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Influence of type of sport on cardiac repolarization assessed by electrocardiographic T-wave morphology combination score

Running head: T-wave morphology in elite athletes

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Conflicts of Interests:
CG and JKK are inventors of a patent regarding T-wave morphology.
SGT, EP and HKR have no conflicts of interests to declare

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Abstract

Introduction: Interpreting repolarization changes in the electrocardiogram of the athlete presents a clinical challenge in cardiac evaluation of athletes.

Aim: Assessment of cardiac repolarization using T-wave morphology by applying the Morphology Combination Score (MCS), and evaluate how this quantitative description of T-wave morphology was influenced by the sport performed.

Materials and methods: A cross sectional study of 469 young elite athletes was performed. Digital electrocardiograms were obtained and analyzed to quantify T-wave morphology in terms of asymmetry, flatness and notching, and combined in the MCS. Athletes >22 years were compared to a sex and age matched control group from the general population (N=198).

Results: MCS increased with increasing endurance component of the sport performed ranging from 0.79±0.15 in low endurance sports to 0.92±0.21 in high endurance sports ($p<0.0001$). MCS was independent of age, sex and body size. All subcomponents of MCS were increased compared to controls. MCS is unrelated to age, sex and ECG findings of the athlete's heart.

Conclusion: This study suggests that sport induces repolarization changes detected by T-wave morphology. The Morphology Combination Score suggests a greater level of repolarization changes in high endurance athletes than low endurance athletes.

Keywords

Athletes; Electrocardiogram; Repolarization; Morphology Combination Score; T-wave morphology.

Introduction

Repolarization abnormalities pose a particular problem in interpretation of the athlete's ECG. The athlete's heart is a combination of structural, functional and electrical adaptations to exercise, and separate recommendations to the interpretation of the athlete's ECG exist.[1] Despite efforts to refine these recommendations concern is still raised as to how benign repolarization changes related to athlete's heart are distinguished from repolarization changes related to cardiac disease with increased risk of arrhythmia and sudden cardiac death.[2–4] The level of repolarization changes is known to depend on age, sex, ethnicity and the sport performed.[5–7]

The increased use of pre-participation screening of athletes [8,9] highlights the need for sensitive measures to identify athletes at risk of sudden cardiac death. Resting 12-lead ECG has been suggested as a useful tool to do so.[1] The search for reliable interpretation methods have included computerized measurement of ECG [10,11] with ambiguous conclusions.

Left ventricular hypertrophy (LVH) and QT prolongation are two grey zone areas in distinguishing the physiological features of athlete's heart from pathologically affected hearts. LVH exists in a pathological form seen in patients with volume overload or increased ventricular pressure, and in patients with cardiomyopathy; and in a physiological form related to exercise training and ethnicity. In animal studies pathological LVH has been shown to down-regulate expression of human ether related a-go-go related gene (*hERG*) causing prolonged QTc and subsequent increased risk of arrhythmia.[12] In contrast, physiological LVH causes prolonged QTc but does not alter genetic expression.[13]

Limits for QTc interval have progressively been widened when recommendations on interpreting the athlete's ECG have been revised in order to avoid false positive ECG results.[1,8,14] Current criteria consider a QTc of 470 ms in men and 480 ms in women

prolonged thus risking a false negative result in the approximately 40% of LQTS patients with a QTc<460.[15] In addition to the discussion of appropriate threshold for QTc, several problems with the use of the QTc interval exist. First, measurement of QT interval by the physician has proved to be problematic in terms of accuracy.[16] Second, the correction for heart rate by Bazett's formula, widely used by clinicians, overcorrects the QT interval (erroneously yields too long QT intervals at high heart rates and too short QT intervals at low heart rates). Thus Bazett's correction may mask a substantially prolonged QT interval in athletes with a low heart rate. Similar but less pronounced problems are seen with Fridericia and Framingham corrections.[17]

A third diagnostic challenge in the athlete's ECG is the presence of T-wave inversion (TWI) in the right pre-cordial leads[18,19] which is a rare finding in the general population, but not uncommon among athletes and a minor criterion for arrhythmogenic right ventricle cardiomyopathy (ARVC), a cardiomyopathy of the right ventricle with increased risk of triggering ventricular arrhythmias during exercise.

