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Electrocardiographic amplitudes: a new risk factor for sudden death in hypertrophic cardiomyopathy

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Aims Assessment of ECG-features as predictors of sudden death in adults with hypertrophic cardiomyopathy (HCM).

Methods and results ECG-amplitude sums were measured in 44 normals, 34 athletes, a hospital-cohort of 87 HCM-patients, and 29 HCM-patients with sudden death or cardiac arrest (HCM-CA). HCM-patients with sudden death or cardiac arrest had substantially higher ECG-amplitudes than the HCM-cohort for limb-lead and 12-lead QRS-amplitude sums, and amplitude–duration products ($P = 0.00003$–$P = 0.000002$). Separation of HCM-CA from the HCM-cohort is obtained by limb-lead QRS-amplitude sum $\geq$7.7 mV (odds ratio 18.8, sensitivity 87%, negative predictive value (NPV) 94%, $P < 0.0001$), 12-lead amplitude–duration product $\geq$2.2 mV s (odds ratio 31.0, sensitivity 92%, NPV 97%, $P < 0.0001$), and limb-lead amplitude–duration product $\geq$0.70 mV s (odds ratio 31.5, sensitivity 93%, NPV 96%, $P < 0.0001$). Sensitivity in HCM-patients $<$40 years is 90, 100, and 100% for those ECG-variables, respectively. Qualitative analysis showed correlation with cardiac arrest for pathological T-wave-inversion ($P = 0.0003$), ST-depression ($P = 0.0010$), and dominant S-wave in V_4 ($P = 0.0048$). A risk score is proposed; a score $\geq$6 gives a sensitivity of 85% but a higher positive predictive value than above measures. Optimal separation between HCM-CA $<$40 years and athletes is obtained by a risk score $\geq$6 (odds ratio 345, sensitivity 85%, specificity 100%, $P < 0.0001$).

Conclusion Twelve-lead ECG is a powerful instrument for risk-stratification in HCM.

Keywords Hypertrophic cardiomyopathy • Sudden death • Electrocardiogram • Screening • Athletes • Gender

Introduction

Hypertrophic cardiomyopathy (HCM) is the commonest medical cause of sudden unexpected death in older children[1] and in athletes.[2] The prevalence of the disease in young adults is approximately 1 in 500.[3] Studies in adult HCM patients have identified some risk factors for sudden death: non-sustained ventricular tachycardia (VT) on 24 h ECG, left ventricular (LV) hypertrophy, in particular a maximal wall thickness $>$3 cm, malignant family history, syncope, and a hypotensive blood pressure response on exercise testing, all compared by Elliot *et al.*,[4] and presence of LV outflow tract obstruction.[5] These risk factors individually have a low positive predictive accuracy,[6–8] and a search for further risk factors has been advocated.[9] Recently it was shown that in childhood HCM increased ECG-amplitudes are a significant risk factor for sudden death, which is independent of echocardiographic measures of hypertrophy.[10] In that study it was found that the QRS-amplitude sum in limb-leads was a better predictor than Sokolow–Lyon index, with a sensitivity of 94%. The limb-lead QRS-amplitude sum can always be quantified in both children and adults, whereas dominant S-waves across precordial leads, invalidating Sokolow–Lyon index, are not rare in HCM. The odds ratios for this risk factor in children were considerably

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larger (up to 34.3) than other risk factors hitherto described in adult patients with HCM (relative risks ranging between 1.8 and 5.3).[8] However, childhood-onset HCM has varying aetiology,[11] including idiopathic cases and children with Noonan's syndrome, with only about one-third having familial disease with autosomal dominant inheritance.[10,12] Thus it is unclear whether these findings are relevant for the more common adult form of familial HCM due to sarcomere mutations. Furthermore it is well known that intensive physical training is associated with an increase in ECG-amplitudes.[13] The current study was undertaken to evaluate whether ECG-amplitudes are also a significant risk factor for sudden death in adulthood HCM, and to compare the predictive accuracy of different ECG-measures. As certain countries, for example Italy, use ECG for compulsory pre-participation screening of athletes we have also assessed to what extent it is possible to differentiate the ECG-features that characterize a high risk for sudden death in HCM from ECG amplitudes that could be encountered in normal athletes.

Methods

Normal subjects

Electrocardiograms from consecutively recruited normotensive adult outpatient attenders that had been referred for cardiological assessment, and had echocardiographic findings that were normal with regard to wall thickness, diastolic function, and tissue-Doppler studies were used as the normal reference group [$n = 44$, age 29 $\pm$ 8 (mean $\pm$ SD) years]. In the athlete group competitive endurance athletes that were volunteers from sports clubs for a study correlating maximal oxygen-uptake and echocardiographic dimensions were included. The athletes were distance runners or competitive long-distance swimmers. They had all been competing at a regional or national level for at least 2 years, although most of them much longer, ($n = 34$, age 23 $\pm$ 5 years).

Hypertrophic cardiomyopathy patients

All case notes from the Sahlgrenska, Mölndal, and the Östra University Hospitals' (Gothenburg, Sweden) data bases with the diagnostic codes for HCM (obstructive and non-obstructive) in patients >17 years of age were retrieved between January 2002 and September 2008: 129 cases were identified. Some of these cases had of course been diagnosed before 2002. Since these hospitals make up all regional referral units in Gothenburg, the case-mix reflects a geographically based cohort. Patients that had had a sudden cardiac arrest, or had concomitant significant hypertension, surgically induced left bundle-branch block or ventricular pacing were excluded, leaving a normotensive comparison cohort with measurable ECGs of 87 patients (52 males, 37 females) with age at diagnosis 42 $\pm$ 17 years, and an average follow-up of 10.2 years. We have based our calculations on the earliest ECG in the case notes, i.e. ECG at diagnosis, (since for some individuals with post-mortem diagnosis we only had ECGs taken at military conscription). Average maximal wall thickness in the cohort was 2.0 [95% CI 1.9–2.1] cm. This Gothenburg HCM-cohort was compared with a group of 29 HCM patients (HCM-CA, age 28 $\pm$ 17 years at diagnosis; 23 males, 6 females) with sudden deaths or cardiac arrests occurring at 36 $\pm$ 16 years of age. They were retrieved from the hospital records of the Sahlgrenska, Mölndal, and the Östra University Hospitals, Gothenburg, and the University Hospital in Lund between 2000 and September 2008, as well as a nationwide study collecting all subjects aged 15–35 years in Sweden that had undergone a forensic post-mortem for a sudden cardiac death between 1992 and 1999.[14] The average duration of follow-up for HCM-CA patients not presenting with sudden death was 10.9 years, and average maximal wall thickness 2.7 [2.3–3.1] cm. The group comprised 18 patients where an ECG had been recorded prior to a subsequent sudden death, and 11 patients where an ICD had been implanted as secondary prevention after a documented resuscitated cardiac arrest or a symptomatic VT requiring medical termination. Two of these patients had pre-arrest ECGs recorded at different times with and without partial left-bundle branch block; both types of ECG-morphology were included in the analysis giving 31 ECGs in the sudden-death/cardiac arrest group.

