T-Wave Alternans and ST Depression Assessment Identifies Low Risk Individuals with Ischemic Cardiomyopathy in the Absence of Left Ventricular Hypertrophy

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Background: Although ECG left ventricular hypertrophy (LVH) by Cornell product (CP) predicts increased mortality in patients with ischemic cardiomyopathy (ICM), those without CP LVH remain at relatively high risk. We examined whether T-wave alternans (TWA) testing and ST depression can improve risk stratification in these patients.

Methods and Results: This study examined 317 patients with ICM, nonsustained ventricular tachycardia, and a resting ECG in sinus rhythm, who presented for electrophysiology and TWA testing, and potential implantable cardioverter defibrillator (ICD) implantation. LVH was defined by CP :[(R_{aVL} + S_{V3}) +6 mm in women] × QRS duration > 2440 mm * msec. ST depression was examined as a categorical variable using an established threshold of depression of ≥50 μV in V₅ or V₆. In Cox multivariate models, abnormal TWA testing and ST depression were independent predictors of mortality in patients without CP LVH (HR 2.52, CI 1.09–5.80, P = 0.030 and HR 2.87, CI 1.41–5.81, P = 0.004, respectively). Individuals with no LVH by CP, normal TWA, and no significant ST depression, comprised 23% of the study population and had a 5.6% 3-year mortality, compared to an overall 20% mortality.

Conclusions: TWA and ST depression testing are strong predictors of mortality among ICM patients without CP LVH, with normal testing conversely predicting low 3-year mortality. Thus, risk assessment with TWA testing and a resting ECG can identify ICM patients at low risk who may be less likely to benefit from ICD implantation.

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Patients with evidence of prior myocardial infarction and a decreased left ventricular ejection fraction (LVEF) are at an increased risk of ventricular arrhythmias and sudden cardiac death (SCD).^{1,2} Current guidelines recommend implantable cardioverter defibrillators (ICDs) for patients with a LVEF of ≤35% persisting after infarction or revascularization, for the primary prevention of SCD.³ However, only a minority of these high-risk individuals has an incident arrhythmia that triggers ICD therapy.^{4–6} This,

in conjunction with the risks and costs of ICD implantation, has led to efforts to better risk stratify this group.

The inexpensive and noninvasive surface electrocardiogram (ECG) has been implicated as a potentially important tool for guiding ICD implantation.^{7–11} Recently, our group demonstrated that ECG left ventricular hypertrophy (LVH), as defined by the Cornell Product (CP), can identify a group of individuals with ischemic cardiomyopathy (ICM) who are at an 81% increased

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risk of 3-year mortality, and thus may be more likely to benefit from ICD implantation.¹² However, patients without CP LVH had an unacceptably high 3-year mortality risk of 15%.¹² In a population based study, echocardiographic LVH has been shown to be an independent predictor of SCD among patients with coronary artery disease (CAD) regardless of whether or not systolic dysfunction is present.¹³ Both studies suggest that while LVH is an important predictor in ischemic cardiomyopathy, patients without LVH are still at substantial risk for arrhythmia and death. Subsequently, patients without CP LVH are not at sufficiently low risk to exclude potential benefit from ICD implantation, and thus require further risk stratification.

Although ST segment depression and microvolt T-wave alternans (MTWA) testing did not significantly predict mortality in the overall study population of patients with ICM in our previous study,¹² it is unclear if these metrics may be useful in the further risk stratification of the subset of patients with normal CP on their ECG. In this study, we conducted a retrospective analysis of patients with ICM presenting for risk stratification for potential ICD implantation, in order to assess whether MTWA and ST depression may be useful for the further risk stratification of the subset of individuals with no evidence of ECG LVH by CP criteria.