An algorithm to quantify T-wave morphology by the degree of T-wave asymmetry, flatness and notching has been approved by FDA,[20] and shown to distinguish malignant I_{Kr} (*hERG*) blockade from quinidine and dofetilide from more benign repolarization abnormalities from ranolazine and verapamil.[21] A Morphology Combination Score (MCS) based on the asymmetry, flatness and notching measurements of the T-wave has also been used to distinguish between malignant I_{Kr} blockade from d,l-sotalol and more benign I_{Kr} blockade from moxifloxacin.[22]

The MCS has been shown to distinguish healthy controls from patients with pathological repolarization changes due to reduced I_{Kr} currents in both congenital LQTS[23] and drug induced QT prolongation[21,24] with higher sensitivity than QTc[23,24] which is often used

to describe ventricular repolarization. The continuous nature of MCS may be superior to TWI in order to identify subtle repolarization abnormalities. MCS and its component scores have a reduced dependence on heart rate in contrast to QT interval where correction for heart rate is needed.[25] Previous studies have shown that elite athletes in bicycling and soccer have significant altered T-wave morphology with increased MCS[7]

The aim of the study was to investigate how T-wave morphology in elite athletes is affected by the endurance component of the sport, and how MCS is related to ECG findings of the athlete´s heart.

Materials and methods

Athletes

The primarily Caucasian athletes participated in a study of voluntary cardiac pre-participation screening [26] conducted between November 2010 and January 2014 and were eligible for this sub-study if they had a digital ECG recorded. A digital ECG was obtained in 469 of 516 athletes. The only reason for not having a digital recording was technical problems.

Athletes were divided into nine groups depending on the static (strength) and dynamic (endurance) component of their sport according to Mitchell et al[27] (Table 1).

Results are reported for the three endurance levels[27]: low endurance (group A, e.g. riflery, curling, bowling and motor sports), medium endurance (group B, e.g. table tennis, badminton and sports dance) and high endurance (group C, e.g. triathlon, rowing, swimming and soccer).

Inclusion criteria were sports participation on a national team or equally high level, and age 12 to 35 years. Exclusion criterion was presence of a cardiac disease diagnosed at time of inclusion.

Participants 15 years or older signed an informed consent form. The consent form was signed by a legal guardian on behalf of athletes younger than 15 years.

Control group

A subgroup control population was found using the Danish General Suburban Population Study[28] to match the athletes and controls 1:1 by sex and age – exact on sex, optimal on age. Due to lack of very young subjects we compared only athletes aged 22 years and older to obtain a reasonable match on age, in this subgroup analysis resulting in a population of 198 athletes (age 26±4 years) matched with 198 controls (age 28±3 years), 60.6% male. The reference population is a free-living population of 20 years and up which was included between 2010 and 2013. Matching was done with replacement using MatchIt in R.[29]

ECG

Following 5 min of rest a digital 10 second 12-lead ECG was recorded in supine position and stored digitally (GE CardioSoft v6.61, Milwaukee, WI, USA) for offline analyses using version 21 of the 12SL algorithm (GE Healthcare, Milwaukee, WI, USA). Offline analyses included automated measurement of PR interval, QRS duration and QT interval as well as the advanced measurements comprising the MCS. The QT interval was corrected for heart rate by Bazett's formula ($QTc=QT/\sqrt{RR}$). Heart rhythm was classified as sinus rhythm or non-sinus rhythm. Presence of incomplete or complete right bundle branch block, or left bundle branch block was noted. TWI was considered significant if a negative T-wave amplitude of more than 1mm was present in two or more of the leads: V2-V6, II and aVF, or in both I and aVL (III, aVR and V1 excluded). Athletes with TWI underwent thorough cardiac examination including echocardiography and cardiac MRI. No cardiac pathology was found (data not shown). Sokolow Lyon-criteria for LVH was used (S-wave in V1 + R-wave in V5 or