Electrocardiographic features

The measures performed on the averages of three to five successive complexes were Sokolow–Lyon index,[15] limb-lead QRS-sum defined as the sum of R+S-waves (or Q if deeper than S) in all six limb-leads,[12] six chest-lead QRS-sum, 12-lead QRS-sum,[16] 12-lead QRS voltage–duration product,[17] and limb-lead QRS voltage–duration product. In addition QRS-duration and QTc (using Bazett's formula) were calculated. ECGs were also evaluated in respect to the presence of QRS-axis deviation, pathological Q-waves, T-wave inversion >1 mm, giant (>10 mm) positive or negative T-waves, ST-depression >2 mm, and an S-wave>R-wave in V_4.

Echocardiographic measures

All subjects included in the normal groups had been assessed with detailed M-mode and 2-D echocardiography including short-axis views and detailed Doppler studies, and found to be normal. For HCM-patients the measurements of wall thickness recorded in the case notes, and carried out by echocardiography technologists unconnected with the study, were used.

Statistics

This is a retrospective case–control study, but as we were unable to match on clinical characteristics (as a number of the individuals in the HCM-CA group were post-mortem diagnoses with mustering ECGs only) we have elected to avoid selection bias in our comparison group by using a complete geographical cohort. In addition, we compared specifically HCM-CA cases with cardiac arrest below the age of 40 years, where coronary artery disease is unlikely to be a contributory factor, with the HCM-cohort cases with initial ECG below 40 years of age, which then provides a well age- and gender-matched comparison group. Statistical analysis was carried out using commercial software (Statgraphics Plus v5.2 and GraphPad Prism 4, and R freeware version 2.7.2). Comparisons of proportions between the groups were carried out by two-tailed Fisher's exact test, and odds ratios and their 95% confidence intervals were calculated. Comparisons between groups were carried out with Mann–Whitney *U*-test. Cut-off values for screening were selected using frequency distribution plots and ROC curves, with optimal cut-offs selected to prioritise sensitivity over specificity; for details of methodology see Supplementary material online, *Detailed Statistical Methodology*, and ROC curves in Supplementary material online, *Figures S2* and *S3*. The calculated absolute values for positive predictive value (PPV) using these cut-offs are probably overestimates, and those for negative predictive value (NPV) underestimates, since the cardiac arrest cohort is recruited from a much larger geographical base than the Gothenburg HCM-cohort, but the relative ranking in PPV and NPV between different screening measures will still be valid. Absolute values of sensitivity and false-positive rate are unaffected by this and true estimates in the Gothenburg cohort. However, like all estimates based on a single sample they may be overly optimistic. We have

thus also carried out the non-parametric bootstrap to calculate the confidence intervals of the cut-off points proposed to assess their statistical accuracy. To extract the cut-off point in each bootstrap sample ($n = 1000$) we defined as criterions that sensitivity should be given a greater weight than specificity, and that sensitivity and NPV should equal or exceed that obtained in the Gothenburg cohort; for details see Supplementary material online, *Detailed Statistical Methodology*.

Results

The results in all comparative groups are illustrated as mean ± 95% CI in *Figure 1A* and *B* in order to facilitate cross-comparisons between groups (the complete summary statistics are given in Supplementary material online, *Table S1*).

Gender differences in normal individuals

Figure 1A shows that there are no significant differences in QRS-amplitude sum in the six limb-leads between males and females ($P = 0.78$), but there are highly significant differences in QRS-amplitude sum from the six chest-leads, with values in females being lower ($P = 0.00001$). This leads to significantly lower 12-lead QRS-amplitude sums ($P = 0.00004$), and Sokolow–Lyon index ($P = 0.0005$) in females than males. As described previously,[18]

