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Role of the Electrocardiogram in Differentiating Genetically Determined Dilated Cardiomyopathy from Athlete's Heart

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Abstract

Background: Physiological cardiac remodeling in highly trained athletes may overlap with dilated cardiomyopathy (DCM).

Objectives: the aim of this study was to investigate the role of the electrocardiogram (ECG) in differentiating between physiological and pathological remodeling.

Methods: The study population consisted of 30 patients with DCM who revealed a pathogenic variant at genetic testing and 30 elite athletes with significant cardiac remodeling defined by a left ventricular (LV) end-diastolic diameter > 62 mm and/or LV ejection fraction between 45% and 50%.

Results: The ECG was abnormal in 22 (73%) patients with DCM. The most common abnormalities were low voltages (n=14, 47%), lateral T wave inversion TWI (n=6, 20%), ventricular ectopic beats (n=5, 17%) and anterior TWI (n=4, 13). Two athletes revealed an abnormal ECG: complete left bundle branch block (LBBB) in one case and atrial flutter in the other. The sensitivity, specificity and accuracy of the ECG in differentiating DCM from physiological adaptation to exercise in athletes was 73% (confidence interval (CI): 54% to 88%), 93% (CI: 78% to 99%) and 0.83 (CI: 0.71 to 0.92) respectively.

Conclusions: While the ECG is usually normal in athletes exhibiting significant LV dilatation and/or systolic dysfunction, this test is often abnormal in patients with DCM harbouring a pathogenic variant. Low voltages in the limb leads and lateral TWI are the most common abnormalities.

Keywords: dilated cardiomyopathy, athlete's heart, electrocardiogram

Abbreviations

CMR Cardiac Magnetic Resonance

DCM Dilated Cardiomyopathy

ECG Electrocardiogram

LV Left Ventricular

LVEDD Left Ventricular End-Diastolic Diameter

SCD sudden cardiac death

TWI T wave inversion

INTRODUCTION

Long-term athletic training is associated with a series of alterations in cardiac structure, function and electrical activity that are collectively termed "athlete's heart"[1–4].

In Olympic athletes, left ventricular (LV) size has been shown to be higher than upper limits of normal (LV end-diastolic diameter, LVEDD > 54 mm) in almost half of the cases and in individuals engaged in high dynamic intensity modalities, such as rowing, cross-country and cycling, the LV end-diastolic diameter LVEDD may exceed 60 mm[3]. Marked cardiac remodelling which is often associated with LV ejection fraction in the lower limits of normal (or even mildly reduced) overlaps with dilated cardiomyopathy (DCM). The differentiation between physiological cardiac adaptation to exercise and DCM has significant implications as this condition may affect young individuals with a predilection for arrhythmias and sudden cardiac death (SCD)[5].

The 12-lead electrocardiogram (ECG) is an essential first line test and abnormal electrocardiographic findings may be suggestive of disorders associated with increased risk of SCD in the young, such as cardiomyopathies and primary electrical disease[6]. However, it is not clearly established whether the ECG may be of help in differentiating between DCM and structural remodeling resulting from physiological adaptation.

The aim of the study was to investigate the role of the ECG in differentiating between physiological adaptation to exercise in athletes showing significant LV enlargement and/or mild reduction of LV ejection fraction and DCM.

METHODS

Study population

Patients with DCM

The St George's University Hospital Inherited Cardiac Disease Clinic (London, UK) and the Ospedali Riuniti and University of Trieste Ambulatorio Cardiomiopatie (Trieste, Italy) are European cardiomyopathy referral centres; each of these institutions hold a database which includes > 1000 patients with cardiomyopathies evaluated in the last 20 years.

Out of a combined analysis of databases from both institutions, we retrospectively searched for patients assessed between 2012 and 2017 fulfilling all of the following criteria: 1) diagnosis of idiopathic DCM (LVEDD >117% of the predicted per age and sex[5] and reduced systolic function (LVEF < 50%)[7] in the absence of abnormal loading conditions such as hypertension or valvular disease and in the absence of significant coronary artery disease; 2) LV ejection fraction between 45% and 50% at echocardiography; 3) presence of a pathogenic variant associated with DCM; 4) proband status; 5) age > 18 years; 6) no significant comorbidities that may affect ECG interpretation such as severe respiratory disease, morbid obesity and significant pulmonary hypertension. We found 37 patients. The final study cohort constituted of 30 patients with idiopathic DCM (after matching for age and sex with a cohort of athletes as described in following chapter).

All patients reached medical attention either because of significant cardiac symptoms or in the context of family screening (proband affected).

