ORIGINAL ARTICLE

Development and Validation of a Prognostic Index for Risk Stratification of Patients with Early Repolarization

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Background: Early repolarization (ER) is associated with increased mortality in the general population. We sought to develop and validate a prognostic index (PI) of mortality in patients with ER.

Methods: We identified 852 consecutive patients (mean age 49 ± 12 years) with ER (J-point elevation ≥ 0.1 mV in inferior or lateral leads), from the VA electronic electrocardiogram (ECG) database. A random sample of age-matched patients with normal ECG was used as control ($n = 257$). The initial cohort was randomly split into a derivation and a validation cohort (2/3 and 1/3 of patients, respectively). A PI was derived from the weighed sum of the regression coefficients of each independent risk factor in the final model using Cox regression analysis.

Results: During a median follow-up of 6.4 years, 170 patients died. ER was associated with increased mortality compared to control (HR 1.49, 95% CI 1.05–2.12; $P = 0.03$). Older age, lower body mass index, non-African American race, current use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or sulfonylureas, prolonged corrected QT (QTc), and higher ER amplitude independently predicted all-cause mortality. Annualized mortality rates were 1.3%, 2.2%, and 3.7% in the low, intermediate, and high-risk groups, respectively, in the derivation cohort (log rank $P < 0.0001$) and 0.8%, 1.9%, and 4.1% in the low, intermediate, and high-risk groups, respectively, in the validation cohort (log rank $P < 0.0001$). Model discrimination was very good (c-statistic = 0.85 and 0.80 for derivation and validation cohort, respectively).

Conclusions: A PI derived from simple clinical and ECG characteristics predicts mortality in patients with ER and may be used clinically for risk stratification.

Ann Noninvasive Electrocardiol 2012;17(4):361–371

early repolarization; sudden cardiac death; prognosis; mortality; risk stratification

An early repolarization (ER) pattern on the electrocardiogram (ECG), defined as elevation of the QRS–ST junction of at least 0.1 mV from baseline in two or more adjacent leads in the inferior or lateral leads with either slurring or notching morphology, is present in 1% to 13% of the general population and is more common in young, black, athletic males.^{1–3} Although ER has been traditionally considered a benign finding,¹ more recent data suggest that it is more prevalent in survivors of

idiopathic ventricular fibrillation.^{4,5} Moreover, the presence of ER in the inferior and inferolateral leads has been associated with increased risk for cardiac and all-cause mortality in the general population.^{2,3} These clinical data are consistent with experimental data, which suggest that an ER pattern can easily convert to one in which phase 2 reentry gives rise to polymorphic ventricular tachycardia and ventricular fibrillation.^{6,7} Although the prognostic significance of ER has been questioned

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recently,^{8,9} the lack of association may have been due to the different definition of ER used in these studies.¹⁰

Prevention of sudden cardiac death (SCD) in the general population with ER requires accurate risk stratification. At present, the only definite way to prevent SCD is with implantable cardioverter defibrillators (ICDs). On the other hand, quinidine has been shown to be very effective in preventing recurrent ventricular fibrillation in a small number of patients who had documented ER-related SCD.¹¹ These interventions can only be justified in individuals at very high risk, such as survivors of ER-related SCD. In the general population with ER, however, the absolute risk of SCD is low and cannot justify the use of an ICD or pharmacologic therapy.¹² Nonetheless, high-risk patients may benefit from an ICD and/or pharmacologic therapy. A few high-risk features have been identified, such as inferior location and higher amplitude of ER,^{2,3} but a more precise risk stratification method is lacking. We aimed to identify high-risk features among patients with ER associated with increased total mortality, and use these features to develop and validate a prognostic index (PI) that could accurately stratify patients with ER into groups by their risk of total mortality.

