Usefulness of Electrocardiographic Patterns at Presentation to Predict Long-term Risk of Cardiac Death in Patients With Hypertrophic Cardiomyopathy

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The objective of this study was to investigate the prognostic significance of 12-lead electrocardiogram (ECG) patterns in a large multicenter cohort of patients with hypertrophic cardiomyopathy; 1,004 consecutive patients with hypertrophic cardiomyopathy and a recorded standard ECG (64% men, mean age 50 ± 16 years) were evaluated at 4 Italian centers. The study end points were sudden cardiac death (SCD) or surrogates, including appropriate implanted cardiac defibrillator discharge and resuscitated cardiac arrest and major cardiovascular events (including SCD or surrogates and death due to heart failure, cardioembolic stroke, or heart transplantation). Prevalence of baseline electrocardiographic characteristics was: normal ECG 4%, ST-segment depression 56%, pseudonecrosis waves 33%, "pseudo−ST-segment elevation myocardial infarction (STEMI)" pattern 17%, QRS duration ≥120 ms 17%, giant inverted T waves 6%, and low QRS voltages 3%. During a mean follow-up of 7.4 ± 6.8 years, 77 patients experienced SCD or surrogates and 154 patients experienced major cardiovascular events. Independent predictors of SCD or surrogates were unexplained syncope (hazard ratio [HR] 2.5, 95% confidence interval [CI] 1.4 to 4.5, p = 0.003), left ventricular ejection fraction <50% (HR 3.5, 95% CI 1.9 to 6.7, p = 0.0001), nonsustained ventricular tachycardia (HR 1.7, 95% CI 1.1 to 2.6, p = 0.027), pseudo-STEMI pattern (HR 2.3, 95% CI 1.4 to 3.8, p = 0.001), QRS duration ≥120 ms (HR 1.8, 95% CI 1.1 to 3.0, p = 0.033), and low QRS voltages (HR 2.3, 95% CI 1.01 to 5.1, p = 0.048). Independent predictors of major cardiovascular events were age (HR 1.02, 95% CI 1.01 to 1.03, p = 0.0001), LV ejection fraction <50% (HR 3.73, 95% CI 2.39 to 5.83, p = 0.0001), pseudo-STEMI pattern (HR 1.66, 95% CI 1.13 to 2.45, p = 0.010), QRS duration ≥120 ms (HR 1.69, 95% CI 1.16 to 2.47, p = 0.007), and prolonged QTc interval (HR 1.68, 95% CI 1.21 to 2.34, p = 0.002). In conclusion, a detailed qualitative and quantitative electrocardiographic analyses provide independent predictors of prognosis that could be integrated with the available score systems to improve the power of the current model.   © 2016 Elsevier Inc. All rights reserved. (Am J Cardiol 2016;■:■−■)

Hypertrophic cardiomyopathy (HC) is the most common genetic cardiac disease and one of the main causes of sudden cardiac death (SCD) in the young. Different noninvasive clinical and instrumental markers, derived from observational cohort studies, have been related to worse prognosis. However, risk stratification is still largely unsatisfactory because of the low positive predictive value of these predictors.[1,2] In recent years, the standard electrocardiogram (ECG) has been shown to provide useful prognostic indications in patients with HC. A normal ECG is generally associated with a mild phenotype and favorable outcome, whereas marked electrocardiographic abnormalities have been shown to be correlated with severe hypertrophy and the presence of myocardial fibrosis.[3,4] However, this universally available, low-cost, and reproducible technique has rarely been tested in multivariable models for SCD and major cardiovascular events' risk stratification.[3−5] In the present study, we aimed to conduct an extensive qualitative and quantitative electrocardiographic analysis to assess the independent long-term predictive value of specific ECG patterns for prognosis in a large, multicenter HC cohort.

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Methods

In this retrospective observational study, we analyzed 1,047 consecutive patients evaluated from 1981 to 2011 at 4 Italian centers (S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy [n = 452], Sapienza University of Rome, Rome, Italy [n = 296], Azienda Ospedaliera Careggi, Florence, Italy [n = 233], Monaldi Hospital, University of Naples, Naples, Italy [n = 66]) with unequivocal diagnosis of HC and a good-quality 12-lead ECG obtained at first evaluation. HC was diagnosed by the presence of hypertrophied and nondilated left ventricle (wall thickness ≥15 mm in adults) at transthoracic echocardiogram, in the absence of other cardiac or systemic conditions that could produce a comparable magnitude of LV hypertrophy.[2] Forty-three patients (4%) were excluded for the following reasons: (1) inadequate technical electrocardiographic quality (n = 14); (2) presence of paced ventricular rhythm (n = 15); and (3) percutaneous septal alcohol ablation or myectomy preceding first evaluation (n = 14). Therefore, 1,004 patients constituted the final study population.