METHODS

Patients

The study population, inclusion criteria, and electrocardiography have been described previously.¹² Briefly, patients with evidence of CAD, a LVEF of $\leq 40\%$, and documented non-sustained ventricular tachycardia, who underwent invasive electrophysiology study (EPS) and MTWA testing via a right atrial stimulation protocol¹⁴ at our institution, were entered into a database and prospectively followed via query of the National Death Index. MTWA testing was performed using the spectral analysis algorithm on the CH2000 or HearTwave system (Cambridge Heart Inc., Bedford, MA, USA). Results were over-read by the attending physician using standard criteria¹⁵ and were classified as normal (no alternans) or abnormal (alternans present or indeterminate

results), based on studies that have suggested that patients with indeterminate and positive results have similar risk.^{9,10,15} ICD implantation was at the physician's discretion, and was generally EPS guided, as per usual practice during the study recruitment period. Patients with a history of sustained ventricular tachycardia or SCD were excluded.

Endpoints

The endpoint in this study was 3-year all-cause mortality, which was assessed via query of the National Death Index.

Electrocardiography

ECGs were obtained via electronic chart review. Patients were required to have a digital resting 12-lead ECG in sinus rhythm within the 30 days prior to EPS testing for inclusion. ECG measurements were determined using MUSE software (GE Healthcare, Milwaukee, WI, USA). LVH was defined by Cornell Product (CP): $[(R_{aVL} + S_{V3}) + 6 \text{ mm in women}] \times \text{QRS duration} > 2440 \text{ mm} \cdot \text{msec}$. Sokolow-Lyon voltage ($S_{V1} + R_{V5/V6} > 35 \text{ mm}$) was used for comparison. ST depression was defined as the maximum depression in either V5 or V6 at the midpoint of the ST segment. ST depression was examined as a categorical variable using the previously established partition of depression $\geq 50 \mu\text{V}$.¹⁶ The presence of left or right bundle branch block was noted. All ECG variables were coded by a physician blinded to patient outcomes.

Statistical Analysis

All statistical analyses were performed using SPSS, Version 17.0 (SPSS Inc., Chicago, IL, USA). Baseline characteristics of patients were examined after patients were divided into 4 groups based on the results of MTWA testing (normal vs. abnormal) and the presence or absence of ST depression. Data are presented as mean $\pm$ 1SD for continuous variables and as proportions for categorical variables. Differences among proportions were assessed using Fisher's exact test and differences in mean values were compared with 2-way ANOVA.

Kaplan-Meier curves, stratified by MTWA results and/or ST depression, were constructed to compare event rates in different subgroups. Differences in event rates were assessed using log rank testing. The relationship of the various

covariates to risk of 3-year mortality was assessed using Cox proportional hazards models. Forward stepwise multivariate Cox analyses were performed to assess if covariates had independent predictive value. In addition to ST depression and MTWA, multivariate analyses included age, sex, LVEF, EPS results, and ACE/ARB use, because these variables have been implicated as predictors of mortality in either this or other similar study populations. In subgroups where ST depression and MTWA results had predictive value, similar univariate and multivariate analyses were conducted using a 4-way variable, instead of the two individual variables, to assess the hazards associated with the different combinations of ST segment and MTWA testing abnormalities. Interactions between CP LVH and ST depression, and CP LVH and MTWA results, were formally tested by adding cross-product terms to models of the entire study population. For all tests, a P-value of <0.05 was required for statistical significance.

RESULTS

Three hundred and seventeen patients met the study criteria. Of these patients, 34% (109/317) had CP LVH, 66% (209/317) had abnormal MTWA testing, and 24% (77/317) had ST depression $\geq 50\mu V$. Three-year mortality was 20% (64/317). The potential interaction between the presence or absence of CP LVH and the ability of ST depression and MTWA to predict 3-year mortality was formally tested using cross-product terms in models of the entire study population. Testing demonstrated that both ST depression and MTWA significantly interact with CP LVH ($P = 0.003$ and $P = 0.001$, respectively), suggesting it is statistically valid to divide the overall population based on CP LVH for further analysis of the predictive values of MTWA and ST depression.

The overall study population was divided into four groups based on the presence of ST depression and abnormal MTWA testing, and the clinical characteristics of these groups are described in Table 1. Individuals with ST depression were more likely to be older, have a longer QRSd, a LBBB, and LVH by Sokolow-Lyon and CP criteria. Individuals with abnormal MTWA testing were more likely to be older, have a more reduced LVEF, a longer QRSd, a LBBB, be inducible during EPS, have an

ICD, use diuretics, and have LVH as defined by Sokolow-Lyon and CP criteria.