METHODS

The Oklahoma City Veterans Affairs Medical Center electronic ECG database was searched to identify patients with ER. All ECGs done at this institution for both inpatients and outpatients are automatically entered in the database. The diagnosis of ER was adjudicated by two trained cardiologists, who were unaware of the clinical data. Any disagreements were resolved by discussion. ER was defined using previously described criteria, as elevation of the QRS-ST junction of at least 0.1 mV from baseline in two or more adjacent leads in the inferior (II, III, and aVF) or lateral leads (I, aVL and V₄ to V₆) with either slurring or notching morphology²⁻⁴ (Fig. 1). Consecutive patients who had an ECG showing ER between January 1990 and December 2009 were included in the study. For patients with multiple ECGs in the database, only the first ECG was considered in the primary analysis, to avoid duplication of data. To evaluate the dynamic nature of J-point elevation, repeat ECGs from the same patient, when available, were examined. A random sample of age-

Figure 1. Representative electrocardiograms from our study population demonstrating early repolarization in the inferior leads with either a slurring morphology (A), or a notching morphology (B). Arrows point to leads with evident early repolarization pattern.

matched patients with normal ECG (stratified by time of index ECG) was selected from the database to serve as a negative control. Routine ECG parameters were obtained from automated measurements. All ECGs were assessed by two trained cardiologists, who were blinded to the clinical data and follow-up status, using paper prints. Leads V₁ to V₃ were not interpreted to avoid confusion with ECG patterns of Brugada syndrome or right ventricular dysplasia.^{2,4} The following parameters were manually extracted: ER location (inferior vs. lateral), amplitude (mV) and morphology (notching vs. slurring), ST segment pattern (upsloping vs. horizontal/downsloping, as described by Tikkanen et al.¹³), presence or absence of left

Table 1. Characteristics of Patients in the Derivation and Validation Cohorts

Variable	Derivation Cohort (n = 595)	Validation Cohort (n = 257)	P-Value
Age (years)	49.2 ± 11.8	48.4 ± 12.9	0.38
Male gender (%)	99.7	99.6	0.90
Race (%)			0.89
Caucasian	58.8	57.2	
African American	40.2	41.6	
Other	1.0	1.2	
Body mass index (kg/m ²)	26.6 ± 5.3	26.5 ± 5.3	0.80
Cardiomyopathy (%)	3.2	2.6	0.66
Diabetes (%)	14.7	9.4	0.04
Hypertension (%)	50.0	50.0	1.0
Coronary artery disease (%)	15.0	15.9	0.76
Current smoker (%)	69.5	72.1	0.46
Cocaine/amphetamine use (%)	19.5	21.0	0.61
Unexplained syncope (%)	0.7	0	0.32
Family history of SCD (%)	0.6	0	0.56
Medications (%)			
Beta-blockers	23.0	22.6	0.91
ACEI/ARBs	23.5	22.2	0.68
Sulfonylureas	8.1	5.0	0.13
ECG parameters			
Heart rate (bpm)	65.3 ± 13.5	65.4 ± 13.6	0.92
PR interval (ms)	161.5 ± 26.5	161.9 ± 23.9	0.82
QRS duration (ms)	89.4 ± 8.4	89.3 ± 8.6	0.87
QTc interval (ms)	408.2 ± 20.6	408.3 ± 20.7	0.95
LVH (%)	22.2	24.9	0.39
Q waves (%)	3.2	1.2	0.10
ER amplitude (mV)	0.14 ± 0.06	0.15 ± 0.06	0.02
ER location (%)			0.56
Lateral	46.0	49.8	
Inferior	14.2	12.5	
Inferolateral	39.8	37.7	
ER morphology (%)			0.67
Notched	45.2	48.3	
Slurred	54.8	51.2	
ST-segment pattern (%)			0.52
Upsloping	77.1	72.4	
Horizontal/downsloping	22.9	27.6	

SCD = sudden cardiac death; ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; LVH = left ventricular hypertrophy; ER = early repolarization.

ventricular hypertrophy and presence or absence of abnormal Q waves. Heart rate (bpm), PR interval (ms), and corrected QT (QTc) interval (ms) were obtained from automated measurements. The following clinical data were collected from available records at the time of the index ECG: age, gender, race, body mass index (BMI), history of syncope, presence of cardiomyopathy (defined as left ventricular ejection fraction of <45%), diabetes (defined as the use of oral hypoglycemic agents, insulin, or both, or self-reported), hypertension (defined as the use of antihypertensive agents or self-reported), and coronary artery dis-

ease (defined as presence of coronary artery stenosis of at least 50% by coronary angiography, or presence of ischemia on noninvasive stress testing), smoking status (smoking vs. nonsmoking), cocaine or amphetamine use, family history of SCD and medications of interest, including beta-blockers, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), and sulfonylureas. Total mortality at follow-up was assessed through chart review and by vital statistic data available at the Veterans Administration Medical Center (last review January 2012). The vital status of all included patients was known at the end

Figure 2. Kaplan-Meier curves for survival in the control population (normal) compared to patients with early repolarization.

of follow-up. Clinical data were available in almost all the patients. There were no missing ECG data. The study was approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ standard deviation. Categorical variables are presented as percentages. Comparisons were made using unpaired *t*-test for continuous variables and chi-square test or Fisher's exact test, as applicable, for categorical variables. Paired *t*-test was used to compare J-point elevation between two consecutive ECGs on the same patient. Kaplan-Meier curves were estimated for the time-to-event distribution of all-cause mortality according to risk group and the differences between the groups were compared with the log-rank test. A two-tailed *P* value of ≤ 0.05 was considered statistically significant.