The study end points were (1) SCD or surrogates, defined as unexpected collapse occurring <1 hour from the onset of symptoms in a patient who had previously experienced a relatively uneventful clinical course or unexpected unwitnessed death or aborted cardiac arrest or appropriate implantable cardioverter defibrillator (ICD) therapy (for ventricular tachycardia/fibrillation with a heart rate ≥200 beats/min).[6] (2) Major cardiovascular events, defined as SCD or surrogates, death due to heart failure or cardioembolic stroke, or heart transplantation.[6] Follow-up was obtained by scheduled or nonscheduled clinical evaluations. For patients who had not been evaluated clinically for >1 year, follow-up was obtained by telephone interview or by contacting the general practitioner.

The scalar 12-lead ECGs (standard calibration 10 mm/1 mV) at first evaluation were performed on commercially available instruments in the supine position during quiet respiration and recorded at a paper speed of 25 mm/s. The following parameters were measured: PR interval, QRS duration, QRS voltages, QT interval, and corrected QT interval (Bazett's formula). Left bundle branch block (LBBB) or right bundle branch block, left anterior fascicular block, and nonspecific intraventricular conduction disturbance were classified according to international criteria.[7] A number of electrocardiographic criteria proposed for the clinical identification of LV hypertrophy were used, including Cornell voltage score (SV3 + R aVL ≥20 mm in women and ≥28 mm in men), modified Sokolow-Lyon score (SV1 or SV2 + RV5 or RV6 ≥35 mm), the amplitude of R wave in aVL (≥11 mm), and the sum of RDI and SDIII (≥25 mm). LV hypertrophy was diagnosed in the presence of at least 1 criteria.[8,9] Massive LV hypertrophy was defined by modified Sokolow-Lyon score ≥50 mm.[7]

We defined specific ECG patterns. Pseudo-necrosis: presence of Q waves ≥1/3 of the ensuing R wave in depth and/or ≥0.04 seconds in duration in at least 2 contiguous leads except aVR and/or the lack of progressive R-wave voltage increase in the precordial leads.[10] Low voltages: QRS complex amplitude <0.5 mV in all limb leads.[11] Repolarization abnormalities: ST-segment depression/elevation ≥0.1 mV below or above the baseline at the J-point in at least 2 leads, except V1-V2-V3, where it was considered only when ≥0.2 mV.[12] T waves were defined as (1) "inverted" when the negative T-wave amplitude was ≥0.1 mV, (2) "giant negative" when amplitude was ≥1.0 mV,[12] and (3) "giant positive" T waves were defined as symmetrical positive T waves ≥1.0 mV.[13] ST-segment elevation and giant positive T waves were considered only in the absence of LBBB. The presence of notching in terminal part of QRS was defined as "J wave." A specific ECG pattern characterized by the presence of ST-segment elevation and/or giant positive T waves in at least 2 contiguous leads in the absence of LBBB was assessed and defined "pseudo−ST-segment elevation myocardial infarction (STEMI)" pattern for its resemblance of the ECG associated with the acute/subacute phase of myocardial infarction (Figure 1).[14] Other prespecified ECG patterns such as massive LV hypertrophy, massive LV hypertrophy associated with right atrial enlargement, and LV hypertrophy with abnormal R/S in V1 were assessed. All ECGs were independently analyzed using manual calipers, and patterns were adjudicated by 2 independent investigators (EB and CP—S.Orsola Malpighi Hospital Bologna) unaware of the clinical details of the patients. Discrepancies were resolved by a senior supervisor (CR).

Standard M-mode and 2-dimensional echocardiographic studies were performed by commercially available instruments to identify and qualify morphologic features of the left ventricle. The greatest wall thickness measured at any site in the LV wall was regarded as the maximal thickness,[6] independently of body surface area and gender or age. LV outflow obstruction in basal conditions was defined as a peak outflow gradient of ≥30 mm Hg, as estimated by continuous-wave Doppler echocardiography.[15]

Continuous data were expressed as mean value ± SD. Data were compared by the chi-square analysis for proportions and Student's t test for continuous variables. Survival rates were obtained using Kaplan-Meier method of estimation. Univariate and multivariable Cox proportional hazard regression models were constructed to identify independent predictors of follow-up events. Each electrocardiographic variable was assessed by Cox proportional univariate survival analysis. Model building followed a backward stepwise approach with entry set at a significance level of 0.1. For each variable, the hazard ratio (HR) with a corresponding 95% confidence interval was reported. Harrell's C index was used to assess model's discrimination. A p value <0.05 was considered statistically significant. Statistical analyses were obtained using Stata/SE 13.1 (Stata-Corp IP, College Station, Texas).