Since MTWA testing and ST depression significantly interact with CP LVH, univariate Cox models were created to assess whether these covariates performed better in the presence or absence of CP LVH (Table 2). ST depression and abnormal MTWA were significant univariate predictors among patients without CP LVH, with both markers predicting an approximately 3-fold increase in mortality. Among patients with CP LVH, ST depression was not a significant predictor of events and surprisingly abnormal MTWA testing predicted a 55% reduction in 3-year mortality. QRSd, QTc, LBBB, RBBB, and ICD implantation were also tested in patients with and without CP LVH, but were not significant univariate predictors in either population (data not shown). Since it is possible that the predictive value of ST depression and MTWA could vary based on the presence or absence of an ICD, we assessed for an interaction by using cross-product terms in models of the population of patients without LVH; no interaction was present.

Kaplan-Meier hazard curves were constructed for patients with and without CP LVH, when stratified by the presence of ST depression or MTWA abnormalities (Fig. 1). Log-rank testing demonstrates that when stratifying by the presence of ST depression, there is a significant difference in the mortality rate among those without CP LVH, though no difference was detected among patients with CP LVH ($P = 0.001$ vs. $P = 0.254$). When stratifying by the presence of abnormal MTWA testing, log rank testing demonstrates significant differences in mortality in patients with and without CP LVH ($P = 0.029$ and $P = 0.013$, respectively), with abnormal results predicting higher mortality in patients without CP LVH, but lower mortality in patients with CP LVH.

Independent predictors of mortality in patients with and without CP LVH were determined using a forward stepwise multivariate Cox analysis including MTWA results, ST depression, age, sex, ACE/ARB use, LVEF, and EPS inducibility (Table 2). Among patients with CP LVH, only ACE/ARB use entered into the multivariate model and its use predicted a 72% decrease in 3-year mortality. Among patients without CP LVH, only abnormal MTWA testing and ST depression entered into the multivariate model, with abnormal MTWA results predicting a 2.5-fold increased

Table 1. Characteristics of All Patients in Sinus Rhythm (n = 317), Stratified by MTWA Results and Presence or Absence of ST Depression

	ST Depression <50 μ V		ST Depression $\geq$ 50 μ V		P Value	
	MTWA- (n = 89)	MTWA+ (n = 151)	MTWA- (n = 19)	MTWA+ (n = 58)	ST Dep +	MTWA
Age	63.8 $\pm$ 12.4	65.9 $\pm$ 11.0	65.8 $\pm$ 12.6	72.7 $\pm$ 9.7	0.008	0.008
Sex, % female	21.3	17.9	5.3	17.2	0.396	0.878
LVEF, %	32.1 $\pm$ 7.2	28.7 $\pm$ 8.4	29.5 $\pm$ 7.2	27.3 $\pm$ 8.0	0.093	0.018
Heart rate	75.3 $\pm$ 13.0	72.2 $\pm$ 13.2	73.8 $\pm$ 12.9	73.7 $\pm$ 13.7	0.989	0.398
QTc, ms	440.2 $\pm$ 37.6	450.8 $\pm$ 37.5	452.7 $\pm$ 46.1	457.9 $\pm$ 38.4	0.085	0.167
QRSd, ms	100.4 $\pm$ 19.6	108.1 $\pm$ 24.5	114.2 $\pm$ 28.6	124.3 $\pm$ 27.5	<0.001	0.010
LBBB, %	3.4	7.9	10.5	24.1	0.001	0.028
RBBB, %	5.6	6.0	5.3	10.3	0.303	0.643
EPS inducible, %	41.6	53.0	31.6	63.8	0.297	0.007
Implanted ICD, %	48.3	61.6	47.4	70.7	0.232	0.008
Sokolow-Lyon LVH, %	4.5	7.3	10.5	32.8	<0.001	0.024
CP LVH, %	19.1	32.5	42.1	60.3	<0.001	0.003
β -Blocker, %	89.9	86.1	73.7	81.0	0.093	0.618
CCB, %	15.7	10.6	26.3	15.5	0.255	0.175
ACE/ARB, %	58.4	66.9	68.4	77.6	0.071	0.102
Nitrate, %	29.2	27.2	31.6	32.8	0.472	0.896
Diuretics, %	40.4	59.6	47.4	56.9	0.794	0.004
Digoxin, %	21.3	19.9	21.1	34.5	0.062	0.674
ASA, %	83.1	81.5	94.7	87.9	0.153	0.748
Aldactone, %	6.7	13.2	15.8	8.6	1.000	0.444
Clopidogrel, %	32.6	33.1	63.2	34.5	0.172	0.457
Statin, %	53.9	57.0	52.6	67.2	0.236	0.338