Model Derivation and Validation

The initial cohort was randomly split into a derivation cohort and a validation cohort (2/3 and 1/3 of patients, respectively), as previously described.¹⁴ We first examined the bivariate relationship between each risk factor and mortality in the derivation cohort using Cox proportional hazard models containing only the risk factor of interest. We then entered all variables associated with

mortality at $P < 0.2$ by univariate analysis into a multivariate Cox proportional hazard model with backward elimination ($P < 0.05$ to retain) to select the final set of independent risk factors. For continuous variables, the presence of a linear association between each variable and mortality was examined by assessing the impact of each variable separately in zones of ranked data.¹⁵ In the absence of a linear gradient across zones of ranked data, "dummy" variables were created, comparing all other categories to a single reference category.¹⁵ In order to retain the predictive discrimination of the model and avoid overfitting, no more than $m/10$ parameters were examined in the multivariate regression model, where m represents the number of uncensored events (in this case, deaths; $n = 122$) in the derivation cohort, according to previous recommendations on multivariate prognostic modeling.¹⁴ Interactions between variables of interest were examined in the initial multivariate Cox regression model. Interactions which did not reach statistical significance were removed from the model. For each independent variable, the respective hazard ratios (HRs) with 95% confidence interval (CI) were calculated. A PI was derived for each patient, by adding the products of each independent risk factor in the final model multiplied by their respective regression coefficients. We also constructed a simplified risk scoring system in which each risk factor was assigned points by dividing each regression coefficient in the final model by the smallest

Table 2. Risk Factors of Total Mortality in the Derivation Cohort by Univariate Analysis

Risk Factor	Hazard Ratio (95% Confidence Interval)	P-Value
Age (years)		
<45	1.0	<0.0001
45 to 64	2.47 (1.57 to 3.88)	<0.0001
≥65	4.97 (2.88 to 8.56)	
Body mass index (kg/m ²)		
>25	1.0	
≤25	1.99 (1.39 to 2.87)	0.0002
Race		
African American	1.0	
Non-African American	1.57 (1.09 to 2.28)	0.017
Cardiomyopathy	1.76 (0.77 to 4.02)	0.18
Diabetes	2.08 (1.34 to 3.20)	0.001
Hypertension	1.87 (1.27 to 2.75)	0.001
Coronary artery disease	2.33 (1.53 to 3.58)	<0.0001
Beta-blocker use	1.36 (0.89 to 2.08)	0.15
ACEI/ARB use	2.08 (1.42 to 3.06)	0.0002
Sulfonylurea use	1.88 (1.11 to 3.20)	0.020
Heart rate (bpm)		
<60	1.0	
60 to 79	1.08 (0.74 to 1.61)	0.71
≥80	2.43 (1.49 to 3.98)	0.0004
QTc interval (ms)		
<440	1.0	
≥440	2.16 (1.29 to 3.61)	0.003
Early repolarization amplitude (mV)		
0.1 to 0.14	1.0	
≥0.15	1.25 (0.89 to 1.80)	0.19
ST segment pattern		
Upsloping	1.0	
Horizontal/downsloping	1.75 (1.20 to 2.55)	0.004

regression coefficient and rounding to the nearest integer.¹⁵ The final simplified risk score was calculated for each patient by adding up the points for each risk factor present. Using the same PI and the simplified risk score, respectively, each patient in the validation cohort was attributed a risk score. The predictive accuracy of the model was assessed by using the c-statistic (discrimination) and the goodness-of-fit test (calibration) in both the derivation and validation cohort. Calibration refers to the degree of bias, whereas discrimination reflects the ability of the risk score to distinguish between patients at low and high risk.¹⁴ All analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Population