Results

Clinical and echocardiographic characteristics and arrhythmic risk profile of the study population are listed in Table 1. In our population, 29 patients had an ICD at first evaluation and 150 underwent ICD implantation during follow-up.

Electrocardiographic variables are listed in Table 2. The pseudo-STEMI pattern was present in 171 patients (17%) including 97 patients with ST-segment elevation, 34 with giant positive T waves, and 40 with both. One hundred twenty-one patients (71%) showed this pattern in anterior
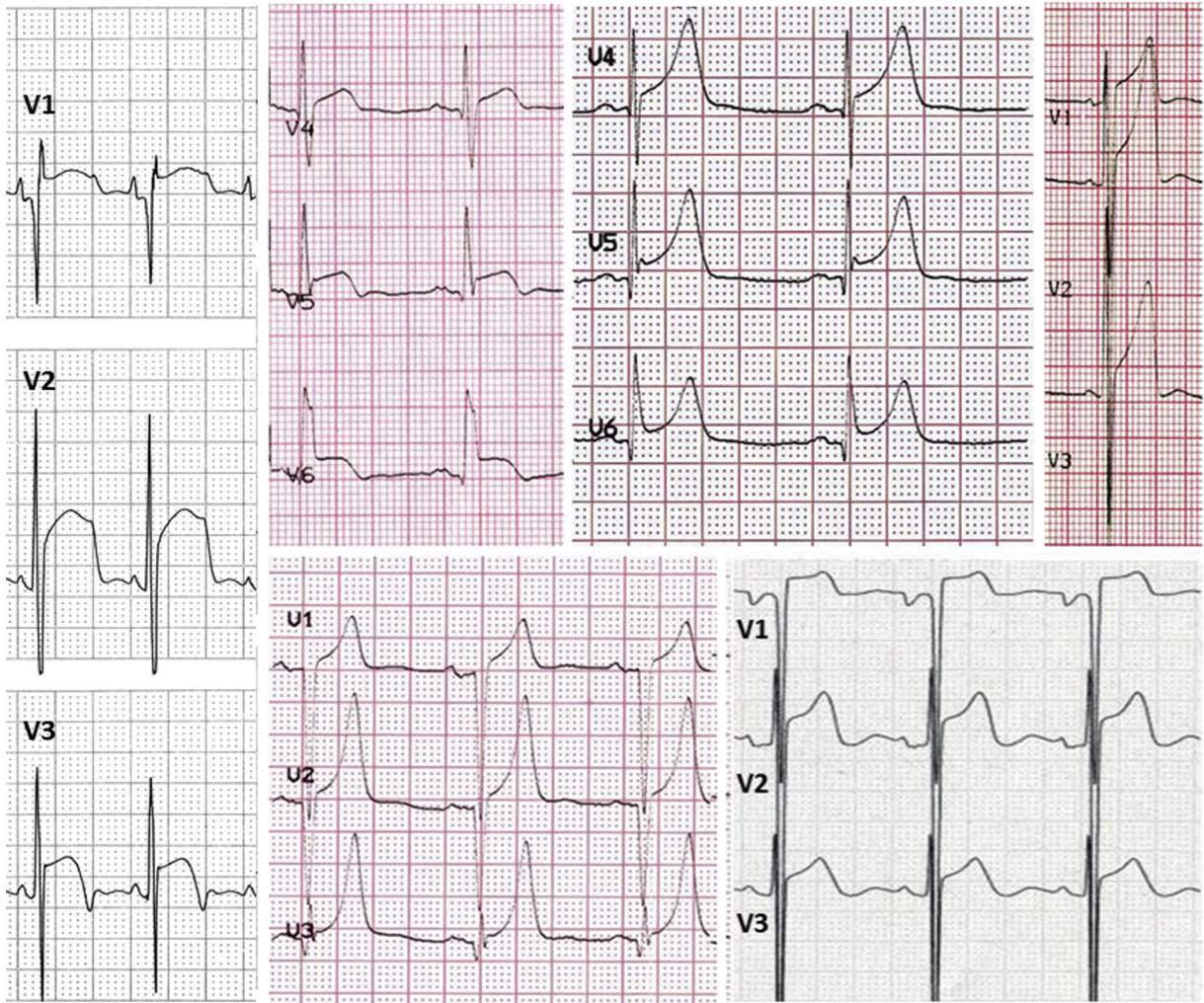
Figure 1. Electrocardiographic examples of the pseudo-STEMI pattern.

leads, 27 patients (16%) in inferior leads, 15 patients (9%) in inferolateral leads, and 8 patients (5%) only in lateral leads. A short PR interval (≤120 ms) was present in 71 cases.