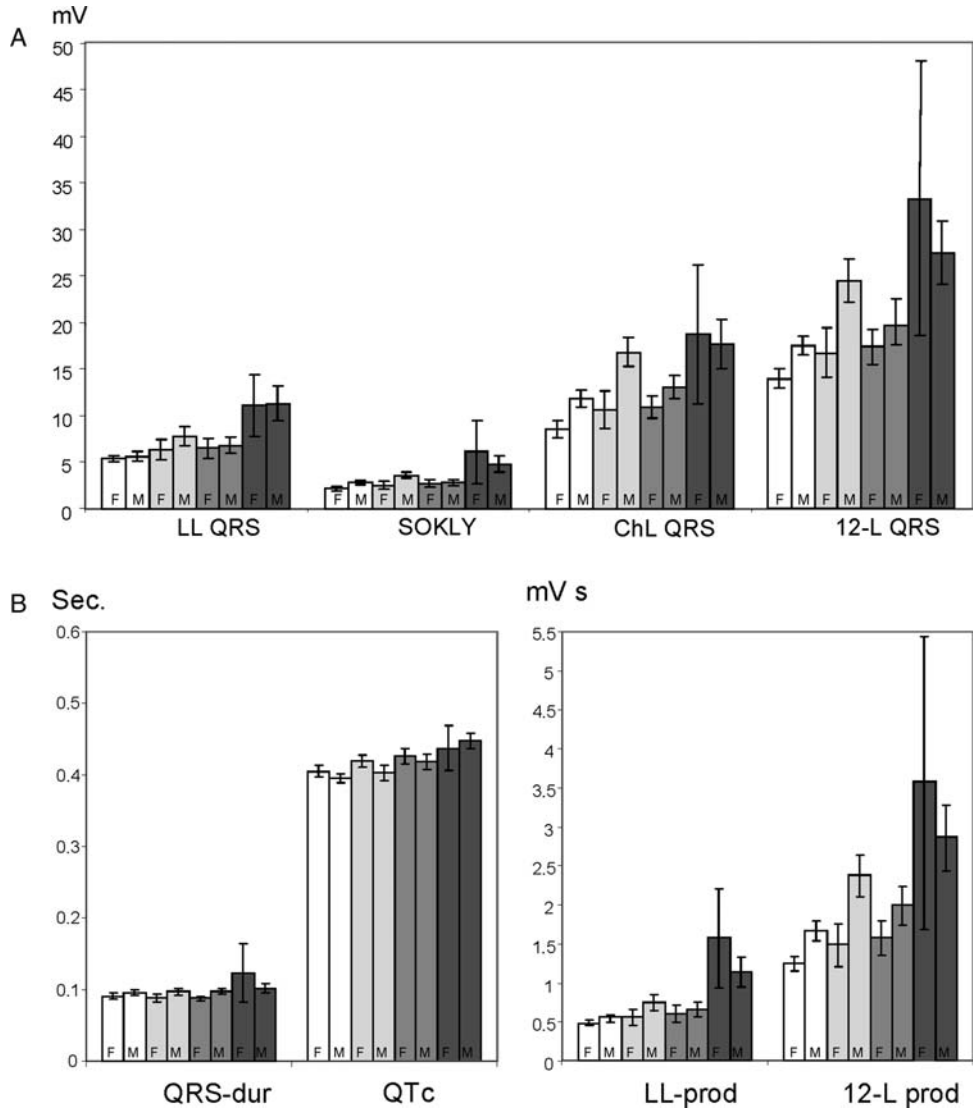

Figure 1 The values of different ECG-measures are represented as staple diagrams, with the 95% CI for the mean given as a bracket. F and M indicates female vs. male values, white columns are normals, light grey athletes, medium grey the Gothenburg hypertrophic cardiomyopathy cohort, and dark grey values from the hypertrophic cardiomyopathy patients that had suffered a cardiac arrest. (*A*) LL QRS, Limb-lead QRS-amplitude sums, SOKLY, Sokolow–Lyon index; ChL QRS, 6 chest-lead QRS-amplitude sums; 12-L, 12-lead QRS-amplitude sums. (*B*) QRS-dur., QRS-duration; QTc, corrected QT-interval; LL-prod., limb-lead amplitude–duration product; 12-L prod., 12-lead amplitude–duration product.

Table 1 Electrocardiographic features in hypertrophic cardiomyopathy with cardiac arrest compared with hypertrophic cardiomyopathy cohort

ECG measure	Hypertrophic cardiomyopathy cohort		HCM-CA		Mann–Whitney *U*-test	
	Male ($n = 52$)	Female ($n = 35$)	Male ($n = 24$)	Female ($n = 7$)	Male (*P*-value)	Female (*P*-value)
Age at ECG (years)	45 ± 16 [41–50]	48 ± 18 [41–54]	32 ± 16 [25–38]	33 ± 19 [15–51]	0.0098	0.037
Limb-lead QRS-sum (mV)	6.8 ± 3.2 [6.0–7.7]	6.5 ± 2.0 [5.4–7.5]	11.3 ± 4.6 [9.4–13.2]	11.1 ± 3.5 [7.8–14.4]	0.000003	0.0027
Chest-lead QRS-sum (mV)	13.0 ± 4.4 [11.8–14.3]	10.9 ± 3.5 [9.7–12.1]	17.7 ± 5.6 [15.0–20.3]	18.8 ± 6.0 [11.3–26.2]	0.0004	0.0043
12-lead QRS-sum (mV)	19.7 ± 6.2 [17.6–22.5]	17.4 ± 5.5 [15.5–19.2]	27.5 ± 7.3 [24.1–30.9]	33.3 ± 11.9 [18.6–48.1]	0.00004	0.0022
12-lead product (mV s)	2.01 ± 0.87 [1.76–2.25]	1.59 ± 0.63 [1.36–1.809]	2.88 ± 0.89 [2.46–3.29]	3.59 ± 1.52 [1.70–5.47]	0.00006	0.0024
Limb-lead product (mV s)	0.66 ± 0.33 [0.57–0.76]	0.61 ± 0.32 [0.50–0.73]	1.14 ± 0.47 [0.95–1.34]	1.47 ± 0.54 [0.94–2.22]	0.000002	0.0012
Sokolow–Lyon index (mV)	2.8 ± 1.0 [2.5–3.1]	2.7 ± 1.0 [2.3–3.1]	4.8 ± 1.9 [3.9–5.7]	6.1 ± 3.2 [2.7–9.4]	0.00002	0.0036
QRS-duration (ms)	97 ± 14 [93–101]	88 ± 9 [85–91]	101 ± 16 [95–108]	123 ± 39 [82–164]	0.32	0.0065
QTc (ms)	417 ± 38 [406–428]	425 ± 30 [414–436]	446 + 23 [435–457]	436 ± 30 [405–468]	0.0029	0.064
Risk score	3 ± 3 [2–4]	3 ± 3 [2–4]	8 ± 3 [7–9]	8 ± 3 [5–11]	0.0000002	0.0011

Values are given as mean ± SD [95% confidence intervals].

QTc is slightly longer in females ($P = 0.029$). The 12-lead QRS amplitude–duration product, which is often used to evaluate LV hypertrophy, is substantially lower in females than in males ($P = 0.00001$; *Figure 1B*; see Supplementary material online, *Table S1*).