Athletes

The UK does not support a state sponsored cardiac screening program in athletes. However, the charitable organisation Cardiac Risk in the Young (CRY, www.c-r-y.org.uk) has an established cardiac screening program for young individuals that also serves many professional sporting organisations in the UK. Details of the screening programme have been reported elsewhere[8].

The cohort of athletes selected for this study relied on 2 sources:

1. A cohort of 2000 professional or competitive athlete aged 14 to 35 years screened by CRY with health questionnaire, ECG and echocardiogram between 2011 and 2013. The average LVEDD was 52 ± 5 mm. The average + 2 standard deviations was 62 mm. We searched our database for individuals fulfilling the following criteria: 1) LVEDD > 62 mm and/or LVEF between 45% and 50% at the echocardiogram; 2) absence of significant cardiac symptoms; 3) free from cardiac disease after appropriate investigations including cardiac magnetic resonance (CMR), 24h Holter and exercise tolerance test; 4) age > 18 years. A total of 50 individuals (2.5%) were found.

2. A cohort of 152 veteran athletes (age > 35 years) recruited from 2011 to 2014 who underwent comprehensive investigations as per a study previously published by our group[9]. We searched our database for individuals fulfilling the following criteria: 1) LVEDD > 62 mm and/or LVEF between 45% and 50%; 2) absence of significant cardiac symptoms; 3) free from cardiac disease after appropriate following investigations including CMR and coronary computed tomography. A total of 10 individuals (6.5%) were found.

The final study cohort comprised of 30 athletes age and sex matched with a cohort of 30 patients with DCM. Most of the subjects in both cohorts (93%) were Caucasian. Nobody

presented family history neither of heart disease at age younger than 50 years, nor of sudden cardiac death.

Electrocardiogram

Standard 12-lead ECGs were performed as described elsewhere[10]. Sokolow-Lyon voltage criterion for LV hypertrophy was defined as the sum of S in V_1 + R in V_5 or $V_6 \geq 35$ mm. ST-segment depression was considered significant if ≥-0.1 mV in ≥2 contiguous leads. Biphasic T-wave inversion was considered abnormal if the negative deflection of the T-wave exceeded ≥−0.1 mV. T-wave inversion (TWI) ≥0.1 mV in ≥2 contiguous leads was considered abnormal. Deep T-wave inversion was defined as a T-wave deflection ≥−0.2 mV. An abnormal Q wave was defined as a Q wave with duration ≥ 40 msec or a Q/R ratio > 0.25. The normal frontal cardiac axis was considered to be > −30° but < 120°. Left atrial (LA) enlargement was defined by a P wave duration > 0.12s in the frontal plane associated with a terminal P negativity in lead V1 of duration ≥ 0.04s and depth ≥ 0.1 mV. ECG voltages were defined as low when the amplitudes of all the QRS complexes in the limb leads were < 0.5 mV[11]. The ECG was interpreted according to the recently published international recommendations blindly from the disease status[6]. An ECG was defined as abnormal if it fulfilled any of the following criteria: 1. ≥1 abnormal indices as defined by the International ECG criteria, 2. ≥2 borderline indices as defined by the International ECG criteria, 3. Low QRS voltages in all limb leads.

Echocardiogram

Two-dimensional echocardiography was performed using either a GE Vivid I (Tirat, Israel), Philips Sonos 7500, Philips iE33 or Philips CPX50 (Bothell, Washington). The echocardiographic protocol consisted of parasternal long axis views of the ventricles, long axis view of the aortic root and ascending aorta, basal short axis view of the origin of the coronary arteries, mid papillary short axis view of the LV, apical 4, 3 and 2 chamber view of the LV, trans-mitral and tissue Doppler. Digitized images of 2 beats were stored while one was analyzed. Digitized images were analyzed offline according to the American Society of Echocardiography guidelines[11] by cardiologists and expert sonographers. LV internal diameter, septal wall thickness, posterior wall thickness and left atrial diameter were measured from two-dimensional images in the parasternal long-axis view at both end-diastole and end-systole[11]. When measuring septal thickness, care was taken to exclude right ventricular septal bands. In measuring the LV posterior wall thickness, care was taken to exclude posterior wall chordae. LV systolic function was measured by using the biplane Simpson's rule from the apical four- and two-chamber views, fractional shortening and visual assessment[12].