Table 2. Univariate and Multivariate Predictors of 3-Year Mortality in Patients with and without CP LVH

	LVH (n = 109)				No LVH (n = 208)		
	HR	95% CI	P Value		HR	95% CI	P Value
Univariate predictors							
MTWA+	0.45	0.21–0.94	0.034	ST Dep +	3.13	1.55–6.32	0.002
ACE/ARB	0.28	0.13–0.57	<0.001	MTWA +	2.74	1.19–6.30	0.017
Multivariate predictors							
ACE/ARB	0.28	0.13–0.57	<0.001	ST Dep +	2.87	1.41–5.81	0.004
				MTWA +	2.52	1.09–5.80	0.030

STDep – = ST depression < 50 μ V; STDep + = ST depression $\geq$ 50 μ V; MTWA – = normal MTWA testing; MTWA + = abnormal MTWA testing. Covariates tested as potential univariate predictors: MTWA results, ST depression $\geq$ 50 μ V, QRSd, QTc, ICD. Covariates tested for inclusion in the multivariate model: age, sex, ACE/ARB use, MTWA testing, ST depression $\geq$ 50 μ V, LVEF, EPS inducibility.

risk of 3-year mortality and ST depression predicting a nearly 2.9-fold increased risk of 3-year mortality.

Because both ST depression and MTWA independently predict mortality in patients without CP LVH, we created a 4-way variable incorporating MTWA and ST depression testing to further explore the utility in combining both these variables in the risk stratification of these patients. When entered into a univariate Cox model, the additive

prognostic value of these two variables is evident (see Table 3). Compared to patients with normal MTWA testing and no significant ST depression, patients with abnormal MTWA testing and no ST depression had a 3.4-fold increased risk of 3-year mortality, those with ST depression and normal MTWA testing a 5.8-fold increased risk, and those with ST depression and abnormal MTWA a 8.2-fold increased risk of 3-year mortality. When this 4-way variable replaces MTWA testing and

Figure 1. Kaplan-Meier hazard curves comparing cumulative mortality between patients with and without CP LVH, when stratified by either MTWA test results or ST depression. (A), Patients with CP LVH, stratified by ST depression (B), patients without CP LVH, stratified by ST depression (C), patients with CP LVH, stratified by MTWA results (D), patients without CP LVH, stratified by MTWA results. STDep – = ST depression < 50 μ V; STDep + = ST depression $\geq$ 50 μ V; MTWA – = normal MTWA testing; MTWA + = abnormal MTWA testing.

ST depression in a forward stepwise multivariate analysis including age, sex, LVEF, ACE/ARB use, and EPS inducibility, it emerges as the only independent predictor of 3-year mortality, and the hazard ratios, confidence intervals, and P-values remain unchanged from the univariate analysis (Table 3).