Athletes

Figure 1A shows that athletes have the same gender differences, with significantly higher chest-lead sums ($P = 0.00006$), Sokolow–Lyon index ($P = 0.0003$), and 12-lead sums ($P = 0.0004$) in males compared with females, but with no significant gender difference in limb-lead QRS-sums. QRS-duration was significantly longer in males ($P = 0.04$; *Figure 1B*, see Supplementary material online, *Table S1*), which may be partly related to the fact that they had significantly higher maximal oxygen uptake (4.57 ± 0.46 vs. 3.37 ± 0.52 L/min; mean ± SD, $P = 0.00008$) and thus almost certainly had hearts with larger diastolic dimensions. Even related to body size the male athletes in our study had a larger oxygen uptake, 65.2 ± 4.6 mL/kg BW vs. 53.5 ± 8.9 mL/kg BW in the females ($P = 0.0003$). There was a weak correlation between limb-lead QRS-sum and oxygen uptake/kg BW, but the scatter was very wide giving a correlation coefficient of only 0.39 ($P = 0.012$). The longer QRS-durations contributed to the fact that not only 12-lead amplitude–duration product ($P = 0.0002$), but also limb-lead amplitude–duration product ($P = 0.01$) was higher in males.

Cohort with hypertrophic cardiomyopathy

Figure 1A shows a larger spread of ECG-amplitude sums and Sokolow–Lyon index in all HCM-patients when compared with controls of the same gender, but they are not significantly higher either in males ($P = 0.07–0.78$) or in females ($P = 0.06–0.19$; see Supplementary material online, *Table S1*); see *Table 1* for summary statistics of HCM-group. QRS-duration is not increased in the HCM-cohort, and consequently neither limb-lead amplitude–duration product nor 12-lead amplitude–duration product is significantly different from male or female normal controls (*Figure 1B*; see Supplementary material online, *Table S1*).

Correlations of electrocardiographic features with known risk factors

Correlation analysis in the Gothenburg HCM-cohort showed that ECG-features that showed a significant positive correlation with the presence of a documented non-sustained VT on 24 h ECG

were the presence of pathological T-wave inversion ($P = 0.016$), dominant S-wave in V4 ($P = 0.028$), and QTc ($P = 0.018$). The only feature that correlated with family history of sudden death was T-wave inversion in the precordial leads ($P = 0.013$).

Hypertrophic cardiomyopathy with cardiac arrest

Figure 1A illustrates that HCM-CA patients have substantially higher ECG-amplitude sums than controls and the HCM-cohort, with near doubling in limb-lead QRS-sums, but at least in males smaller increases in chest lead sums; see *Table 1* for summary statistics. Males with cardiac arrest, where we have most statistical power, have compared with Gothenburg HCM-cohort males significantly higher limb-lead QRS-amplitude sums, Sokolow–Lyon index, 12-lead amplitude sums, limb-lead amplitude–duration products, and 12-lead amplitude–duration products; see *Table 1*. The QRS-duration is not significantly different, but QTc is slightly longer than in the HCM-cohort. When comparing males with cardiac arrest with male athletes (*Figure 1A* and *B*) only the QTc ($P = 0.00016$) and limb-lead derived measures remain significantly different, with higher limb-lead QRS-sums ($P = 0.0095$) and

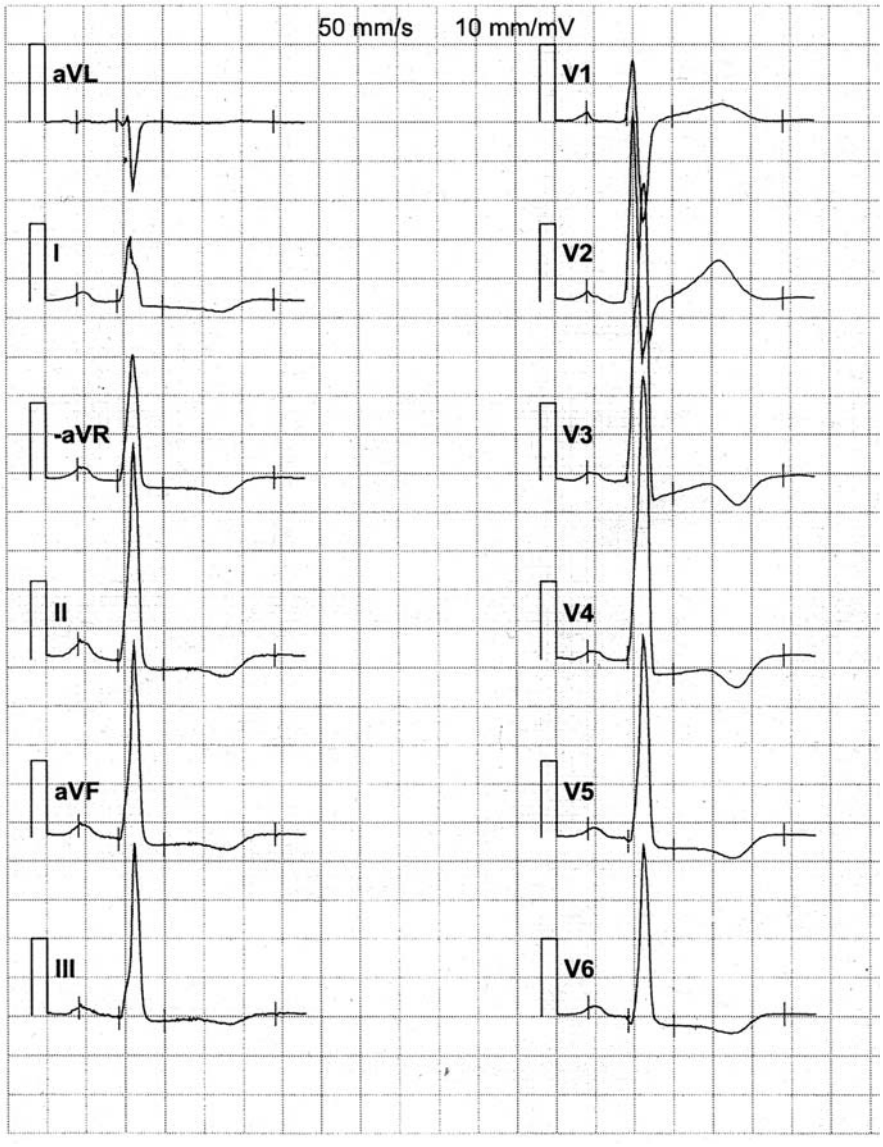

Figure 2 The ECG of a 25 year-old female with hypertrophic cardiomyopathy, who suffered a cardiac arrest while rushing to catch a train but was successfully rescuscitated. Echocardiographically she has moderate hypertrophy with septal thickness 2.5 cm, posterior left ventricular wall 0.8 cm, and maximal wall thickness of 2.6 cm on short-axis and apical views, and there is no dynamic left ventricular outflow tract obstruction, nevertheless there are extensive ST-T-wave abnormalities. Her values on important ECG-measures on her first ECG were: limb-lead amplitude sum = 10.9 mV; limb-lead amplitude–duration product = 0.89 mV s; 12-lead amplitude–duration product = 2.29 mV s; risk score = 8 points; all above high-risk cut-offs. Sokolow–Lyon index on the other hand is normal, 3.8 mV.

limb-lead amplitude–duration products ($P = 0.012$; see Supplementary material online, *Table S1*). The differences in females with cardiac arrest follow the same patterns, with if anything larger increases in ECG-amplitudes compared with normal controls and athletes than that seen in males with cardiac arrest.