After a mean follow-up of 7.4 ± 6.8 years, 77 patients experienced SCD or surrogates including 41 who actually died suddenly (4%), 24 with appropriate ICD discharge (2%), and 12 with aborted cardiac arrest (1%). A total of 154 patients (15%) experienced major cardiovascular events, including the 77 with SCD or surrogates, 60 (6%) with heart failure−related death (15 of which underwent heart transplantation), and 17 (2%) who died after cardioembolic stroke. The electrocardiographic findings associated with SCD or surrogates at univariate analysis were QRS ≥120 ms, pseudo-STEMI pattern, ST-segment elevation, and low QRS voltages (Table 3). The electrocardiographic findings associated with major cardiovascular events at univariate analysis were QRS ≥120 ms, prolonged corrected QT interval, left and right atrial enlargement, and pseudo-STEMI pattern (Table 3).

At multivariable analysis (Table 4), unexplained syncope (hazard ratio [HR] 2.47, 95% confidence interval [CI] 1.37 to 4.47, p = 0.003), nonsustained ventricular tachycardia

(NSVT) during Holter monitoring (HR 1.68, 95% CI 1.06 to 2.65, p = 0.027), LV ejection fraction <50% (HR 3.55, 95% CI 1.89 to 6.66, p = 0.0001), pseudo-STEMI pattern (HR 2.28, 95% CI 1.38 to 3.77, p = 0.001), QRS duration ≥120 ms (HR 1.78, 95% CI 1.05 to 3.03, p = 0.033), and low QRS voltages (HR 2.26, 95% CI 1.01 to 5.07, p = 0.048) were independently associated with SCD or surrogates. Harrell's C index was 0.68. Sensibility and specificity of QRS duration in predicting SCD were 26% and 84%, respectively; positive and negative predictive values were 12% and 93%, respectively. Sensibility and specificity of pseudo-STEMI pattern in predicting SCD were 30% and 84%, respectively; positive and negative predictive values were 13% and 93%, respectively. Sensibility and specificity of low QRS voltages in predicting SCD were 9% and 97%, respectively; positive and negative predictive values were 21% and 93% respectively.

Multivariable Cox proportional model for major cardiovascular events (Table 4) identified age (HR 1.02, 95% CI 1.01 to 1.03, p = 0.0001), LV ejection fraction <50% (HR 3.73, 95% CI 2.39 to 5.83, p = 0.0001), pseudo-STEMI pattern (HR 1.66, 95% CI 1.13 to 2.45, p = 0.010), QRS

Table 1
Baseline characteristics of the study population (n = 1004)

Variable	
	1004
• Age ≥ 18	984 (98 %)
• Age 14-17	20 (2%)
Males	640 (64%)
Age (years), mean ± SD	50 ± 16
Family history of HC	441 (44%)
Family history of SCD	196 (20%)
LV outflow tract obstruction (≥30 mmHg)	335 (33%)
Unexplained syncope	91 (9%)
NSVT on Holter monitoring	281 (28%)
NYHA functional class III-IV	71 (7%)
Maximal LV wall thicknes (mm) mean ± SD/n patients*	20 ± 5/997
LV end-diastolic dimension, (mm) mean ± SD/n patients*	45 ± 7/955
LV ejection fraction <50%	51 (5%)
Dilated-hypokinetic evolution	44 (4%)

HC = hypertrophic cardiomyopathy; LV = left ventricle; NYHA = New York Heart Association; NSVT = nonsustained ventricular tachycardia; SCD = sudden cardiac death.

* Data missing: n patients with available data.