Genetic test

Cardiac gene panel sequencing was undertaken in all samples (both sites) using the Illumina Trusight Cardiac panel, which consists of 174 genes (coding sequence region only) associated with 17 inherited cardiac conditions[13]. Candidate genes were interrogated for rare variants associated with inherited heart disease. Bioinformatic pipelines were then used for annotation of putative mutations identified in these genes. Variants were confirmed with Sanger sequencing. Variants with a minor allele frequency (MAF) >1 in

10,000 in the Exome Aggregation Consortium (ExAC)[14], synonymous variants not located at splice sites and non-truncating variants in titin (TTN) gene were excluded[15]. Variants were classified as pathogenic, likely pathogenic, or as variant of unknown significance (VUS) using the American College of Medical Genetics (ACMG) guidelines[16]. For the purpose of this study, only patients harbouring a pathogenic were considered.

Ethical approval

Ethical approval was granted by the National Research Ethics Service, Essex Research Ethics Committee in the UK (CRY screening). Ethical approval was granted by the Ethical Committee of Friuli Venezia Giulia for Italian DCM patients (# 43/2009, amendment: 211/2014/Em). As far as the cohort of veteran athletes is concerned, written consent was obtained from all participants and ethical approval was granted by the National Research Ethics Service; South West-Central Bristol committee. The investigation conforms with the principles outlined in the Declaration of Helsinki and with the local legal requirements[17].

Statistical analysis

Statistical analysis was performed using the PASW software (PASW 18.0 Inc, Chicago, IL). The case-control matching was performed using the software Medcalc (version 17.4, Ostend, Belgium). Results are expressed as mean ± SD for continuous variables or as number of cases and percentage for categorical variables. Comparison between groups was performed using student's t-tests for continuous variables with adjustment for unequal

variance if needed and chi-square tests or Fisher Exact Tests for categorical variables. Receiver operating characteristic curve analysis was performed according to DeLong et al[18].

RESULTS

Patients with DCM

The average age was 49 ± 13 years, 19 (63%) were male and 28 (98%) were white (Table 1).

All patients harboured a pathogenic variant: truncating titin (TTN) variants were the most common (n=7, 23%), followed by filamin-C (FLNC) mutations (n=5, 17%), troponin (TNNT) mutations (n=5, 17%), desmoplakin (DSP) mutations (n=4, 13%) and lamin (LAMA) mutations (n=3, 10%) (Table 1 in Supplementary material).

The ECG was abnormal in 22 patients (73%). The most common abnormalities were low voltages (n=14, 47%), lateral TWI (n=6, 20%), ventricular ectopic beats (n=5, 17%) and anterior TWI (n=4, 13%) (Table 2). Of the 8 patients who were classified as having a normal ECG, isolated low voltages was present in 1 case. In the subgroup of patients with a normal ECG, the most common rare variants were found in the TTN gene (5 cases); the other 3 patients harboured respectively a FLNC, TTNT2 and MYH7 mutation. All patients with DCM were treated with beta-blockers and ACE-inhibitors according to contemporary International guidelines[19].

Athletes

The average age was 44 ± 16 years, 26 (87%) were male and 28 (98%) were white (Table 1).

Athletes trained for 14.5 ± 7.4 hours per week and participated in 8 different sports, including running (n=12, 40%), cycling (n=8, 27%), rugby (n=4, 13%), football (n=3, 10%), swimming (n=1, 3%), volleyball (n=1, 3%) and handball (n=1, 3%).

The LV size was similar in athletes and patients with DCM (LV end-diastolic diameter of 59 ± 9 mm in athletes compared with 57 ± 8 mm in DCM, p=0.384).

Two veteran athletes were found to have an abnormal ECG: complete left bundle branch block (LBBB) in one case and atrial flutter at a heart rate of 60 bpm in the other. Further investigations including coronary computerized tomography and cardiovascular magnetic resonance didn't reveal any significant structural abnormalities. Athletes exhibiting a particularly significant cardiac remodelling (LVEDD > 65 mm and/or LVEF < 50%) were investigated with CMR and exercise echocardiography which didn't reveal additional features of DCM and normal inotropic response to exercise. Athletes were followed up yearly and none of them complained any cardiac symptom or exhibited signs of cardiac disease.

Role of the ECG in differentiating DCM from physiological adaptation to exercise

Differences in ECG parameters between athletes and patients with DCM are shown on table 2. Heart rate was significantly lower in athletes (52 ± 11 vs 66 ± 14, p<0.001); while low voltages were relatively frequent in DCM (n=14, 47%), none of the athletes showed this ECG feature (p<0.001). Ventricular ectopic beats were observed in 5 (17%) patients with DCM and in none of the athletes (p=0.06).

The sensitivity, specificity and accuracy of an abnormal ECG in differentiating DCM from physiological adaptation to exercise in athletes was 73% (confidence interval (CI): 54% to 88%), 93% (CI: 78% to 99%) and 0.83 (CI: 0.71 to 0.92) respectively (Table 3). Sensitivity, specificity and accuracy increased when low voltages were included (Table 3).