A Kaplan-Meier hazard curve comparing event rates of patients without CP LVH when divided into subgroups based upon results of MTWA testing and presence of ST depression (Fig. 2), demonstrates the overall plot is statistically significant ($P < 0.001$). Of note, individuals with normal MTWA and no ST depression had a 5.6%

Table 3. Univariate and Multivariate Models* for a 4-Way Variable Describing MTWA Test Results and Presence of Absence of ST Depression in Patients without CP LVH

	HR	95% CI	P Value
STDep-/MTWA- (n = 72)	1.00	—	—
STDep-/MTWA+ (n = 102)	3.43	1.16–10.13	0.026
STDep+/MTWA- (n = 11)	5.82	1.30–25.98	0.021
STDep+/MTWA+ (n = 23)	8.20	2.52–26.64	<0.001

*The hazard ratios, confidence intervals, and P-values for the univariate and multivariate models are identical. STDep - = ST depression < 50μV; STDep + = ST depression ≥ 50μV; MTWA - = normal MTWA testing, MTWA + = abnormal MTWA testing. Covariates tested for inclusion in the multivariate model: age, sex, ACE/ARB use, MTWA testing, ST depression ≥ 50μV, LVEF, EPS inducibility.

Figure 2. Kaplan-Meier hazard curve depicting cumulative mortality of patients without CP LVH, when stratified into groups based on the results of MTWA testing and the presence or absence of ST depression. STDep - = ST depression < 50 μV; STDep + = ST depression ≥ 50 μV; MTWA - = normal MTWA testing; MTWA + = abnormal MTWA testing.

3-year mortality, which is significantly less than all other groups. Furthermore, this low risk group comprises 23% of the original 317 patients who met study criteria.

Patients with LBBB and RBBB typically have abnormal patterns of repolarization and as such we performed additional sensitivity analyses to assess the performance of ST depression and MTWA in the population of patients without

bundle branch block or ECG LVH. In univariate analyses, both MTWA (HR 3.60, CI 1.37–9.43, P = 0.009) and ST depression (HR 2.71, CI 1.24–5.96, P = 0.013) remain robust predictors of 3-year mortality. After multivariate adjustment, MTWA remained a significant predictor of 3-year mortality (HR 3.01, CI 1.14–7.93, P = 0.026) and ST depression only trended towards significance (P = 0.109), though this may be related to a reduction in the power associated with exclusion of 28 patients from a relatively small study population (n = 208).

Previous work^{17,18} has suggested that the utility of MTWA testing may be reduced among individuals with a prolonged QRS. As such, we performed additional analyses of the entire study population (n = 317) to compare QRS duration and CP LVH in the identification of the subset of patients in whom MTWA may be most useful. When assessing the interaction between QRS duration and MTWA in the prediction of 3-year mortality, neither QRS as a continuous variable nor QRS as a categorical variable with a 120ms partition demonstrated a significant (P < 0.05) interaction. In contrast, CP LVH and MTWA demonstrated as highly significant interaction (P = 0.001). Similarly, ST depression did not significantly interact with QRS duration as a continuous or categorical variable, though there was a significant interaction with CP LVH (P = 0.003).

DISCUSSION

This study demonstrates that MTWA testing and ST depression are independent predictors of 3-year mortality in ICM patients without ECG evidence of CP LVH. These markers of elevated risk have the potential to improve the risk stratification of patients with ICM and potentially guide a more targeted approach to ICD implantation. However, MTWA testing and ST depression were not independent predictors of 3-year mortality in patients with CP LVH.

The association between LVH and the predictive value of ST depression and TWA finding is especially relevant in the risk stratification of patients with ICM, because in this study population, patients with CP LVH have a high rate of abnormal MTWA testing (77%) and ST depression (39%), accounting for a large percentage of the patients in the overall population with

abnormal MTWA testing and ST depression (40% and 56%, respectively). Thus, MTWA testing and assessment of ST depression in LVH patients may not facilitate improved risk stratification, and furthermore, inclusion of these patients in analyses assessing the utility of these metrics may underestimate the ability of MTWA and ST depression to risk stratify in other subgroups of patients with ICM (i.e., those without LVH).