As a number of our HCM-CA subjects were post-mortem diagnoses, we only have echocardiographic data on maximal wall thickness from case notes on 15 subjects, which ranged between 1.6 and 5.0 cm, mean 2.7 [2.3–3.1] cm, with only three out of fifteen subjects having a wall thickness >3 cm. This commonly cited risk factor did not predict well in our study, as the proportion of HCM-CA cases with wall thickness >3 cm was not significantly higher than in the Gothenburg HCM-cohort with an odds ratio of 5.1 [0.9–26.3], ($P = 0.08$), and sensitivity was only 20 [4–48]%, specificity 95%, PPV 50% and NPV 84%. There was no significant correlation between maximal wall thickness on echocardiography with limb-lead amplitude sum ($P = 0.57$), Sokolow–Lyon index ($P = 0.84$), 12-lead amplitude–duration product ($P = 0.78$) or QRS-duration ($P = 0.64$). Cox proportional hazards regression analysis on this subgroup suggests that both ECG-amplitudes and maximal wall thickness are independent risk factors (limb-lead QRS-sum $P = 0.002$, septal thickness $P = 0.001$). Cox regression analysis on the total HCM group also suggests that gender does not come out as separate significant risk factor for sudden death, either when tested against RS-sum at diagnosis (RS-sum $P = 0.008$, gender $P = 0.20$) or 12-lead product (12-lead product $P = 0.0000$, gender $P = 0.18$). See Supplementary material online, *Results* and *Figure S1* for more data showing that neither age at ECG nor gender are significant confounders.

Comparing qualitative electrocardiographic features

Supplementary material online, *Table S2* shows the relative frequency of abnormalities in ECG morphology. The HCM-CA group shows a significantly increased occurrence of pathological T-wave inversion in any lead ($P = 0.0003$), precordial T-wave inversion ($P < 0.0001$), ST-depression ($P = 0.0010$), and a dominant S-wave in V_4 ($P = 0.0048$) compared with the Gothenburg HCM-cohort. QRS-axis deviation is possibly increased ($P = 0.05$). On the other hand, the frequency of bundle-branch block, pathological Q-waves, or giant negative or giant positive T-waves were not significantly different between the groups. *Figure 2* illustrates the repolarization abnormalities often present in young HCM-patients with cardiac arrest.

Risk score

In order to be able to quantify the number of ECG-abnormalities present, a risk score was constructed (*Table 2*) including both quantitative and qualitative risk features shown to be correlated with the risk for a cardiac arrest/sudden death (see Supplementary material online, Development of Risk Score for method). The risk score showed a significant correlation with presence of documented VT in the Gothenburg HCM-cohort ($P = 0.0030$). The risk score in HCM-patients with no documented VT averaged 2 [2–3], vs. 5 [3–6] in patients with VT on Holter-monitoring ($P = 0.0006$). Among 12 patients in the HCM-cohort with a risk score ≥6, six had had a potentially life-threatening arrhythmia documented. In the HCM-CA group the risk score averaged 8 [6–9], range 1–12.

Table 2 Electrocardiographic scoring system to assess risk

Any deviation in QRS-axis		1 point
Pathological T-wave inversion limb leads		1 point
Pathological T-wave inversion precordial leads[a]		2 points
ST-segment depression ≥2 mm		2 points
Dominant S in V_4		2 points
Limb-lead QRS-amplitude sum	≥7.7 mV	1 point
	≥10.0 mV	2 points
	≥12.0 mV	3 points
12-lead amplitude–duration product	≥2.2 mV s	1 point
	≥2.5 mV s	2 points
	≥3.0 mV s	3 points
QTc	≥440 ms	1 point
		Max score = 14

QTc = corrected QT-interval.
[a]The two points for precordial T-wave inversion does not get added on top of the 1 point for limb-lead T-wave inversion, thus total score available for T-wave abnormalities is 2 points.

All hypertrophic cardiomyopathy-groups combined

Varying degrees of obesity had little influence on limb-lead ECG-amplitudes in HCM-patients as there were no correlations with body mass index (BMI) for limb-lead amplitude sum ($r = -0.12$, $P = 0.51$) or limb-lead amplitude–duration product ($r = -0.12$, $P = 0.47$).

Screening performance of electrocardiographic measures

When dealing with an outcome that is potentially fatal, it would seem best to use screening cut-offs that maximize sensitivity and NPV, at the expense of a lower specificity. *Table 3* shows that the best single screening measures in terms of sensitivity for both sexes are limb-lead QRS-amplitude sum ≥7.7 mV (odds ratio 18.8, $P < 0.0001$), 12-lead amplitude–duration product ≥2.2 mV s (odds ratio 131.0, $P < 0.0001$), and limb-lead amplitude–duration product ≥0.7 mV s (odds ratio 31.5, $P < 0.0001$). A wider range of cut-offs in both genders, and in all ages compared with age ≤ 40 years, are illustrated for possible additional screening measures in Supplementary material online, *Table S3*. The highest PPV is obtained by a risk score ≥6 points (*Table 3*), which also has the largest area under the curve (0.89) in the ROC curves (see Supplementary material online, *Figure S2*). The calculated absolute values for PPV may be overestimates, as mentioned in *Statistics*, but the relative ranking in PPV between different screening measures will still be valid. However, if the above amplitude cut-offs were applied to ECG-screening in athletes there

Table 3 Screening performance of the ECG-measures that discriminates best, comparing hypertrophic cardiomyopathy cohort with hypertrophic cardiomyopathy with cardiac arrest, [with the 95% CI]

