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Detection of hypertrophic cardiomyopathy is improved when using advanced rather than strictly conventional 12-lead ECG

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Brief Title: Detection of hypertrophic cardiomyopathy with advanced ECG

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Abstract

Introduction: 12-lead ECG is used to screen for hypertrophic cardiomyopathy (HCM), but up to 25% of HCM patients do not have distinctly abnormal ECGs while up to 5-15% of healthy athletes do. We hypothesized that a ~5-min resting advanced 12-lead ECG test ("A-ECG score") could detect HCM with greater sensitivity than pooled conventional ECG criteria and distinguish healthy athletes from HCM with greater specificity.

Materials and Methods: Five-minute 12-lead ECGs were obtained from 56 HCM patients, 56 age/gender-matched healthy controls, and 69 younger endurance-trained athletes. ECGs were analyzed using recently suggested pooled conventional ECG criteria and also A-ECG scoring techniques that considered results from multiple advanced and conventional ECG parameters.

Results: Compared to pooled criteria from the strictly conventional ECG, an A-ECG logistic score incorporating results from just three advanced ECG parameters (spatial QRS-T angle, unexplained portion of QT variability and T-wave principal component analysis ratio) increased the sensitivity of ECG for identifying HCM from 89% (78-96%) to 98% (89-100%) (P=0.025) while increasing specificity from 90% (83-94%) to 95% (92-99%) (P=0.020).

Conclusions: Resting 12-lead A-ECG scores can be constructed that are simultaneously more sensitive than pooled conventional ECG criteria for detecting HCM and more specific for distinguishing healthy athletes and other healthy controls from HCM. Pending further prospective validation, such scores may lead to improved ECG-based screening for HCM.

Keywords: QRS-T angle; QT variability; sudden cardiac death; athletes' heart; screening

Introduction

Hypertrophic cardiomyopathy (HCM) is a heterogeneous, genetic cardiac disorder that is a common cause of sudden cardiac death in young people, but which can also be associated with normal longevity.[1, 2] In the U.S., HCM accounts for more than one-third of fatal cardiac arrests in young competitive athletes.[3] Early identification of patients with HCM is essential due to the high risk of SCD in this population. To this end, 12-lead ECG has been suggested as an inexpensive and useful screening tool, one that in certain situations may be more sensitive than echocardiogram.[1, 2]

Common ECG abnormalities in HCM include increased precordial and standard lead voltages potentially indicative of left ventricular hypertrophy, ST-T changes including T-wave inversion, and pathologic Q waves.[2, 4] Significantly, however , up to 25% of individuals with HCM in the general community do not have abnormal ECGs,[2, 5] and patients with nonobstructive HCM are especially likely to have false negative ECGs.[4] Additionally, approximately 40% of trained athletes have ECG abnormalities, with 5-15% having abnormalities that are severe enough (T-wave inversion, deep Q waves) to warrant evaluations for cardiac disease.[6] Because many of the ECG abnormalities observed in athletes are similar to those observed in HCM, it is often difficult to distinguish HCM patients from healthy athletes using strictly conventional ECG. Therefore, any resting ECG technique that might increase sensitivity for detecting HCM[7-11] as well as increase specificity for distinguishing between HCM and athlete's heart would be clinically relevant.

Over the past 20 years, several advanced ECG techniques implemented within software have improved the diagnostic and prognostic value of resting ECG. These

techniques include beat-to-beat QT variability (QTV)[8-10, 12, 13] and R-wave to R-wave variability (RRV);[14, 15] "3-dimensional" (spatial and spatiotemporal) ECG;[16-19] high-frequency (HF) QRS ECG;[20] and detailed studies of waveform complexity by singular value decomposition (SVD).[7, 19, 21-23] A theoretical advantage of computerized ECG systems is that they allow for multiple conventional and advanced ECG techniques to be performed in software during a single digital recording. Related results can then be integrated (scored) automatically by using statistical or pattern recognition techniques to maximize diagnostic or predictive accuracy. In practice, these procedures can also be performed rapidly and relatively inexpensively.

The hypotheses of the present study were that a ~5-min resting "advanced 12-lead ECG" (A-ECG) test, defined as the multivariate logistical integration (scoring) of key results from both the conventional and advanced ECG, could detect HCM with greater sensitivity than presently utilized pooled conventional ECG criteria, and could distinguish HCM patients from healthy athletes with greater specificity. To test these hypotheses, we compared the pooled conventional ECG and A-ECG score results of HCM patients with those from an age and gender matched set of controls and from a set of younger, endurance-trained athletes.