When combined with our prior work on CP LVH,¹² the results from this study suggest a potential risk stratification method involving sequential testing (Fig. 3). Using this approach, all patients would initially have a resting ECG for CP LVH screening. Patients with LVH would be considered for ICD implantation, and patients without LVH would undergo further stratification via measurement of ST depression. Since there is not a significant difference in survival between patients with both abnormal MTWA testing and ST depression and those with ST depression alone (based on life table analysis, data not shown), only patients without both ST depression and LVH would require MTWA testing. This approach would maximize the utility of the nearly universally used resting ECG, and reserve MTWA testing for patients in whom it has prognostic value (i.e., those without LVH) and in whom the results might change management (i.e. those without both ST depression and CP LVH). Perhaps most importantly, this approach is able to select a sizeable subset (23%) of the overall high-risk population with a <2% annual mortality during 3-years of follow-up, thus identifying a group that may be less likely to benefit from ICD implantation.

The finding that MTWA predicted improved outcomes among LVH patients in a univariate but not multivariate model may be related to the fact that 73% of patients with abnormal MTWA testing were on an ACE or ARB compared to only 56% of patients with normal MTWA testing. This association is likely to be related to chance and is not statistically significant ($P = 0.115$).

Repolarization Abnormalities and LVH

The increased prevalence of abnormal repolarization in patients with LVH has been described previously. Studies have demonstrated that QTc prolongation,^{19,20} QT dispersion,¹⁹ and novel T-wave abnormality indices²⁰ are related

to echocardiographic LVH in hypertensive individuals; that ST depression is more common among patients with echocardiographic LVH in a high risk population of Native Americans²¹; and that abnormal MTWA testing is correlated with increased LVM in patients when LVH is attributed to arterial hypertension,^{22,23} hypertrophic obstructive cardiomyopathy,²³ or CAD.²⁴ Studies have assessed the ability of repolarization measures to predict mortality in patients with LVH defined by varying methods. QTc prolongation is associated with increased all-cause mortality²⁵ and LV strain is associated with increased cardiovascular mortality²⁶ in individuals with hypertensive ECG LVH. Quantitative ST depression is associated with increased mortality in American Indians with echocardiographic evidence of LVH; the relative prognostic ability of ST depression in individuals with and without LVH was not directly assessed.²¹ However, since the etiology of hypertrophy in most of these studies differs from our study population, caution must be taken when generalizing these results. A study by Narayan and colleagues²⁴ found that in patients with CAD and echocardiographic evidence of LVH, the association between abnormal MTWA testing and the combined endpoint of arrhythmia and mortality demonstrated only a trend towards significance. Given the small study size ($n = 28$) and lack of head to head comparison with patients without LVH, it is difficult to interpret these results and compare them with those from this study.

Prior studies have demonstrated that MTWA testing has poor discriminative ability among patients with a prolonged QRSd^{17,18}; this is of potential relevance to the current study because of the relationship between QRSd and CP LVH. Interestingly, when interaction terms were calculated for QRSd and ST depression or MTWA in this study population, all terms were nonsignificant ($P > 0.05$), whether QRSd was considered as a continuous or categorical variable using a 120ms partition value. This suggests that CP LVH is more appropriate than QRSd for identifying a subset of ICM patients whom may benefit from ST depression and MTWA testing.

Prior studies evaluating MTWA have yielded results both for^{10,27-29} and against^{30,31} its use in the risk stratification of patients with ICM. Explanations for these conflicting data have largely centered on the prevalence of ICDs in the study

Figure 3. A sequential approach to risk stratification of ICM patients using the 12-lead ECG and MTWA testing. Mortality data regarding patients with CP LVH was adapted from prior work by our group.¹²

population, as well as the nonequivalence of SCD and the commonly used endpoint of sustained ventricular arrhythmias.³² Though it is purely speculative, it is interesting to consider that these varying outcomes may also be in part due to a varying prevalence of LVH in the individual study populations.