ECG measure	Cut-off	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	Odds ratio	Fisher's (*P*-value)
Cohort-estimates							
Limb-lead QRS sum (mV), both genders	7.7 **[6.5–9.7]**	87 [70–96]	74 [66–95]	54 [39–68]	94 [86–98]	18.8 [5.9–59.5]	<0.0001
12-lead product (mV s), both genders	2.20 **[1.8–2.5]**	92 [74–99]	73 [62–82]	50 [35–65]	97 [89–100]	31.0 [6.7–142]	<0.0001
Limb-lead product (mV s), males	0.70	92 [73–99]	69 [54–80]	60 [42–75]	94 [81–99]	24.2 [5.0–117]	<0.0001
Limb-lead product (mV s), males	0.77	83 [63–95]	79 [65–89]	65 [45–81]	91 [79–98]	18.6 [5.3–65.9]	<0.0001
Limb-lead product (mV s), females	0.70	100 [55–100]	72 [53–86]	40 [16–68]	100 [85–100]	32.2 [1.6–630]	0.0018
Limb-lead product (mV s), females	0.77	100 [54–100]	77 [60–90]	43 [18–71]	100 [87–100]	42.1 [2.1–827]	0.0007
Limb-lead product (mV s), both genders	0.70 **[0.70–0.89]**	93 [78–99]	69 [58–79]	54 [39–68]	96 [88–100]	31.5 [6.9–143]	<0.0001
Risk score, both genders	≥6 **[6–8]**	84 [66–95]	85 [75–91]	67 [50–81]	93 [85–98]	28.4 [9.2–87.5]	<0.0001

Sens., sensitivity; Spec., specificity; PPV, positive predictive value; NPV, negative predictive value; see *Table 2* for definition of risk score.
Bootstrap estimates of the 95% CI of cut-off is given within bold brackets (B = 1000).

Table 4 Screening performance of ECG-measures at various cut-offs, comparing athletes with hypertrophic cardiomyopathy with cardiac arrest age <40 years, [with 95% CI]

ECG measure	Cut-off	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	Odds ratio	Fisher's (*P*-value)
Cohort-estimates							
Limb-lead QRS sum (mV), both genders	10.0 **[7.67–12.10]**	70 [46–88]	88 [73–97]	78 [52–94]	83 [67–94]	17.5 [4.2–72.1]	<0.0001
12-lead product (mV s), both genders	3.0 **[2.15–4.50]**	50 [21–73]	94 [80–99]	78 [40–91	82 [64–91]	14.0 [2.4–80.8]	0.0019
12-lead product (mV s), both genders	3.5 **[2.15–4.50]**	36 [13–65]	100 [90–100]	100 [90–100]	79 [64–90]	40.0 [2–789]	0.0012
Limb-lead product (mV s), both genders	0.90 **[0.89–1.29]**	79 [54–94]	85 [69–95]	75 [51–91]	88 [72–97]	42.0 [7.6–232]	<0.0001
Limb-lead product (mV s), both genders	1.00 **[0.89–1.29]**	65 [38–86]	91 [76–98]	79 [49–95]	84 [68–94]	18.9 [4.0–89]	<0.0001
Risk score, both genders	>6 **[3–8]**	85 [62–97]	100 [90–100]	100 [80–100]	92 [78–98]	345 [16.9–7064]	<0.0001

Sens., sensitivity; Spec., specificity; PPV, positive predictive value; NPV, negative predictive value; see *Table 2* for definition of risk score.
Bootstrap estimates of the 95% CI of the cut-off values with sensitivity given equal weight to specificity are given within bold brackets (B = 1000).

would be a large number of false positives, particularly among male athletes. ROC-curve analysis suggests that the most useful single screening measure in athletes with an acceptable specificity is limb-lead amplitude–duration product at the higher cut-off of ≥0.90 mV s which has a specificity of 85%, whereas sensitivity for HCM-patients at risk for cardiac arrest drops to 79%, and an area under the ROC curve of 0.90. However limb-lead QRS-sum at the same cut-off as is optimal in children, namely ≥10 mV, has the higher specificity of 88%, and a sensitivity of 70%. A more useful screening measure for athletes is a risk score ≥6 points, which has a specificity of 100% and a sensitivity of 85%, and an area under the ROC curve of 0.96 (*Table 4* and Supplementary material online, *Figure S3*). Twelve-lead sums and 12-lead amplitude–duration product values have large overlaps between athletes and HCM-patients with cardiac arrest with sensitivity of only 30% for 12-lead product at a cut-off that optimises specificity (*Figure 1A* and *B*; *Table 4*); thus they would appear of little value in screening athletes.

Bootstrapping assessment of cut-offs and sensitivity

As shown in *Tables 3* and *4*, the 95% confidence intervals for the cut-offs obtained by bootstrapping are fairly symmetrically spread on both sides of the cut-offs we propose for both limb-lead QRS-sum [6.5–9.7 mV] and 12-lead product [1.8–2.5 mV s].

The exception is the limb-lead product, where we elected to propose a cut-off of 0.7 mV s, which is at the lower end of the 95% CI for the whole cohort [0.70–0.89 mV s]; that choice is based on the fact that the cut-off of 0.77 mV s suggested by the ROC curve in combined genders had both significantly lower sensitivity and a lower odds ratio than 0.7 mV s in males (*Table 3*), and as males constitute the majority of sudden deaths we chose the cut-off that optimized sensitivity for males, accepting some loss in specificity. Further details of bootstrapping estimates are given in Supplementary material online, *Tables S4* and *S5*. It is of note that the average estimates of sensitivity obtained from our bootstrapping procedure for the above measures are all within 1–3% of the average values in *Table 3*, thus they give no reason to suppose that the sensitivity estimates in our cohort group are unduly optimistic; see *Further Results of Bootstrapping* for details.