DISCUSSION

Highly trained athletes may exhibit significant LV remodelling which resembles a DCM phenotype. Differentiation between the two entities can be challenging and may require comprehensive multimodality evaluation. The results of our study suggest that an abnormal ECG is likely to indicate pathology and should prompt detailed evaluation and follow-up for DCM, while a normal ECG is more in keeping with physiological adaptation to exercise even in athletes with marked cardiac remodelling.

Athlete's heart or DCM?

Left ventricular structural changes in athletes may be particularly marked [20,21] resulting in a significant overlap with DCM[22,23]. Idiopathic DCM is currently defined by the presence of LV or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions or coronary artery disease sufficient to cause global systolic impairment. It is often a familial disease with a genetic basis[24] which involves multiple genes that encode the sarcomere, cytoskeleton, nuclear envelope, transcriptional pathways, and mitochondrial proteins[25]. The main genes involved are TTN and LMNA and the yield of genetic testing in DCM ranges from 15% to 57% depending on patient selection and family history[26,27]. Sudden cardiac death due to ventricular arrhythmias or electro-mechanical dissociation is one of the most feared outcomes[28]. As intense exercise may increase the propensity for fatal

arrhythmias in individuals with DCM, it is imperative to accurately differentiate between pathological and physiological remodelling. Previous studies have mainly focused on the role of imaging and specifically on contractile reserve as diagnostic indicator and prognostic marker[25,29]. Recently Claessen et al.[30] showed that CMR exercise evaluation of cardiac reserve enables differentiation between these 2 entities. While healthy athletes with a baseline LV ejection fraction in the lower limits of normal revealed a significant increase in LVEF, the same was not observed in patients with DCM and in athletes showing myocardial fibrosis at baseline CMR. This study included patients without an identifiable mutation at genetic testing. Conversely, our cohort comprised only patients where the genetic testing revealed a pathogenic mutation.

A prior study from our group[31] showed that exercise stress echocardiography has the greatest discriminatory value in differentiating between grey-zone athletes (n=25) and asymptomatic patients with DCM (n=35). In this study, the definition of DCM was based mainly on imaging parameters and genetic testing results were not included. Patients with DCM exhibited an abnormal ECG in 40% of the cases (compared to 73% in our study), while grey-zone athletes (enlarged LV and borderline or mildly reduced LVEF) had an abnormal ECG in 8% of the cases (compared to 7% in our study).

Our findings show that most of patients with DCM exhibit an abnormal ECG and the most common abnormalities were low voltages in the limb leads and lateral TWI. Athletes often exhibit voltage criteria for LVH, which is considered a physiological finding that doesn't require further investigations[6]. Interestingly, the presence of low voltages on the limb leads, which is currently not considered a red flag according to the International criteria for the electrocardiographic interpretation in athletes, emerged as a feature suggestive of DCM in

almost 50% of the cases and was found in none of the athletes with marked structural changes. Athletes commonly exhibit LVH, particularly the type of athletes most likely to exhibit a "DCM-like" phenotype and that often participate in endurance sports. As such, although low voltage criterion in isolation may not require further investigation, our study indicates that in the context of a dilated LV cavity +/- mildly reduced EF should prompt comprehensive evaluation for DCM.

Our findings suggest that in asymptomatic athletes with no significant family history of premature cardiac disease or SCD who exhibit significant LV dilatation and/or borderline or mildly reduced LVEF at echocardiography, a normal ECG is highly suggestive of a physiological process and may prevent further cardiac investigations aimed at ruling out DCM. In this context, low voltages in the limb leads and lateral TWI are red flags for genetically determined DCM and comprehensive investigations should be offered to the patient.

Limitations

Our study has some limitations. Our purpose was to investigate the differences between athletes exhibiting physiological cardiac adaptation and patients with DCM harbouring a pathogenic mutation; although this makes our cohort more homogenous in comparison with previous studies, as all patients had a clear genetic background, we concede that our study didn't encompass the whole spectrum of patients with DCM as the genetic testing is often negative in these patients even in the presence of a severe phenotype, possibly due to a predominance of environmental factors. Also, this is a retrospective study, with a small population. Moreover, our cohort of patients exhibited a wide range of genes involved which reflects the intrinsic heterogeneity of the disease. It is possible that patients with

DCM harbouring pathogenic variants in other genes than the ones that characterized our cohort, would show also different ECG patterns. Finally, in line with the retrospective nature of our study, not all athletes with significant cardiac remodelling were comprehensively investigated with tests aimed at ruling out a myocardial disease (a CMR was performed only in athletes exhibiting a marked LV remodelling, i.e. LVEDD > 65 mm).