V6≥35mm) and first degree AV block defined as PR>200 ms. The ECGs were classified as being normal, with common and training-related changes, or with abnormal and training-unrelated changes according to the "Seattle Criteria".[1]

Morphology Combination Score

Definitions

MCS is based on the flatness, asymmetry and notching of the T-wave[24] defined as:

Flatness: Measures kurtosis of the T-wave similar to the measurement of peakedness in a probability distribution. (Dimensionless)

Asymmetry: Evaluates the differences in slopes of the ascending and descending parts of the T-wave considering both slope steepness and duration. (Dimensionless)

Notching: Reflects presence and size of any visible notches on the T-wave. A notch is given the value of either 0.5 or 1 depending on the protuberance. Absence of notch is given the value of 0. (Dimensionless)

MCS= Asymmetry + Notch +1.6 x Flatness (Dimensionless)

A schematic description of asymmetry, flatness and notching as well as normal, moderately abnormal and severely abnormal is shown in figure 1.

The mean MCS for a healthy, adult population is approximately 0.7 [23,24] and for LQTS2 patients 1.5-1.8.[24,25]

Statistical analysis

Statistical analysis was made using commercially available software (STATA 13, College Station, TX, USA). Descriptive statistics are presented by mean and standard deviation or range where appropriate. Unpaired t-test was used for comparison of continuous variables

between two groups. Analysis of variance (ANOVA) and logistic regression was used to test for differences between >2 groups in continuous and binary variables, respectively. Scheffe's post hoc test was used to adjust for multiple comparisons. Multiple regression analysis was used to test level of endurance sport as an independent factor of MCS. Chi-squared test was used for comparison of categorical data between groups. A probability level of 95% ($p<0.05$) was considered to be statistically significant.

Ethics approval

The study was approved by the Regional Ethics Committee for research in the Capital Region (H-4-2010-056), and data collection was approved by the Danish Data Protection Agency (2010-41-4886).

Results

The elite athletes (N=469, 61% men) represented 29 different sports. Soccer (N=97), handball (N=64) and rowing (N=40) were the most frequent. Demographic data are shown in table 2. A complete list of participating sports can be found in Supplementary material.

ECG

In total, 386 (82%) of the athletes exhibited one or more training related ECG changes according to the Seattle criteria,[1] including IRBBB (N=123), first degree AV block (N=40), LVH (N=131) and sinus bradycardia (N=326).

Sixteen athletes exhibited TWI, and two of these were diagnosed with Wolff-Parkinson-White syndrome.

Heart rate, PR Interval, QRS duration and QTc interval were significantly different between men and women ($p=0.02$, <0.0001, <0.0001 and <0.0001, respectively). Basic and advanced ECG measurements are shown in table 3.

Morphology Combination Score

Mean MCS was 0.90±0.22 with a non-significant difference between men and women (0.88 vs. 0.92, p= 0.1).

In regression analyses MCS was significantly (p<0.0001) but only moderately related to heart rate, QT and QTc duration (r^2=0.07, r^2=0.23, and r^2=0.05, respectively). There was no significant correlation between MCS and the PR interval (p=0.1), QRS duration (p=0.2), age (p=0.1), BSA (p=0.1), current amount of training (p=0.6), or years in training (p=0.2). MCS was neither associated with the presence of training related ECG changes: IRBBB (N=123, p=0.7), LVH (N=131, p=0.2), first degree AV block (N=40, p=0.9), nor presence of TWI (N=16, p=0.1).

Mean asymmetry was 0.15±0.09, mean flatness 0.46±0.06, and eight athletes exhibited presence of a notch of which five were given the value 0.5 and three the value 1.0.