Screening performance of electrocardiographic measures in young hypertrophic cardiomyopathy patients

As the Gothenburg HCM-cohort had a higher average age than the patients that died suddenly, we have also compared the ECG-measures of HCM-cohort patients $\leq$40 years of age (age at diagnosis 25 $\pm$ 10 years) with HCM-patients that had their cardiac arrest at age $\leq$ 40 years (age at diagnosis 20 $\pm$ 9, age at arrest 26 $\pm$ 5 years); see Supplementary material online, *Table S3* for details and 95% CI. This comparison shows that all the three best screening measures have still higher sensitivity and odds ratios in young adults: 90% sensitivity and odds ratio 27.0 ([5.0–147]: $P < 0.0001$) for limb lead sum $\geq$7.7 mV; sensitivity of 100% and odds ratio 51.7 ([2.8–959]; $P < 0.0001$) for 12-lead amplitude–duration product $\geq$2.2 mV s; and 100% sensitivity and odds ratio of 76.0 ([4.1–149]; $P < 0.0001$) for limb-lead amplitude–duration product $\geq$0.7 mV s. In this age range too, a risk score $\geq$6 points has the highest PPV.

Discussion

Comparison with performance of current risk-stratification strategies

Sudden cardiac death due to arrhythmia is a significant cause of death in both adults and children with HCM,[1,2,14,19] but the risk factors that have hitherto been identified in adults (see Introduction) each individually have low predictive accuracy (relative risks around 1.8–5.3).[6–8] To have an accurate risk-stratification is important not only in consideration of medical therapy, but because treatment with an implantable cardiac defibrillator (ICD) offers a way of protecting high-risk HCM patients from death by acute ventricular fibrillation.[20] However, the procedure has a large impact on quality of life, affects employment opportunities, and has both morbidity and a mortality.[20] Current algorithms for predicting high-risk HCM-patients are not working ideally as shown by a study on 103 HCM-patients with particularly severe cardiac hypertrophy (LV wall thickness >3 cm), where there were 13 sudden deaths among 87 patients without ICD, whereas there were no device discharges among any of 11 patients that had had ICD implantation for primary prevention.[21] It is also illustrated by a review of studies from large tertiary HCM centres describing annual appropriate ICD-discharge rates in HCM-patients of about 0.1% (range 0.05–0.2%; calculation based on total patient population rather than just patients with ICD), when compared with annual sudden death rates of 0.9–2.0%.[22] Thus there is an approximate 1:10 ratio between appropriate ICD-discharges and sudden cardiac deaths, which testifies to current difficulties in selecting the correct patients for ICD implantation. Whereas the annual appropriate discharge rate is 10.6% for patients receiving an ICD for secondary prevention (i.e. after a resuscitated cardiac arrest), the annual discharge rate is only 3.6% in patients having an ICD for primary prevention.[20] Thus, appropriate selection of patients for this therapy remains incompletely resolved, and identification of additional independent risk factors would likely aid risk-stratification and patient selection.[9]

Electrocardiographic amplitudes as risk predictors

Children have a higher risk of sudden death in HCM than adults,[23] and therefore offer higher statistical power to detect new risk factors. Electrocardiographic amplitudes measured as limb-lead amplitude sums have been shown to be a powerful predictor of risk for sudden death, but not for heart failure-related death, in childhood HCM, with odds ratio of 8.4 for the ECG at diagnosis, and 34.3 for the ECG closest to the time of death, and surprisingly this risk factor was independent of echocardiographic wall thickness, which was, as in adults, an additional significant risk factor.[10] Electrocardiographic amplitudes in relation to risk for death in general in adult HCM-patients, not specifically sudden cardiac death, has only been explored in one previous study.[24] This found only a weak correlation between 12-lead amplitude sum and degree of cardiac hypertrophy, but did not compare 12-lead amplitude sum in survivors and non-survivors; in any case 33% of the deaths were not sudden deaths, which might preclude detection of risk factors specific for sudden deaths.[24] The current study in contrast, focuses on risk factors in adult HCM patients for sudden death/cardiac arrest only. It confirms that, as in childhood HCM, the limb-lead QRS-amplitude sum is a highly significant risk factor for sudden death, although for non-athletes the optimal high-risk cut-off is a lower voltage than in childhood HCM, with $\geq$7.7 mV in adult HCM (giving an odds ratio of 18.8 in the whole group, and 27.0 in patients $\leq$40 years of age; *Table 3* and Supplementary material online, *Table S3*) compared with the high-risk cut-off of >10 mV in childhood HCM.[10] A new finding is the fact that increased QRS-duration is an additional risk factor, which results in the amplitude–duration products discriminating high-risk status in adult HCM even better than amplitude sums, with 12-lead amplitude–duration product $\geq$2.2 mV s giving an odds ratio for sudden death of 31.0 (51.7 in $\leq$40 year olds), and limb-lead amplitude–duration product $\geq$0.7 mV s giving an odds ratio of 31.5 (76.0 in $\leq$40 year olds). One might assume that large ECG-amplitudes simply reflect a generalized cardiac hypertrophy, but although an association with echocardiographic wall thickness exists for some measures,[24] it is very weak, and we found no association between wall thickness

and ECG-voltages in our HCM-CA group, and in the sub-group where we had echocardiographic wall thickness measurements the wall thickness was an independent risk factor from ECG-amplitudes, just as we previously found in childhood-HCM.[10] The same has been reported in some adult familial HCM with marked myocyte disarray on histology due to a Troponin T-mutation, where many members had no increased wall thickness on echocardiography or post-mortem, but 'LV hypertrophy' on ECG and a high rate of sudden death.[25,26] The illustrated ECG has a limb-lead ECG-amplitude sum of 12.4 mV, well above the high-risk cut-off in our study.[25] It is known that electrocardiographic phenotypes such as Sokolow–Lyon voltage show heritability.[27] We have shown here, by absent correlation between ECG-measures and wall thickness, age and obesity in our HCM-groups, that in HCM-patients a raised ECG-amplitude sum is a phenotypic characteristic affected by additional unidentified factors, and at least one of these factors has a strong correlation with risk of fatal arrhythmia. Not much is known about the association between ECG voltages and particular HCM mutations, but in a family with beta-myosin heavy chain mutations and two sudden deaths (Asp778Glu mutation) 40% of family members had increased Sokolow–Lyon index,[28] and patients with mutations in the gamma-2 subunit of AMP-activated protein kinase have strikingly large ECG amplitudes even when hypertrophy is very mild.[29] One could also speculate that in some circumstances strikingly large ECG-amplitudes may reflect inheritance of a co-malignant factor other than the sarcomeric protein mutation, possibly ion-channel mutations or factors determining degree of myocyte disarray.