One thousand seven hundred forty ECGs with ER pattern pertaining to 852 consecutive patients were identified from the electronic database. To avoid duplication of data, only the first ECG for each patient was used in the mortality analysis. Among the 214 patients who underwent a repeat ECG at least 1 year after the index ECG, J-point elevation remained essentially unchanged (0.16 ± 0.05 mV vs. 0.16 ± 0.07 mV; $P = 0.93$). Five hundred ninety-five and 257 patients were randomly assigned to the derivation and validation cohort, respectively. Two hundred fifty-seven age-matched patients with normal ECG (mean age 49.5 ± 10.4 years) were randomly selected from the database to serve as negative controls. There were no differences in the baseline characteristics of the control population and the derivation cohort, except for the presence of ECG left ventricular hypertrophy, which was more frequent in patients with ER (data not shown). The characteristics of patients in the derivation and validation cohorts are shown in Table 1. The mean age of patients in the derivation cohort was 49.2 ± 11.8 years, 99.7% were men and 40.2% were African American. In the validation cohort, the mean age was 48.4 ± 12.9 years, 99.6% were men and 41.6% were African American. The derivation and validation cohorts were well matched, except for diabetes, which was more frequent in the derivation cohort ($P = 0.04$) and the magnitude of J-point elevation, which was slightly higher in the validation cohort ($P = 0.02$). In the derivation cohort, during a median follow-up of 6.3 years (interquartile range 2.5–11.9 years), 122 patients (20.5%) died, corresponding to an annualized mortality rate of 2.4% per year. In the validation cohort, 48 patients (18.7%) died during a median follow-up of 6.5 years (interquartile range 2.4–11.8 years), corresponding to an annualized mortality rate of 2.1% per year. In the control population, 38 patients (14.8%) died during a median follow-up of 6.1 years (interquartile range 3.0–12.7 years), corresponding to an annualized mortality rate of 1.6% per year. Compared to control, patients with ER had a significantly increased risk of total mortality (HR 1.49, 95% CI 1.05–2.12; $P = 0.03$) (Fig. 2). The presence of horizontal/downsloping ST segment conferred a significantly higher risk of total mortality compared to the control population without ER (HR 1.96; 95% CI: 1.40–2.75;

$P < 0.0001$), whereas upsloping ST segment was not associated with increased mortality (HR 1.24, 95% CI 0.93–1.64; $P = 0.14$) compared to control, consistent with previous reports.^{13,16}

Predictors of Death

By univariate analysis, variables associated with increased risk of death ($P < 0.2$) included older age, non-African American race, lower BMI, presence of diabetes, hypertension, and coronary artery disease, use of beta-blockers, ACEI/ARB and sulfonyleureas, higher heart rate, longer QTc interval, horizontal/downsloping ST segment, and higher amplitude of ER (Table 2). Of those variables, only seven were independently associated with increased mortality in multivariate analysis (Table 3), including age of ≥ 45 years, BMI < 25 kg/m², non-African American race, use of ACEI/ARB and sulfonyleureas, prolonged QTc interval (≥ 440 ms), and more prominent ER amplitude (≥ 0.15 mV). The ER amplitude by age or by race interaction was not significant, suggesting that the effect of ER amplitude on mortality was similar in the different age or race groups, respectively. Although horizontal ST segment was associated with total mortality in the univariate analysis (HR 1.75, 95% CI 1.20–2.55; $P = 0.004$), the significance was lost after adjustment for other covariates in the multivariate analysis. Of note, patients with horizontal ST segment were older compared to those with upsloping ST segment (52.8 ± 11.8 vs. 48.4 ± 12.0 , $P = 0.0001$). This may account for the lack of prognostic significance of ST segment pattern in the multivariate analysis.

The PI, derived by the weighed sum of the regression coefficients of each of the independent risk factors in the final model, was used to predict risk of death during follow up. By tertiles of predicted risk, median mortality rates sequentially increased from 1.3% per year in the low risk group, to 2.2% per year in the intermediate risk group and to 3.7% per year in the high-risk group in the derivation cohort (log rank $P < 0.0001$) and from 0.8% to 1.9% and to 4.1% in the low, intermediate, and high-risk groups in the validation cohort (log rank $P < 0.0001$), respectively (Table 4). The calibration of the model was good (goodness-of-fit test $P = 0.88$ and $P = 0.64$ for derivation and validation cohort, respectively). The discrimination of the model was very good and was slightly better in the derivation cohort (c-statistic = 0.85, 95% CI 0.79–0.90) com-

pared to the validation cohort (c-statistic = 0.80, 95% CI 0.69–0.89).