CONCLUSIONS

While the ECG is usually normal in athletes characterized by significant LV dilatation and/or systolic dysfunction, this test is often abnormal in patients with DCM harbouring a pathogenic rare variant. Low voltages in the limb leads and lateral TWI are the most common abnormalities. The ECG shows a good accuracy in differentiating DCM from cardiac remodelling in athletes.

Perspectives

Physiological cardiac remodeling in highly trained athletes may overlap with DCM with important clinical implications. Our study shows that the ECG, despite being a basic and rather inexpensive test has a good accuracy in differentiating genetic DCM from physiological remodeling in athletes. Further studies should determine the prevalence and clinical relevance of low voltages in large cohort of athletes. Future research should attempt to establish the cost-effectiveness of a diagnostic model mainly based on the ECG, when approaching young individuals or athletes with LV remodelling at the echocardiogram.

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FIGURE LEGENDS

Central Illustration. Main study findings.

Figure 1. ECG of a cyclist with LVEDD 63 mm and LVEF 50% at transthoracic echocardiogram (A). ECG of a 50 years old man with DCM (FLNC mutation) (B). Note the low voltages and the TWI in the inferolateral leads.

Abbreviations: CRY: cardiac risk in the young; DCM: dilated cardiomyopathy; ECG: electrocardiogram; G+: genotype positive; LVEDD: left end-diastolic diameter; LBBB: left bundle branch block; LVEF; left ventricular ejection fraction; SGUL: ST George's University of London; UITS: Università di Trieste; TWI: T wave inversion.

Table 1. Demographic and echocardiographic characteristics of athletes and patients with DCM.

	Athletes (n=30)	**DCM (n=30)**	**P**
Demographics			
Age (years)	44 ± 16	49 ± 13	0.146
Males n (%)	26 (87)	19 (63)	0.06
Caucasian n (%)	28 (93)	28 (93)	0.56
Echocardiogram			
LVEDD (mm)	59 ± 9	57 ± 8	0.384
LVESD (mm)	42 ± 5	43 ± 7	0.587
IVS wall thickness (mm)	10.5 ± 0.7	9.1 ± 1.6	<0.001
PW wall thickness (mm)	10.3 ± 0.9	8.9 ± 1.6	<0.001
LA (mm)	43 ± 4	35 ± 7	<0.001

Abbreviations: IVS: interventricular septum; LA: left atrium; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; PW: posterior wall.

Table 2. ECG in athletes and patients with DCM.

	Athletes (n=30)	**DCM (n=30)**	P
SR n (%)	29 (97)	28 (93)	0.95
Heart rate (bpm)	52 ± 11	66 ± 14	<0.001
LA enlargement n (%)	3 (10)	4 (13)	0.967
RA enlargement n (%)	1 (3)	1 (3)	0.449
QRS duration (ms)	100 ± 14	99 ± 23	0.839
QRS > 100 ms n (%)	11 (37)	10 (33)	0.956
QRS > 120 ms n (%)	1 (3)	2 (7)	0.905
p-RBBB n (%)	1 (3)	3 (10)	0.564
RBBB n (%)	0	1 (3)	0.951
LBBB n (%)	1 (3)	3 (10)	0.564
SL criteria for LVH n (%)	12 (40)	6 (20)	0.16
Anterior TWI	0	4 (13)	0.13
Inferior TWI n (%)	1 (3)	2 (7)	0.905
Lateral TWI n (%)	0	6 (20)	0.03
Low voltages n (%)	0	14 (47)	<0.001
Ventricular Ectopic beats ≥ 1 n (%)	0	5 (17)	0.06
LAD n (%)	1 (3)	3 (10)	0.564
Normal ECG* n (%)	28 (93)	8 (27)	<0.001

Abbreviations: LAD: Left Axis Deviation; RBBB: right bundle branch block SR: Sinus Rhythm; TWI: T-wave Inversion

* According to the International recommendations for ECG interpretation in athletes (Sharma et al., 2017)

Table 3. Role of the ECG in differentiating DCM from physiological cardiac adaptation to exercise.

Abnormal ECG	
Sensitivity	73% (54% to 88%)
Specificity	93% (78% to 99%)
AUC	0.83 (0.71 to 0.92)
Abnormal ECG + isolated low voltages	
Sensitivity	77% (58% to 90%)
Specificity	93% (78% to 99%)
AUC	0.85 (0.73 to 0.93)

Figure 1.