Table 2
Baseline electrocardiographic characteristics of the study population

Characteristics	Prevalence
Normal ECG	38 (4%)
QRS duration ≥120msec	172 (17%)
Prolonged corrected QT interval (≥440 msec)	297 (30%)
Prolonged corrected QT interval (≥ 480 msec)	65 (6%)
Left atrial enlargement	448 (45%)
Right atrial enlargement	85 (8%)
LV hypertrophy*	562 (56%)
Massive LV hypertrophy	139 (14%)
Massive LV hypertrophy associated to right atrial enlargement	11 (1%)
LV hypertrophy in presence of abnormal R/S in V1	23 (2%)
Low QRS voltages	33 (3%)
Pseudo-necrosis Q waves	335 (33%)
Repolarisation abnormalities	778 (77%)
Negative T wave	746 (74%)
Giant inverted T waves (≥10 mm)	56 (6%)
Giant positive T waves (≥10 mm)	74 (7%)
ST-segment depression	557 (56%)
ST-segment elevation	137 (14%)
"Pseudo-STEMI" pattern	171 (17%)
ST segment elevation without giant positive T waves	97 (10%)
Giant positive T waves without ST segment elevation	34 (3%)
ST segment elevation and giant T waves	40 (4%)
J wave	34 (3%)
Abnormal R/S wave in V1	60 (6%)
Complete RBBB	67 (7%)
Complete LBBB	63 (6%)
Unspecified intraventricular block	73 (7%)
Left anterior fascicular block	133 (13%)

ECG = electrocardiogram; HC = hypertrophic cardiomyopathy; LV = left ventricle; NSVT = non sustained ventricular tachycardia.

* At least 1 criteria satisfied.

duration ≥120 ms (HR 1.69, 95% CI 1.16 to 2.47, p = 0.007), and prolonged QTc interval (HR 1.68, 95% CI 1.21 to 2.34, p = 0.002) as independent predictors. Harrell's C index was 0.71.

Kaplan-Meier survival curves for the end point SCD or surrogates in patients with and without the pseudo-STEMI pattern and QRS duration ≥120 ms are reported in Figure 2. Survival curves were also constructed stratifying the patients according to the number of risk factors (n = 0, n = 1, n ≥ 2). In Figure 2, patients were stratified according to the presence of the 4 conventional risk factors for SCD (family history of SCD, unexplained syncope, NSVT during 24-hour Holter monitoring, and maximal LV wall thickness ≥30 mm). The annual SCD event rate in patients with no risk factors was 0.62%, 1.19% in patients with 1 risk factor, and 1.92% in patients with ≥2 risk factors (log-rank test p value = 0.0006). The addition of the 3 electrocardiographic variables independently related to SCD improved the model (Figure 2). In patients with no risk factors, the annual SCD event rate was 0.38% and was 0.91% and 1.94% in patients with 1 and ≥2 risk factors, respectively (log-rank test p value = 0.00001). The Cox proportional hazard regression model stratified the patients well according to the number of the conventional risk factors; however, the addition of the electrocardiographic variables in a second model resulted in a higher predictive power for SCD (chi-square from 14 to 32, p value 0.0001).

Discussion

This study highlights the potential contribution of standard ECG—interpreted with a quantitative and qualitative approach—to risk stratification of patients with HC. Different ECG patterns can be observed and their recognition can contribute to guide the physician toward a correct differential diagnosis and to stratify the risk of SCD and major cardiovascular events.[3,4]

The proportion of our cases with normal ECG (4%) is similar with that reported from other groups.[3] "Repolarization abnormalities" was the commonest single abnormality (77%), followed by LV hypertrophy (56%), left atrial enlargement (45%), and pseudonecrosis Q waves (33%). Interestingly, some patterns were observed, including pathologic Q waves with positive T waves in the same lead ("Q/T discordance," 24%), tall R waves in V1-V2 (R ≥S) in the context of LV hypertrophy (6%), right atrial enlargement and LV hypertrophy (2%), giant negative T waves in the precordial leads (1%), low QRS voltages (3%), and pseudo-STEMI pattern (17%). The relation between ECG and prognosis in HC has been investigated with conflicting results in the past.[3-5,16-22] Studies have focused mainly on the degree of LV hypertrophy and the overall electrical instability, expressed by QT duration and dispersion and by T-wave complexity.[16-22] The sole presence of an "abnormal ECG" has been found to be associated with a more severe HC phenotype and worse cardiovascular outcome—compared with a normal ECG—in 2,485 patients with HC.[3]

The main finding of our study is that specific features of the standard ECG, namely QRS duration ≥120 ms, pseudo-STEMI pattern, and low QRS voltages, are independent risk factors for SCD or surrogates (Table 4) and could be usefully integrated with the traditional risk factors (Figure 2). Whereas pseudo-STEMI pattern and QRS duration >120 ms, together