Simplified Scoring System

The points assigned to each of the final risk factors according to the simplified scoring system are shown in Table 3. Each patient was assigned a risk score by adding the points of each risk factor that was present. For example, a 40-year-old Caucasian male (1 point) with a BMI of 23 kg/m² (2 points), QTc of 460 ms (2 points), and a 0.2 mV J-point elevation (1 point) would have a risk score of 6 points, which would place him in the high-risk category, according to our risk scoring system. Risk scores ranged from 0 to 10 in the derivation cohort, with a mean score of 1.5 ± 0.8 points. Patients were divided into three risk categories of approximately equal size according to their risk score. During follow-up, the median annualized mortality rates in the derivation cohort ranged from 1.1% per year in the low risk category (0 to 2 points), to 2.1% per year in the intermediate risk category (3 to 4 points), to 3.8% per year in the high-risk category (≥ 5 points). A similar trend was seen in the validation cohort, with mortality ranging from 0.8% per year, to 1.8% per year, to 4.0% per year, in the low, intermediate, and high-risk categories, respectively (Table 4). The scoring system was well calibrated (goodness-of-fit $P = 0.54$ and $P = 0.64$ for derivation and validation cohort, respectively). The simplified scoring system demonstrated a good overall performance, with slightly better discrimination in the derivation cohort (c-statistic = 0.83, 95% CI 0.76–0.88) than in the validation cohort (c-statistic = 0.78, 95% CI 0.67–0.88). Kaplan-Meier survival curves in both the derivation and the validation cohort demonstrated significantly different survival rates for the three risk groups (Fig. 3). Importantly, the differences in survival among the three risk groups were evident within the first few years of follow up and persisted over the entire follow up period.

DISCUSSION

Accurate prediction of the risk of death in patients with ER is important in identifying those at high risk, who might benefit from further interventions. Currently, however, a reliable way to risk stratify these patients is lacking. Moreover, there is neither a reliable provocative drug testing to augment ER, nor any value in performing

Table 3. Independent Risk Factors of Total Mortality in the Derivation Cohort by Multivariate Analysis

Risk Factor	Hazard Ratio (95% Confidence Interval)	P-Value	Points
Age (years)			
<45	1.0		
45 to 64	2.36 (1.43 to 3.91)	0.0008	2
≥65	4.54 (2.52 to 8.19)	<0.0001	4
Body mass index (kg/m ²)			
≥25	1.0		
<25	1.90 (1.28 to 2.80)	0.001	2
Race			
African American	1.0		
Non-African American	1.66 (1.12 to 2.48)	0.013	1
ACEI/ARB use	1.82 (1.21 to 2.73)	0.004	1
Sulfonylurea use	1.84 (1.05 to 3.23)	0.034	1
QTc interval (ms)			
<440	1.0		
≥440	2.00 (1.16 to 3.42)	0.012	2
Early repolarization amplitude (mV)			
0.1 to 0.14	1.0		
≥0.15	1.51 (1.03 to 2.20)	0.033	1

Table 4. Validation of Prognostic Index: Mortality Rates in the Derivation and Validation Cohorts by Risk Group

Risk Group	Derivation Cohort Mortality Rate (% per Year)	Validation Cohort Mortality Rate (% per Year)
Prognostic Index (PI) by Cox Regression Model		
Low risk	1.3	0.8
Intermediate risk	2.2	1.9
High risk	3.7	4.1
C-statistic (95% CI)	0.85 (0.79 to 0.90)	0.80 (0.69 to 0.89)
Simplified Risk Score		
Low risk (0 to 2 points)	1.1	0.8
Intermediate risk (3 to 4 points)	2.1	2.0
High risk (≥5 points)	3.8	4.0
C-statistic	0.83 (0.76 to 0.88)	0.78 (0.67 to 0.88)

CI = confidence interval.

electrophysiologic studies.¹⁷ Based on seven easily available clinical and ECG parameters, the PI and simplified scoring system derived from our cohort of patients with ER, appears to accurately reflect the risk of death in this patient population. The discrimination of both the PI and the simplified scoring system, which reflects their ability to distinguish between patients at low and high risk, although not perfect, was very good, as indicated by the high values of the c-statistic. Of note, other risk stratification schemes with widespread use, such as the CHADS₂ score for prediction of thromboembolic events in patients with atrial fibrillation have a c-statistic of <0.7.¹⁸ Importantly, the predictive discrimination of our models was not com-

promised by overfitting, which occurs when the number of events in the derivation cohort is disproportionately small in relation to the number of candidate risk predictors. In line with previous recommendations on multivariate prognostic modeling, we did not examine more than 12 variables (10 events per variable) in the multivariate model.¹⁴ Although the PI performed slightly better compared to the simplified scoring system, the latter is much easier to calculate at the bedside.