Methods

Participants. Five-minute resting 12-lead ECGs were recorded in 56 patients with HCM (age range 19-71 years; mean 48.7 ± 14.0 years) and age- and gender-matched to ECGs collected from 56 healthy control subjects (age range 20-71 years; mean 48.7 ± 14.0 years). The HCM patients had been recruited principally at The Heart Hospital

(London, U.K.), and at Lund University Hospital (Lund, Sweden), and the corresponding control subjects at both Lund University Hospital and NASA's Johnson Space Center (Houston, TX). Similar ECGs were also obtained from a set of 69 younger, endurance-trained athletes (age range 17-57 years; mean 25.3 ± 6.8) who had also been recruited at Lund University.

Patients with HCM carried their clinical diagnosis based on echocardiographic identification of a hypertrophied, nondilated left ventricle in the absence of other cardiac or systemic diseases capable of producing hypertrophy to that extent.[24] All control subjects, including the athletes, were asymptomatic volunteers with no evidence of cardiac disease based on a negative history and physical examination. The athletes comprised Swedish triathletes as well as semi-professional soccer and handball players of both genders who had cardiac magnetic resonance imaging scans demonstrating no evidence of HCM or any other clinical pathology. No patient or healthy subject with complete bundle branch block, sinus tachycardia, non-sinus rhythm, paced rhythm, pre-excitation, or a noisy or incomplete ECG recording was included in the study.

Data collection. High-fidelity (1000 samples/sec/channel) ECG systems from Siemens-Elema AB (Solna, Sweden),[24] or Cardiax/CardioSoft (Budapest, Hungary/Houston, TX)[21, 25] were utilized to acquire a minimum of 256 waveforms acceptable for both signal averaging and variability analyses (see below). Imaging was performed using standard clinical techniques as previously described,[24, 26] with the clinicians who produced the clinical imaging reports being blind to the A-ECG results, which were in turn produced in the automated fashion described below.

Analysis of ECG signals.

A. Conventional ECG parameters. Signals from the conventional ECG were analyzed automatically in software with respect to the RR, PR, P-wave, QRS and uncorrected and Bazett-corrected QT and JT intervals; P, QRS and T-wave amplitudes; frontal plane QRS and T-wave axes; and ST segment levels. Strictly conventional 12-lead ECGs were defined as being "abnormal", as automatically measured, when any of the following criteria were present as recently suggested by Corrado and McKenna:[27] *1)* left atrial enlargement (negative portion of the P wave in lead V1 ≥ 0.1 mV in depth and ≥ 0.04 s in duration); *2)* ST-segment depression in 2 or more leads; *3)* pathological Q waves (abnormal Q waves ≥ 0.04 s in duration or ≥0.25% of the height of the ensuing R wave, or QS pattern in ≥ 2 leads); *4)* inverted T waves in ≥ 2 consecutive leads; *5)* left axis deviation/left anterior hemiblock (frontal plane QRS axis deviation between -30° to -90°); *6)* right axis deviation/left posterior hemiblock (frontal plane QRS axis deviation ≥ +120º); *7)* prolonged QTc interval (>0.44s in men and >0.46 s in women); or *8)* Brugada-like (coved type) early repolarization.

B. Advanced ECG parameters derived from signal averaging. Signal averaging was performed using software developed by the authors[20, 21, 25, 28] to generate results for parameters of: *1*) 12-lead HF QRS ECG;[20] *2*) derived 3-dimensional ECG, using the Frank-lead reconstruction technique of Kors et al[29] to derive several vectocardiographic parameters previously described by Draper et al,[30] including for example the spatial mean QRS-T angle[17, 28, 31] and the magnitude,[30] azimuth /elevation[30] and beat-to-beat variation[16] of the spatial ventricular gradient and its components; and *3*) QRS and T-waveform complexity via SVD, for example to derive parameters such as the principal component analysis (PCA) ratio,[21, 22, 32] the "relative residuum"[21, 23] and the dipolar and

nondipolar voltages[19, 25] of the QRS and T waveforms. The majority of the parameters studied and their related detailed methods have been described in other recent publications.[20, 21, 25, 28, 33]