Table 3
Univariate analysis in the overall population

Characteristics	SCD or surrogates Univariate Analysis		Major cardiovasculare events Univariate Analysis	
	H.R. (95% CI)	P value	H.R. (95% CI)	P value
Age	0.99 (0. 98 - 1.01)	0.610	1.02 (1.01 - 1.03)	0.0001
Male	0.83 (0.49 - 1.43)	0.268	1.20 (0.87 - 1.66)	0.286
Family history of SCD	1.66 (0.97 - 2.84)	0.007	1.86 (1.33 - 2.61)	0.0001
Familiar HC	1.92 (1.16 - 3.19)	0.011	1.57 (1.14 - 2.16)	0.006
Unexplained syncope	2.51 (1.34 - 4.73)	0.004	1.48 (0.89 - 2.46)	0.128
NSVT 24 hour Holter monitoring	1.81 (1.11 - 2.98)	0.024	1.47 (1.07 - 2.65)	0.018
Maximal LV wall thickness	1.38 (0.93 - 2.04)	0.419	1.12 (0.85 - 1.46)	0.420
Maximal LV wall thickness ≥ 3 cm	1.51 (0.74 - 3.06)	0.274	1.40 (0.86 - 2.27)	0.170
LV end-diastolic dimension	1.12 (0.72 - 1.75)	0.017	1.71 (1.32 - 2.22)	0.0001
LV outflow tract obstruction	1.05 (0.60 - 1.82)	0.675	0.98 (0.67 - 1.42)	0.905
LV ejection fraction < 50%	4.47 (2.44 - 8.18)	0.0001	4.52 (2.95 - 6.94)	0.0001
Normal ECG	0.35 (0.05 - 2.52)	0.297	0.34 (0.08 - 1.39)	0.135
QRS duration ≥120msec	2.09 (1.25 - 3.49)	0.005	2.59 (1.84 - 3.66)	0.0001
Prolonged corrected QT interval (≥440 msec)	1.56 (0.99 - 2.47)	0.056	1.86 (1.35 - 2.56)	0.0001
Prolonged corrected QT interval (≥ 480 msec)	1.23 (0.54 - 2.85)	0.618	2.45 (1.58 - 3.80)	0.0001
Left atrial enlargement	1.31 (0.79 - 2.16)	0.288	1.53 (1.08 - 2.16)	0.015
Right atrial enlargement	0.89 (0.36 - 2.21)	0.803	1.85 (1.12 3.03)	0.015
LV hypertrophy*	0.90 (0.57 - 1.42)	0.654	1.06 (0.76 1.46)	0.733
Massive LV hypertrophy	0.97 (0.51 - 1.83)	0.917	0.92 (0.58 - 1.46)	0.724
Massive LV hypertrophy associated to right atrial enlargement	1.05 (0.15 - 7.46)	0.956	1.68 (.53 - 5.28)	0.375
LV hypertrophy in presence of abnormal R/S in V1	0.66 (0.09 - 4.79)	0.686	1.79 (0.73 - 4.37)	0.201
Low QRS voltages	2.71 (1.24 - 5.91)	0.012	1.80 (0.91 - 3.53)	0.089
Pseudo-necrosis Q waves	1.35 (0.86 - 2.13)	0.191	1.03 (0.74 - 1.43)	0.858
Repolarisation abnormalities	1.09 (0.61 - 2.0)	0.754	1.08 (0.71 - 1.63)	0.715
Negative T wave	0.66 (0.36 - 1.19)	0.170	0.85 (0.58 - 1.25)	0.409
Giant inverted T waves (≥10 mm)	0.36 (0.09 - 1.46)	0.152	0.44 (0.18 - 1.07)	0.152
Giant positive T waves (≥10 mm)	0.94 (0.51 - 1.75)	0.493	1.25 (0.72 - 1.73)	0.407
ST-segment depression	1.07 (0.67 - 1.70)	0.772	1.15 (0.83 - 1.61)	0.389
ST-segment elevation	2.42 (1.50 - 3.89)	0.004	1.45 (0.99 - 2.12)	0.525
"Pseudo-STEMI" pattern	2.07 (1.26 - 3.38)	0.0001	1.60 (1.07 - 2.35)	0.020
J wave	1.93 (0.78 - 4.80)	0.154	1.93 (0.78 - 4.80)	0.154
Abnormal R/S wave in V1	0.40 (0.09 - 0.64)	0.207	1.03 (0.54 - 1.97)	0.914
Left anterior fascicular block	0.87 (0.44 - 1.70)	0.682	0.89 (0.56 - 1.42)	0.646

ECG = electrocardiogram; HC = hypertrophic cardiomyopathy; LV = left ventricle; NSVT = non sustained ventricular tachycardia; SCD = sudden cardiac death.

* At least 1 criteria satisfied.