It is not immediately clear why MTWA and ST depression are only independent predictors of mortality in patients with ICM and no ECG evidence of LVH, when repolarization abnormalities have been shown to have predictive value in patients with other types of LVH. MTWA has been proposed as a potentially useful tool for risk stratification because it is believed to detect a pro-arrhythmic disposition by measuring repolarization heterogeneity. These abnormalities are related to abnormal cardiac myocyte calcium cycling due to impaired sarcoplasmic reticulum calcium reuptake.³² This abnormality of calcium handling is thought to amplify preexisting heterogeneity in repolarization leading to areas of conduction block predisposing to monomorphic

ventricular tachycardia or ventricular fibrillation in the presence of scar or a prolongation of the QT interval, respectively. ST depression is related to chronic subendocardial ischemia, which is also thought to be pro-arrhythmic.

Why are MTWA and ST depression poor predictors among patients with ICM and LVH when they theoretically should reflect a pro-arrhythmic disposition? An incident ventricular arrhythmia is the result of a combination of an anatomic/functional substrate (i.e., coronary artery disease, hypertrophy with resulting fibrosis), a transient initiating event (ischemia, drugs, metabolic abnormalities, stretch), and a mechanism of arrhythmia (i.e., reentry circuit, automaticity, triggered activity, and block/cell-to-cell uncoupling).³³ Furthermore, hypertrophied myocardium is known to have many electrophysiological abnormalities thought to predispose towards ventricular arrhythmias, including conduction disturbances, repolarization abnormalities, fibrosis, and increased risk of ischemia.³⁴ Though the combination of ICM and

LVH leads to a multitude of *potential* mechanisms for arrhythmogenesis, it does not necessarily follow that all potential combinations occur and are clinically important. It is possible that while highly prevalent among ICM patients with LVH, subendocardial ischemia (as indicated by ST depression) and repolarization heterogeneity (as measured by MTWA) are not commonly involved in arrhythmogenesis in this specific population.

There are other potential explanations for why ST depression and MTWA are poor prognostic indicators among patients with ICM and LVH. The high prevalence of ST depression and MTWA in patients with CP LVH may also be a factor, because predictors of disease tend to lose their discriminative power if they are highly prevalent in a population. Thus, the repolarization properties of individuals with CP LVH may need to be evaluated differently than that of individuals without CP LVH, perhaps by using different partition values to define "abnormal." It is unclear if the relationship between ST depression and MTWA and ICM LVH reported in this study represents a dictum regarding repolarization abnormalities and ICM LVH (i.e., measures of abnormal repolarization only have predictive value among those without ECG LVH), or simply two independent observations. Studies of other measures of repolarization, including principle component analysis and T-wave residual, are warranted to test this hypothesis.

Study Limitations

This study is a retrospective analysis of a cohort of patients with ICM who presented to our institution for risk stratification for potential ICD placement and was not designed to detect the predictive value of MTWA and ST depression in patients with normal LV mass. ICD implantation was nonrandomized and was at the treating physician's discretion. Since ICD implantation was generally EPS guided during the enrollment period, EPS results and ICD implantation were highly correlated. MTWA testing in this study was conducted via right atrial pacing and not via the more commonly used exercise protocol. However, studies have suggested that the results from both methods are generally concordant.^{35,36}

CONCLUSIONS

This study demonstrates that ST depression and TWA are independent predictors of mortality in patients with ICM without CP LVH making these metrics important tools in the risk stratification of patients with ICM. However, these repolarization measures are not independent predictors of mortality in ICM patients with CP LVH. Individuals with ICM, without ECG LVH, with no significant ST depression, and normal MTWA testing, have a relatively low 3-year mortality and thus may be less likely to benefit from ICD implantation. Additional study is required to determine the warranty period of a normal ECG and MTWA in these patients and whether repeat testing at 3-year or greater intervals will be required to adequately assess potential change in risk in the ICM population. Future studies are needed to assess whether novel T-wave morphology markers (i.e., principle component analysis and T-wave residual) may allow for further risk stratification of patients with and without CP LVH.

DISCLOSURES

Drs. Bender, Friedman, and Lerman have no disclosures. Dr. Markowitz has received honoraria from Medtronic, Boston Scientific, St. Jude Medical, and Biotronik. Dr. Okin serves on a medical advisory board for GE Medical Systems, Inc. and serves as a consultant for and receives grant support from Novartis Pharmaceuticals.

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