C. Advanced parameters derived from variability analyses. Several parameters of beat-to-beat RRV and QTV that have been described in previous publications[12, 25, 33, 34] were again evaluated via custom software programs developed by the authors.[12] These included the "QT variability index" (QTVI), but using the means and variances of the RR interval[9, 34] rather than those of the heart rate[13] in the denominator of the QTVI equation, and the "unexplained" part of the QT variability.[33, 34] For the latter, the QTV signal was decomposed into two parts as previously described: one part that can be accounted for by the concomitant HRV and/or by the concomitant variability of the QRS-T angle and ECG voltages, and the other part representing the "unexplained" part of QTV.[33, 34] The QT signals were fit by a linear combination of the RR interval, QRS-T angle and voltage signals, with the fitted part representing the "explained" QTV and the remaining "error" part representing the "unexplained" QTV. The "index of unexplained QTV" (IUQTV) was then calculated as follows: IUQTV = log (unexplained QTV/explained QTV).[33, 34]

Statistics. Promising candidate sets of ECG parameters for potential inclusion in A-ECG multivariate logistic scores were first identified using a branch-and-bound feature selection procedure[35] implemented in SAS 9.1.3 (Cary, NC). To avoid the so-called "curse of dimensionality", the number of ECG parameters incorporable into any potential A-ECG score was limited to fewer than one-tenth of the minimum number of training samples available in a given group or subgroup.[35] Logistic regression was used to retrospectively estimate the probability, assuming equal prior probabilities, of any subject

being a member of the HCM group based strictly on his/her A-ECG-based independent variables. The best candidate sets of parameters (A-ECG scores) were then subjected to further validation by bootstrap analysis[36] in which for each fixed score, the data were iteratively resampled 1000 times and the parameter coefficients re-estimated. The bootstrap analyses, implemented in Stata (version 10.0, College Station, TX), revealed not only the variability in the estimated logistic regression coefficients, but also those candidate A-ECG scores that should be discarded because of their doubtful use for classifying later subjects whose status was unknown, for example scores that produced coefficients that greatly varied over the bootstrap samples or that did not have the expected sign over all 1000 bootstraps. Performance of the best A-ECG scores in a simulated prospective setting was also tested via jackknife analysis,[36] in which the score's sensitivity, specificity and accuracy were evaluated by using the data for all but one observation to classify the omitted observation, then repeating the process for each observation in turn. For simple illustrative comparisons between groups, the Wilcoxon rank sum and receiver operating curve characteristic statistics were used, whereas for comparison of accuracies between strictly conventional and A-ECG classifiers, Cochran's Q[37] was used.

Results

Table 1 shows basic demographic information for the HCM, control, and athlete groups. Both the control and athlete groups demonstrated lower use of medication. In addition, the athlete group was younger than the HCM and control groups.

Table 2 shows that when employing the recently suggested set of pooled conventional ECG criteria optimized for detecting cardiac disease in athletes,[27] a total of six HCM patients had false negative ECG results while 13 healthy subjects (three age-gender-matched controls and 10 athletes) had false positive results. Thus, the overall sensitivity and specificity of the pooled conventional ECG criteria for HCM were 89% and 90%, respectively.

Of the parameters evaluated by the branch-and-bound procedure, the best single parameter (conventional or advanced) for distinguishing patients with HCM from all healthy subjects was the spatial mean QRS-T angle derived from the Frank-lead reconstruction technique of Kors et al. When using only the result of this angle at its most accurate retrospective cutoff (>76º), six HCM patients had false negative results while 12 healthy subjects had false positive results. Even when the spatial mean QRS-T angle was subsequently subject to cross-validation via the jackknife procedure, it alone still provided results that were essentially equivalent to that of the entire pooled set of conventional ECG criteria (Table 2).

As additionally shown in Table 2, optimal sensitivity and specificity resulted when, through the use of the feature selection procedure, an A-ECG logistic score was constructed that utilized results from the following three parameters: *1)* the spatial mean QRS-T angle; *2)* the IUQTV in lead II (which itself was the best single parameter for distinguishing healthy athletes from HCM patients); and *3)* the natural log of the PCA ratio of the T wave. In the purely retrospective analyses (Table 2), this optimal 3-parameter A-ECG score yielded only a single false negative result (sensitivity of 98%) and four false positive results (specificity of 97%), with none of the false positive results

occurring within the healthy athlete group. Further evaluation through the jackknife procedure showed no additional false negative results (P=0.025 for the resulting difference in sensitivity vs. the pooled conventional criteria) but an increase in the number of false positives from four to six. However, although specificity decreased to 95% in the jackknife, the resulting difference in specificity vs. the pooled conventional criteria remained statistically significant (P=0.020).