Table 4
Multivariate analysis in the overall population

Variables	SCD or surrogates Multivariable analysis		Major cardiovascular events Multivariable analysis	
	H.R. (95% CI)	P value	H.R. (95% CI)	P value
Age			1.02 (1.01 - 1.03)	0.0001
Unexplained syncope	2.47 (1.37 - 4.47)	0.003		
NSVT 24 hour Holter monitoring	1.68 (1.06 - 2.65)	0.027		
LV ejection fraction <50%	3.55 (1.89 - 6.66)	0.0001	3.73 (2.39 - 5.83)	0.0001
QRS duration ≥120 msec	1.78 (1.05 - 3.03)	0.033	1.69 (1.16 - 2.47)	0.007
Low QRS voltages	2.26 (1.01 - 5.07)	0.048		
"Pseudo STEMI" pattern	2.28 (1.38 - 3.77)	0.001	1.66 (1.13 - 2.45)	0.010
Prolonged QTc interval (≥440 msec)			1.68 (1.21 - 2.34)	0.002

LV = left ventricle; NSVT = non sustained ventricular tachycardia; SCD = sudden cardiac death.

with prolonged QTc interval, were found to be independent predictors not only of SCD and surrogates but of all the major cardiovascular events, they have been analyzed in detail.

The negative prognostic role of prolonged QRS duration is somewhat expected and, indeed, has been reported by Bongioanni et al[16] as regard to HC-related death.[5] An
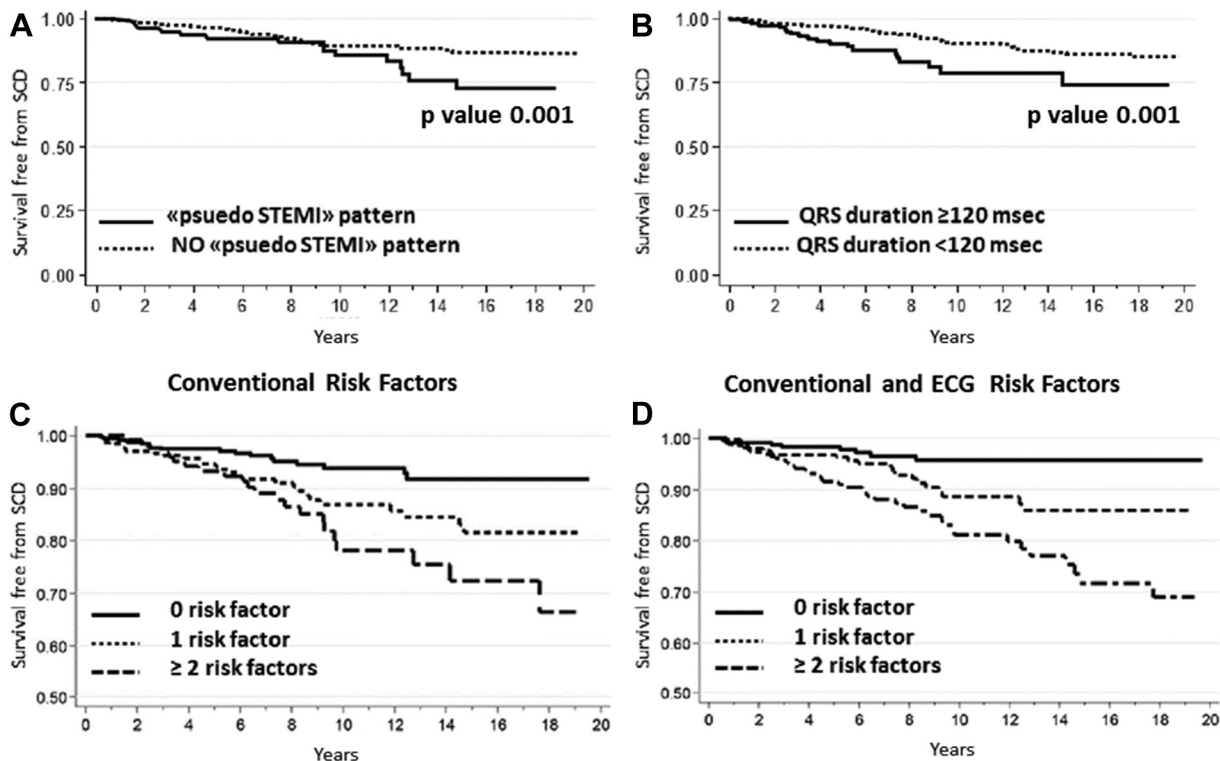
Figure 2. Kaplan-Meier survival curves for the end point SCD or surrogates according to the presence/absence of the pseudo-STEMI pattern *(panel A)* and QRS duration $\geq$120 ms *(panel B)*. *(Panels C and D)* Kaplan-Meier survival curves for the end point SCD or surrogates stratifying the patients according to the number of conventional risk factors (family history of SCD, unexplained syncope, nonsustained ventricular tachycardia during electrocardiographic Holter monitoring, maximum wall thickness $\geq$30 mm), or after the addition of the 3 ECG patterns (pseudo-STEMI pattern, QRS duration $\geq$120ms, and low QRS voltages).