Type of sport

Group C-athletes (high endurance) exhibited significant differences in both basic and advanced ECG parameters compared to group A (low endurance) (Table 3). These differences remained after adjusting for sex. The association between MCS and level of endurance component and QT-interval remained significant in multiple regression analysis after correction of heart rate and QT interval in a forward stepwise model.

The differences between endurance groups were seen in both asymmetry and flatness, and even though the largest number of athletes with a positive notch was found in the high endurance group, this was not significant. (Table 3) The corresponding analysis for strength groups (Mitchell groups 1-3) did not show a similar difference (Test for trend between groups 1-3: MCS: p=0.1).

Athletes vs controls

Compared to controls, athletes exhibited significantly longer QT interval, longer RR interval, and higher MCS, asymmetry and flatness scores. (Table 4)

Discussion

This study investigates how T wave morphology can be assessed automatically by the morphology combination score, and how this score is affected by the sport performed. Assessment of T-wave morphology showed that increasing degree of endurance training in elite athletes results in greater repolarization changes. The MCS measurement was not related to those standard ECG changes, which are generally accepted as normal and training related in athletes ie IRBBB, first degree AV block or, importantly, LVH, and the significant relationship with heart rate did only account for 7% of the variation in MCS. Nor was MCS associated with age or sex.

However, we did find an increase in all components of MCS with increasing amount of endurance training represented by sports classified as Group C. This indicates that increasing level of endurance component in sports induced repolarization changes which is captured by MCS but are not explained solely by those ECG measurements commonly used to describe the athletes' heart. On average the athletes did not attain MCS values (MCS=0.93) as high as those seen in LQTS2 patients (MCS=1.50)[23], and (MCS=1.80).[24] Compared to a control group from the general population matched for age and sex, the athletes exhibit higher values of MCS, flatness and asymmetry which is also consistent with data from literature.[23,24]Gademan et al[11] also found type of sport to influence ECG measurements with most pronounced effect of endurance sports. Compared to the MCS a difference between male and female athletes was found in the many various measurements which favours the MCS as a more simple method to assess the athlete's ECG.

We found athletes to exhibit longer QT intervals and higher MCS than controls, and both these measurements increase with increasing level of endurance. The QT interval, however, is corrected by heart rate reducing this tendency whereas the MCS has shown little dependency of heart rate thus still reflecting a change in repolarization. The advantage of a single numeric automatically calculated score to assess ventricular repolarization is underlined in the newest consensus statement regarding interpretation of the athlete's ECG[30] where a 6-step method to assess QT interval is suggested including evaluation of the morphology of the T-wave. This is time consuming and a source of error for the clinician in general.

The challenge of athletes with TWI was documented by Brosnan et al[19] who found TWI to be present in 15 % of endurance athletes. Similar to our study no cardiac pathology was found in these athletes, and TWI in our athletes was not associated with a higher MCS suggesting that the MCS may help in the evaluation of athletes presenting TWI.

Limitations

A cross sectional and case-control study can only serve as hypothesis generation and more studies including both athletes and non-athletes with cardiac pathology, structural and electrical – is needed to assess MCS as a tool for differential diagnostic. Also our participants were almost solely Caucasians and studies on different ethnic groups are also warranted. Lastly, the temporal stability of the MCS in the cause of a year or during an athletic career needs to be determined.

Conclusion

The electrocardiographic Morphology Combination Score (MCS) increased with increasing level of endurance training which was not caused by a lower heart rate, and was unrelated to age, sex and body size as well as normal and training related ECG changes. MCS of athletes was higher (MCS=0.93) than that of controls (MCS=0.68)), but not as high as in patients with

known risk of arrhythmia due to LQTS2 (MCS=1.50-1.80). We suggest that MCS can be a simple and helpful additional measurement in the evaluation of ventricular repolarization in athletes compared to QTc interval and visual assessment of T-wave morphology currently recommended.

Competing interests

CG and JKK are inventors of a patent regarding T-wave morphology.