Table 3 shows the exact coefficients of the optimal 3-parameter A-ECG score. This score made full use of the ~5-min (so called "full-disclosure") 12-lead ECG recording because it incorporated results from the IUQTV. However, results from the other two components of the optimal score (the spatial mean QRS-T angle and the PCA ratio of the T wave) can be reliably and reproducibly obtained from 10-sec "snapshot" ECGs.[17, 21] Therefore further feature selection procedures were carried out in order to ascertain which of the parameters we studied that can be reliably obtained from 10-sec ECGs might be used to construct an optimal "snapshot" A-ECG score. While again identifying the spatial mean QRS-T angle and the PCA ratio of the T wave, these procedures additionally identified P-wave duration as the most optimal third parameter available from snapshot ECGs that might replace the IUQTV, albeit with some deterioration in diagnostic performance. As shown in Table 2, a "snapshot" A-ECG logistic score incorporating the spatial mean QRS-T angle, the natural log of the PCA ratio of the T wave and the natural log of the P-wave duration resulted in three (purely retrospective) and four (jackknifed) false negative results, and in six (purely retrospective) and eight (jackknifed) false positive results, respectively. Whereas in the jackknife the specificity of the "snapshot" A-ECG score was still statistically

significantly higher than that of the pooled conventional ECG criteria, the trend toward simultaneously improved sensitivity was not. The addition of more parameters to any of the above A-ECG scores did not further improve diagnostic performance when using the present data set.

Discussion

While retrospective in nature, our findings suggest that A-ECG logistic scores incorporating the results of just three advanced ECG parameters can improve sensitivity for detecting HCM compared to recently suggested and arguably more complex pooled conventional ECG criteria. Particularly when optimized through the use of full-disclosure (~5-min+) ECG recordings, such A-ECG scores also appear to offer superior specificity for separating patients with HCM from healthy controls, especially athletes. The results of our study are in agreement with the recent results of Caselli et al.[11] Their group similarly constructed A-ECG-type logistic scores derived from full-disclosure 12-lead ECG recordings (although without the benefit of the spatial QRS-T angle or studies of QT variability) and concluded that such scores offer an improved clinical tool, compared to strictly conventional ECG, for distinguishing athlete's heart from HCM.[11]

Debate regarding pre-participation 12-lead ECG screening for athletes continues. Although such screening has been successful in detecting HCM and other cardiomyopathies in Italian and other athletes, it is not currently systematically implemented in the United States.[3, 38] The American Heart Association, unlike the European Society of Cardiology and the International Olympic Committee, has for the time being chosen not to endorse pre-participation ECG screening, in part due to concerns about potentially high costs associated with universal

implementation within the U.S.[38] Regardless of any formalized recommendations for or against such pre-participation screening, the improved specificity of A-ECG scoring, if corroborated in future prospective studies, might aid in reducing those costs that are now incurred when truly unnecessary further testing occurs based on strictly conventional ECG analysis. Additionally, because of improved sensitivity, A-ECG scoring with full-disclosure ECG might also be preferred over isolated conventional ECG for initial screening of higher-risk individuals, such as those with syncope or family histories of HCM.

After further validation, the implementation of A-ECG scoring might be also accomplishable with only modest software upgrades to many existing ECG machines, including to the majority of those machines in the installed base that presently only store "snapshot" (10-sec) recordings. Although A-ECG scores derived from "snapshot" ECGs do not provide the same level of sensitivity and specificity as the more optimized scores that utilize results from full-disclosure ECGs, such snapshot-based A-ECG scores might nonetheless yield incremental diagnostic improvements over presently utilized pooled criteria from the strictly conventional ECG.

In conclusion, 12-lead A-ECG scores can be constructed that are simultaneously more sensitive than pooled conventional ECG criteria for detecting HCM and more specific for distinguishing HCM from healthy athletes and other healthy controls. Pending further prospective validation, such A-ECG scores may be useful for improved ECG-based HCM screening.