association with apical aneurism development has also been reported by other investigators. QRS prolongation in (dilated) cardiomyopathies is accepted as a marker of myocardial damage and as a factor of contractile dysfunction.[23,24] Our study extends the independent prognostic value of this pattern to SCD or surrogates. Patients with abnormally prolonged QRS duration tend to be older, have more frequently a family history of SCD or NSVT during Holter monitoring, and a higher frequency of LV dysfunction (Supplementary Table 1).

The independent prognostic significance of low QRS voltages is interesting but unfortunately of little clinical relevance because of the very low prevalence of this finding (3%). In cardiomyopathies, low QRS voltages are often secondary to the expansion of myocardial interstitial space (amyloidosis, fibrosis, edema, and flogistic infiltrates) or to diffuse myocellular damage.[11] In HC, the mechanism has yet to be investigated, but it could be related to a greater degree of myocardial fibrosis. Unfortunately, the absence of magnetic resonance imaging data did not allow us to investigate the phenomenon. No association between low QRS voltages and heart failure development during follow-up and death due to heart failure and transplant were recorded.

The pseudo-STEMI pattern has never been evaluated in HC. In our study, this pattern (observed in 17%) is associated with a risk of SCD and surrogates and to major cardiovascular events of 2.28 and 1.66, respectively, at the

multivariable analysis. The high negative predictive value (93%) is particularly intriguing. The reasons of this finding are not clear, and our study does not have the characteristics necessary to unravel the issue. It is notably that the pattern is not associated with a more severe morphologic or arrhythmic phenotype. Patients with the pseudo-STEMI pattern were younger, more frequently men, and with a higher rate of LV outflow obstruction (Supplementary Table 1). It is reasonable that the peculiar repolarization abnormality could be the expression of a genetically determined ion-channel dysfunction accidentally associated with HC. Some published data are potentially in line with this hypothesis. Lopes et al[25] documented a very high number of sarcomeric and nonsarcomeric genetic variants associated with the classic HC mutations and hypothesized that some of these variants could influence the expression of HC phenotype. In HC probands, a relation between rare variants in the *SCN5A* gene and left atrial enlargement at last evaluation or LV outflow obstruction have been reported.[25] Additionally, SCN5A variants appear to influence the fibrotic process in patients with sarcomeric protein mutations.[26] A similar explanation (i.e., involving ion channels) has been proposed for the cases of SCD associated with early repolarization in the general population.[27,28] In our series, however, the prevalence of early repolarization, defined as the sole presence of J wave (3%), is decidedly low and prognostically irrelevant. A single study on a small cohort of patients with HC[29] reports a prevalence of early

repolarization (defined as J-point elevation ≥ 0.1 mV in at least 2 consecutive inferior/lateral leads excluding V1-V2-V3) of 12% and found that the presence of a J wave was more frequent in patients who died suddenly. Prospective studies are required to test these hypothesis.

Beyond the incomplete understanding of the mechanisms, it is noteworthy that when added to the conventional SCD risk factors, electrocardiographic variables, despite their low positive predictive value, improved the risk stratification model (Figure 2), especially the ability to identify subjects at very low risk (annual SCD or surrogates rate in patients without any conventional risk factors or electrocardiographic markers is 0.3%). It should be noted that survival curves of patients with/without prolonged QRS tend to diverge soon after the initial observation, differently from what occurs with the pseudo-STEMI pattern. These new observations may be included in the recently proposed algorithm for quantitative 5-year risk calculation.[1]

The main limitations of this study are the retrospective design that may have introduced a selection bias and the relatively small size that may have limited the prognostic significance of the statistical analysis. Also, appropriate ICD activation is a surrogate marker of sudden death and its use for outcome analysis may have led to an overestimation of events. Because of the lack of genetic data, we can only speculate that ion-channel mutations could be associated with the pseudo-STEMI pattern, and further prospective studies are required to investigate this hypothesis.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2016.05.023.

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