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Figure captions

Figure 1: The components of the Morphology Combination Score (MCS) quantify the degree of asymmetry, flatness and notching of the T-wave. Healthy subjects have MCS values around 0.7 with symmetric T-waves that do not appear flat. There is no notching of the T-wave. Borderline abnormal MCS values are close to 1.0. The T-waves in this range appear more asymmetric and flat but without notches. Markedly abnormal MCS values are close to 2.0. In this range there is pronounced flattening and asymmetry of the T-wave with clear notching. With permission from Hong et al.[7]

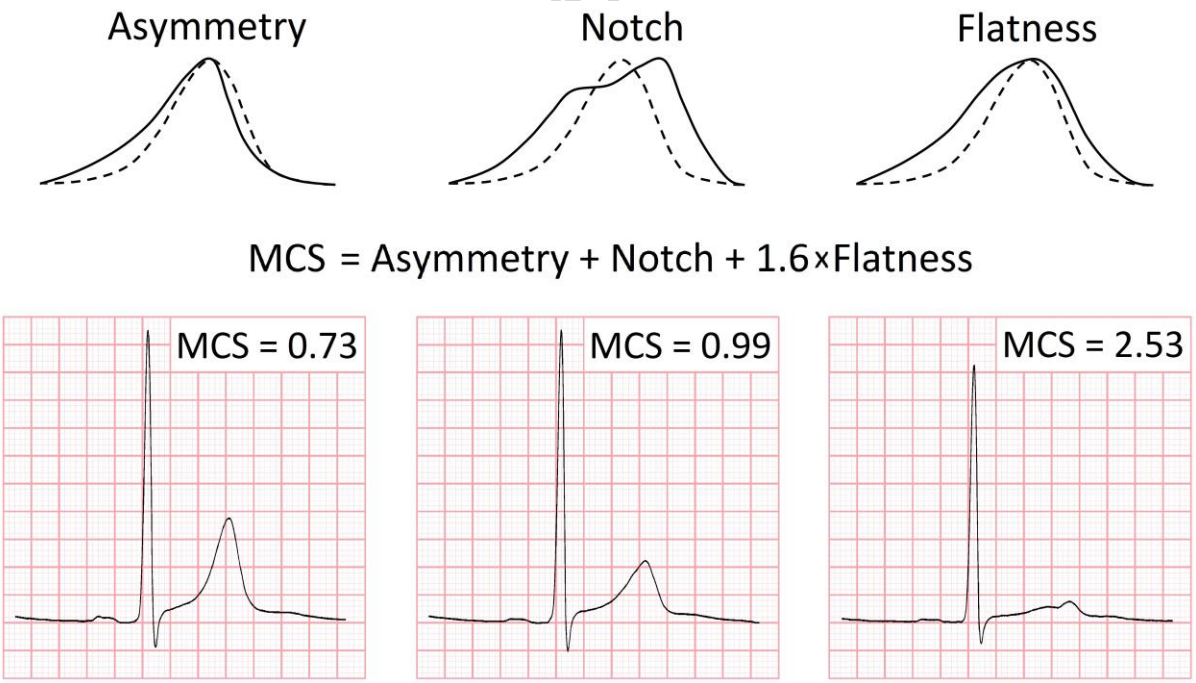

Table 1 : Participating sports according to The Mitchell-classification of sports.[23]

Dynamic component / Static Component	A. Low	B. Moderate	C. High	Total
3. High	Field events (throwing) Taekwondo Sailing Water skiing N=31		Canoeing Cycling Rowing Triathlon N=78	109
2. Moderate	Archery Auto racing Equestrian Motorcycling N=13	Field events (jumping) Running (sprint) N=27	Ice hockey Cross country skiing Swimming Handball N=139	179
1. Low	Bowling Curling Golf Shooting N= 30	Table tennis Volleyball N=14	Badminton Orienteering Soccer Tennis N= 137	181
Total	74	41	354	469

Table 2: Characteristics of participating athletes

Characteristics of the participating athletes divided in groups according to the level of endurance component of their sport: Age, height, weight, body surface area, current amount of training, and accumulated years in training (number of years participating in competition level sports).