Our study confirmed, in a large population of patients with ER, that this ECG finding (defined as J-point elevation rather than ST segment elevation) is associated with increased mortality. These findings are consistent with the results of two recent large

Figure 3. Kaplan-Meier curves for survival according to risk category based on the simplified risk scoring system in the derivation cohort (A) and validation cohort (B).

population-based studies.^{2,3} It has been suggested that the inconsistency in documenting the prognostic significance of ER between various population-based studies is a result of the differential definition of ER used in these studies.¹⁰ The studies that failed to show an association between ER and mortality focused on ST segment elevation rather than J waves.^{1,19} In contrast, studies that focused on J waves reported a significant association of ar-

hythmic death with ER.^{2,3,20,21} Our data support this notion. Moreover, our analysis revealed that the combination of J waves with horizontal or downsloping ST segment conferred a significant risk of death in our patient cohort, as previously shown in a population of middle-aged subjects¹³ and in patients with ER syndrome and idiopathic ventricular fibrillation.¹⁶ Similarly, ER with upsloping ST segment is probably a benign

variant. In our analysis, we modeled all-cause mortality rather than death from cardiac causes or arrhythmia, since this information was not available in our data set. However, two large community-based studies of ER found an association of ER pattern with all-cause mortality in the general population.^{2,3} Although initial case control studies suggested that the cause of death associated with ER is due to ventricular fibrillation,^{4,5} it is also possible that J-point elevation, which indicates transmural heterogeneity in ventricular repolarization, is a risk factor for fatal arrhythmias during cardiac ischemic events.³ The latter is supported by the fact that approximately 80% of SCDs are attributable to coronary artery disease, which is the main underlying disease primarily in the elderly, whereas SCD without underlying structural heart disease is more common in younger individuals.²² Our analysis, by showing that older age was a strong predictor of death in this population, further supports this notion.

A more prominent J-point elevation was predictive of the risk of death in our patient population. This finding is consistent with the results of a large population-based study,³ which showed that subjects with J-point elevation ≥ 0.2 mV in inferior leads had a higher risk of death from cardiac causes and a markedly elevated risk of death from arrhythmia, compared to those with J-point elevation ≥ 0.1 mV. Furthermore, experimental evidence supports the role of a more prominent J-point elevation in arrhythmogenesis. A net outward shift of current during phase 1 of the action potential leads to a marked abbreviation of the action potential in some epicardial cells but not others, creating a marked dispersion of repolarization within the epicardium, which in turn results in local re-excitation and phase 2 reentry.^{7,23} In addition, an often dramatic accentuation of J-point elevation before an arrhythmic episode was observed in patients with ER-related ventricular fibrillation, indicating the presence of a highly arrhythmogenic substrate.^{4,24} The same mechanism of arrhythmogenesis applies to the early phases of acute myocardial infarction, in which enhanced dispersion of repolarization and phase 2 reentry function as a substrate and trigger, respectively, for the development of ventricular fibrillation.^{6,25} Although the exact cause of death could not be determined in our patient population, it is reasonable to speculate that ischemic heart disease was the underline cause for

most of the deaths and that ER modified the risk for ventricular fibrillation in the context of an acute ischemic event. Recent data, indicating that ER is associated with ventricular fibrillation in patients with acute myocardial infarction,²⁶ support this hypothesis. A prospective study, where the cause of death is precisely defined and rigorously sought, is necessary to clarify the mechanistic link between ER and the increased risk of death.

Contrary to previous studies that suggested that the morphology²⁷ and location^{4,5} of ER pattern is predictive of the risk of death, we did not find such an association in our study. However, these studies included patients with idiopathic ventricular fibrillation and controls, rather than asymptomatic individuals with ER, as in our study. Moreover, the available prospective population-based studies^{2,3} showed that ER pattern in any lead was associated with an increased risk of death, although the association was stronger for ER pattern in the inferior leads. The significance of global J-point elevation, which was found to be associated with electrical storm in a previous study,²⁴ and theoretically represents a much more diffuse repolarization abnormality could not be assessed in our study, since none of our patients demonstrated this ECG pattern.