T-wave changes and risk of sudden death

Surprisingly, few previous studies appears to have examined the association of T-wave changes with the risk of sudden death. A Japanese study found that T-wave alternans correlated with risk for ventricular arrhythmias, and with particularly marked myocardial disarray on histology,[30] and T-wave complexity assessed with principal component analysis showed that increased complexity correlated with risk for syncope in HCM (Yi *et al.*, 1998[31]). Maron *et al.*[32] found no significant difference in 'ST-T-wave changes' between cardiac arrest victims and a tertiary centre referred HCM-cohort, but they had made no attempt at analysing different types of ST-T-wave alterations separately, and we found particularly strong correlations with precordial T-wave negativity and ST-segment depression, and no correlation with giant T-waves (see Supplementary material online, *Table S2*). Patients with Troponin T-mutations with high incidence of sudden death and marked myocardial disarray also have marked T-wave changes in both limb leads and precordially as shown by ECG-illustrations, even when hypertrophy is minimal.[25] Thus, a reasonable interpretation would be that T-wave changes, particularly when seen in young normotensive HCM-patients, may be a marker for myocardial disarray and denote a high susceptibility to arrhythmia.

Our results pinpointing ECG-amplitudes and morphology on ordinary 12-lead ECG, a test available in every district hospital, as significant risk factors for sudden death in HCM that can be recognized already at the first consultation, offers a simple and convenient approach for selecting individuals at increased risk of sudden death for accelerated investigations and early appropriate therapy. Our proposed risk score offers an approach of combining ECG-amplitude risk factors with qualitative risk factors; the risk score does not increase sensitivity when compared with amplitude–duration products, but does increase the positive predictive accuracy.

Gender differences

Male gender is associated with higher risk of sudden cardiac deaths in general,[14,33] and sudden deaths in athletes,[34] and in young adults with HCM, where male:female ratios in sudden deaths between 2.8:1 and 10:1 have been reported.[14,19] It is therefore not surprising that our sample of females with sudden death/cardiac arrest is smaller than that of males (M/F ratio 3.8). In keeping with earlier studies we also found a longer QTc in our female normal subjects, as well as in our female athletes (*Figure 1B*).[18]

There are known gender differences in the sensitivity of various ECG-voltage criteria for detection of LV hypertrophy.[35] That the differences are caused by significant differences in chest-lead amplitudes only, resulting in significant gender differences in the 12-lead amplitude sums and Sokolow–Lyon index, but not in limb-lead amplitudes (*Figure 1A*), is a new finding. Thus for risk-stratification gender-appropriate cut-offs should be used, or one should use the limb-lead voltages which do not differ between the gender.

Pre-participation screening of athletes

Pre-participation screening of athletes is compulsory in Italy, and appears largely effective in detecting individuals with HCM[36] with a concomitant reduction in sudden deaths caused by cardiomyopathy.[37] The Italian screening programme incorporates a 12-lead ECG in all tested individuals, but the criteria for abnormality are not differentiated for gender and are based on single-lead amplitudes, mostly chest-lead criteria.[37] Athletes are known to have larger ECG-amplitudes than sedentary subjects, and male athletes show higher ECG-amplitudes than females (*Figure 1A* and *B*).[13] It would therefore appear that pre-participation ECG-screening of athletes could potentially be made more specific and sensitive by either using gender-specific voltage criteria, or by incorporating the six limb-lead amplitude sum which is gender-neutral in normal subjects, and which might help detect HCM-patients at high risk for sudden death. If one prioritizes specificity, to avoid too many false-positives, our results suggest that a suitable cut-off for pre-participation screening of athletes, leading to consideration of echocardiographic examination, might be a limb-lead QRS-sum >10 mV, the same cut-off that delineates high-risk status in children with known HCM, and/or a limb-lead amplitude–duration product at the higher cut-off of >0.9 mV s which retains a fair sensitivity of 79% for HCM-associated cardiac arrest. A risk score ≥ 6 has both high sensitivity (85%) and higher specificity (100%) and PPV, than either of the above. As it has a clearly better area under the ROC curve (0.96) than the other measures, it would appear to be the best approach for screening athletes (see Supplementary material online, *Figure S3* for comparative ROC curves).

Limitations of the study

As a number of our subjects had post-mortem diagnosis only, with ECGs retrieved from military conscription records, we do not have complete echocardiographic data to formally test whether ECG-amplitudes in adult HCM patients are an independent risk factor for sudden death when compared with maximal wall thickness in the whole cohort, like it is in childhood HCM.[10] However, the lack of correlation between maximal wall thickness and ECG-amplitudes both in those patients with sudden death where we do have echocardiographic data and in the total HCM-group, and Cox regression analysis in this group, strongly suggest that they do indeed represent independent risk factors even in adults. For the same reason, we cannot formally compare ECG-amplitudes as risk factor with other recognized clinical risk factors. To establish accurate PPV and NPV, a prospective study in a geographical cohort is required.

Conclusions

Electrocardiographic features show a significant correlation with risk of sudden death in HCM-patients, and provide an additional and conveniently accessible tool for the early identification of high-risk patients for appropriate therapy. Because of sizeable gender differences in normal values for chest-lead-based ECG-amplitudes, but not for limb-lead-based ECG amplitude sums, the limb-lead amplitude sums, limb-lead amplitude–duration products, and a risk score incorporating morphological changes provide the best tools for ECG-screening for high-risk patients with HCM. T-wave inversion, particularly in precordial leads, denotes a high-risk status in young normotensive HCM-patients. The cut-off values proposed here offer considerably higher odds ratios and sensitivity, and better NPVs, than previously described risk factors for sudden death in adult HCM. For example, sensitivity for limb-lead amplitude–duration product $\geq$0.7 mV s has an odds ratio of 31.5 [6.9–143] and a sensitivity of 93% [78–99%] vs. an odds ratio of 5.1 [0.9–26.3] and a sensitivity of only 20% [4–48%] for the commonly used risk factor of $>$3 cm maximal wall thickness. As the PPVs were similar, 54 vs. 50%, we therefore propose that ECG-features should be included in routine risk-stratification of HCM patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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