Demographic data	Total N=469	Group A Low endurance N=74	Group B Medium endurance N= 41	Group C High endurance N=354
Age (years) (mean, range)	22±5 (13-35)	24 (15-34)	22 (15-34)*	21 (13-35)*
Height (cm) (mean ±SD)	179.3±9.6	175±8	176±11	181±9*
Weight (kg) (mean ±SD)	73±12	70±11	66±12	74±11*
BSA (m^2) (mean ±SD)	1.91±0.20	1.8±0.2	1.8±0.2	1.9±0.2*
Training hours/week (mean ±SD)	17.0±7.1	18±9	20±8	16±7
Years in training (mean±SD)	7.0±4.1	7±4	8±5	7±4

BSA: Body surface area

*: $p<0.05$ vs Low endurance group

Table 3: ECG measurements

ECG Characteristics of the participating athletes divided in groups according to the level of endurance component of their sport. Basic measurements, Components of the Morphology Combination Score: Asymmetry, Flatness, Notching and total MCS. Training unrelated and training related findings according to the Seattle criteria.[1]

	Total N=469	Group A Low endurance N=74	Group B Medium endurance N=41	Group C High endurance N=354
HR (bpm)	56±10	60±10	57±12	55±21*
PR Interval (ms)	161±31	156±26	163±28	162±32
QRS duration (ms)	96±11	92±10	94±17	96±10*
QT (ms)	429±31	411±29	420±35	434±29*
QTc (ms)	410±22	407±21	402±25	411±22
Advanced measurements				
Asymmetry	0.15±0.09	0.12±0.08	0.12±0.07	0.15±0.09*
Flatness	0.46±0.06	0.42±0.06	0.44±0.07	0.47±0.06*
Notch (N)	8	0	1	7
MCS	0.89±0.21	0.79±0.15	0.85±0.25	0.92±0.21*
Training unrelated				
T-wave inversion (N)	16 (3%)	0	1 (2%)	15 (4%)
Ventricular pre-excitation (N)	2 (0.4%)	0	1 (2%)	1 (0.03%)
Training related				
First degree AV block (N)	40 (9%)	4 (5%)	5 (12%)	31 (9%)
IRBBB (N)	123 (26%)	11 (3%)	13 (32%)*	99 (29%)*
LVH (N)	131 (28%)	11 (3%)	13 (32%)*	107 (30%)*
Sinus bradycardia (N)	326 (70%)	38 (51%)	26 (63%)	262 (74%)*

AV: Atrioventricular; bpm: Beats per minute; HR: Heart rate; IRBBB: Incomplete right bundle branch block; LVH: Left ventricle hypertrophy by Sokolow-Lyon criteria; QTc: QT interval corrected for heart rate (Bazett)

*:$p<0.05$ vs Low endurance group

Table 4: Characteristics of athletes and control subjects participating in the case-control sub-study

	Controls (N=198)	Athletes (N=198)	p-value
Male (N, %)	120 (60.6)	120 (60.6)	1.0
Age (years) (mean±SD)	28±3	26±4	<0.0001
QT(ms) (mean±SD)	400±26	432±32	<0.0001
RR interval (ms) (mean±SD)	984±169	1141±199	<0.0001
MCS (mean±SD)	0.68±0.24	0.87±0.20	<0.0001
Flatness (mean±SD)	0.38±0.07	0.46±0.06	<0.0001
Asymmetry (mean±SD)	0.08±0.11	0.13±0.08	<0.0001
Notch (mean±SD)	0.01±0.07	0.01±0.11	0.404

Highlights

- Sport induces changes in repolarization which can be detected by MCS
- Endurance sports induce a greater change in repolarization than strength training
- MCS is independent of age, sex and body size
- MCS is unrelated to ECG changes normally associated with Athlete's heart