Prolonged QTc is a known risk factor of SCD in the general population.^{28,29} Consistent with these findings, we demonstrated that patients with prolonged QTc in the presence of ER have a higher risk of death. African American race exerted a protective effect. This finding is consistent with two recent population-based studies, which showed that, although ER is more prevalent in African Americans, it does not confer an increased risk of cardiovascular or arrhythmic death in this population.^{19,21} Differential distribution of genotypic variations, which are associated with a similar phenotype (ER pattern), between various racial groups may account for this effect. These data support the notion that ER in African Americans may be a more benign variant. Obesity was also independently associated with a lower risk of death in our study. Although the explanation for this observation is unclear, it should be noted that a similar paradoxical association among excess weight and mortality was shown for patients with chronic diseases such as coronary artery disease and heart failure.^{30,31} The association of use of ACEI/ARB and sulfonyleureas, respectively, with

total mortality in patients with ER was independent of the disease process for which they were prescribed. Although diabetes, hypertension, and coronary artery disease were associated with all-cause mortality in the univariate analysis, their effect became nonsignificant when examined in the presence of other factors in the multivariate analysis. Changes in the ionic currents activated during the early phases of the action potential, induced by these agents^{32,33} may explain, at least in part, these associations. This hypothesis requires further investigation.

Given that only approximately 10% of SCD patients have a high-risk profile, such as heart failure due to ischemic or nonischemic cardiomyopathy with low left ventricular ejection fraction, better screening methods are necessary to identify those individuals who are at risk in the general population, who represent, in absolute numbers, the largest group of patients with SCD.³⁴ Our results contribute to the global aim to recognize asymptomatic patients at risk, who may benefit from an intervention, including ICD implantation and/or pharmacologic treatment (e.g., with quinidine).¹¹ The important question is whether the mortality rate observed in the high-risk population in our study (approximately 4% per year) is sufficient to warrant prophylactic implantation of an ICD. For comparison, the annual (2007 estimate) all-cause mortality rate in men of age 35 to 74 years in the general population in the United States was 869 per 100,000.³⁵ It should be noted that the annual all-cause mortality rate in the high-risk population in our study was approximately half of that observed in the control group of primary prevention ICD trials in patients with heart failure.^{36,37} However, the mode of death in patients with heart failure varies from SCD due to malignant ventricular arrhythmias (for which ICD is effective) to progressive pump failure (for which ICD is not effective).³⁸ On the other hand, patients with ER-related death are expected to die predominantly of ventricular arrhythmias. Therefore, the relative benefit of an ICD and/or pharmacologic therapy in patients with high-risk ER might be comparable to that observed in patients with heart failure. A randomized clinical trial of ICD and/or pharmacologic therapy versus placebo in patients with high-risk features according to our risk stratification scheme may be indicated to provide a more definitive answer to this important issue.

Limitations

Our patient population consisted predominantly of middle-aged men. Therefore, caution is advised when extrapolating these results to younger age groups or to female patients. Moreover, our patient population was sampled from a hospital-based ECG database and thus may not be representative of the general population. Because our study consisted of existing data, details on family history of SCD and personal history of syncope were not always available. Potential association of these factors with ER-associated mortality was suggested by retrospective data.¹⁷ Further studies prospectively collecting information regarding these factors are very important to clarify their role in risk stratification in these patients. The inherent limitations of any observational study apply to our data. Although we used multivariate analysis to control for known confounders, we were not able to account for unknown confounders. However, we obtained a nearly unbiased internal assessment of the accuracy of our model using data-splitting, as previously described.¹⁴ Nonetheless, external validation of our model in an independent cohort of patients would be preferable.

CONCLUSIONS

Our risk score provides a potentially useful prognostic tool to estimate the risk of death in asymptomatic middle-aged men with ER and may be used clinically for risk stratification. The simplified risk score derived from seven easily available clinical and ECG variables had good discrimination and calibration, and was internally validated for its accuracy. These characteristics suggest that our risk score may be useful for guiding clinical care of these patients. Further studies are required to assess the efficacy of interventions based on risk stratification.

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