Limitations. The most important limitation of this study was its retrospective nature, which is only partially mitigated by our additional use of cross-validation (jackknife and bootstrap) procedures. Further prospective studies are therefore necessary for ultimate validation

prior to consideration of clinical implementation. It is also important to note that we did not attempt to use A-ECG techniques to distinguish HCM from other cardiovascular diseases. Coronary artery disease, non HCM-related left ventricular hypertrophy and other cardiomyopathies are also often accompanied by increases in T-wave complexity, QT variability and the spatial mean QRS-T angle,[25] such that other A-ECG scores would likely need to be used as part of any attempt to distinguish these other pathologies from HCM. We also could not control for the fact that cardioactive medication use was significantly greater in the HCM patients than in the healthy subjects. It is therefore quite possible that this difference in medication use affected our results, although the medication type most commonly administered to our HCM patients (beta blockers) tends to improve, not worsen, advanced electrocardiographic measures of repolarization.[39, 40] Finally, our study was not designed to investigate the pathophysiological reasons for the diagnostic utility of the optimal parameters in the scores, nor have we studied the prognostic utility, if any, of A-ECG scores in predicting HCM-related events. Further studies are therefore also required to address these other issues.

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Table 1. Basic Demographic Information for the HCM, Control and Athlete Groups

Parameter	HCM Group (N=56)	Control Group (N=56)	Athlete Group (N=69)
Age [years]	48.7 ± 14.0	48.7 ± 14.0	25.3 ± 6.8
Males (%)	37 (66)	37 (66)	40 (58)
Blood pressure			
Systolic [mm Hg]	124 ± 19	124 ± 14	126 ± 9
Diastolic [mm Hg]	74 ± 12	76 ± 8	72 ± 8
Mean [mm Hg]	90 ± 13	92 ± 9	90 ± 6
Cardioactive medications	45 (80)	0 (0)	0 (0)
NYHA class (I/II/III/IV)	39/5/1/0	NA	NA
LV Mass (g)	253 ± 102	NA	130 ± 34
LVEF (%)	66.1 ± 6.1	NA	58.5 ± 5.8

Values are mean ± standard deviation or the total number (percent) of affected individuals. HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; NA, not applicable or available; LV mass and LVEF: left ventricular mass and ejection fraction, respectively, obtained in the HCM patients by echocardiography according to the method of Devereux and Reichek[41] and in the athletes by cardiac magnetic resonance imaging according to the method of Cain et al.[26]

Table 2. Sensitivity, Specificity and Accuracy of Conventional Pooled versus A-ECG Score-related Criteria in Detecting Hypertrophic Cardiomyopathy

	Disease (N=56)		Healthy (N=125)				
	TP	FN	TN	FP	Sensitivity(CLs)	Specificity(CLs)	Accuracy(CLs)
Conventional ECG status							
Abnormal (using pooled criteria[27])	50	6	112	13	89%(78-96%)	90%(83-94%)	90%(84-94%)
Best single parameter status							
SM QRS-T angle >76º (retrospective)	50	6	113	12	89%(78-96%)	90%(84-95%)	90%(85-94%)
SM QRS-T angle >Xº (jackknifed)	50	6	112	13	89%(78-96%)	90%(83-94%)	90%(84-94%)
Optimized 3-parameter A-ECG score status							
Abnormal (retrospective)	55	1	121	4	98%(90-100%)*	97%(92-99%)*	97%(94-99%)*
Abnormal (jackknifed)	55	1	119	6	98%(89-100%)*	95%(92-98%)*	96%(93-97%)*
3-parameter "snapshot" A-ECG score status							
Abnormal (retrospective)	53	3	119	6	95%(85-99%)	95%(90-98%)†	95%(91-98%)
Abnormal (jackknifed)	53	3	117	8	95%(88-96%)	94%(88-97%)†	94%(90-96%)

TP, true positive; FP, false positive; TN, true negative; FN, false negative; CLs, exact 95% binomial confidence limits for all but the retrospective Advanced ECG (A-ECG) scores. CLs for the retrospective A-ECG scores were obtained by nonparametric bootstrap to reflect variability in the estimated logistic regression coefficients. *P<0.03 and †P≤0.05 versus the sensitivity, specificity or accuracy of the pooled strictly conventional ECG criteria.

Table 3. Components and Coefficients of the 3-Parameter A-ECG Scores

A-ECG Components	Optimum score	Snapshot ECG score
Conventional ECG		
Ln P duration (Ln ms)		+5.754033
3D ECG		
SM QRS-T angle (°)	+0.1017083	+0.0945369
T-wave Complexity		
Ln T PCA Ratio (Ln %)	+4.694176	+4.351765
QTV		
IUQTV (II, units)	+3.977682	
Constant	-24.79388	-47.37005

A-ECG, advanced electrocardiography; Ln, natural logarithm; SM, spatial mean; PCA, principal component analysis; IUQTV, index of unexplained QT variability (in lead II).