9] García J, Lander P, Sörnmo L, Olmos S, Wagner G, Laguna P. Comparative study of local and karhunen-loève-based st-t indexes in recordings from human subjects with induced myocardial ischemia. Comput Biomed Res Aug 1998;31(4):271–92.

[10] Yan GX, Antzelevitch C. Cellular basis for the normal t wave and the electrocardiographic manifestations of the long-qt syndrome. Circulation Nov 1998;98(18):1928–36.

[11] Opthof T, Coronel R, Wilms-Schopman FJG, Plotnikov AN, Shlapakova IN, Danilo Jr P, Rosen MR, Janse MJ. Dispersion of repolarization in canine ventricle and the electrocardiographic t wave: Tp-e interval does not reflect transmural dispersion. Heart Rhythm Mar 2007;4(3):341–8.

[12] Blinc A, Gubenšek M, Sabovič M, Grmek M, Berden P. Nonischemic st segment elevation in hypertrophic cardiomyopathy due to chest wall deformity from kyphoscoliosis. Int Med Case Rep J 2010;3:43–7.

[13] Ostman-Smith I, Wisten A, Nylander E, Bratt EL, Granelli AdW, Oulhaj A, Ljungström E. Electrocardiographic amplitudes: a new risk factor for sudden death in hypertrophic cardiomyopathy. Eur Heart J Feb 2010;31(4):439–49.

Address for correspondence:

Ana Minchole
Department of Computer Science, University of Oxford Wolfson Building
ana.minchole@cs.ox.ac.uk