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Relationships between the T-peak to T-end interval, ventricular tachyarrhythmia, and death in left ventricular systolic dysfunction

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Aims The interval between the T-wave's peak and end (Tpe), an electrocardiographic (ECG) index of ventricular repolarization, has been proposed as an indicator of arrhythmic risk. We aimed to clarify the clinical usefulness of Tpe for risk stratification.

Methods and results We evaluated 327 patients with left ventricular ejection fraction (LVEF) $\leq$35% (75% male, LVEF 23 $\pm$ 7%). All patients had an implanted implantable cardioverter-defibrillator (ICD). Clinical data and ECGs were analysed at baseline. Prospective follow-up for the endpoints of appropriate ICD therapy and mortality was conducted via periodic device interrogation, chart review, and the Social Security Death Index. During device clinic follow-up of 17 $\pm$ 12 months, 59 (18%) patients had appropriate ICD therapy, and during mortality follow-up of 30 $\pm$ 13 months, 67 (21%) patients died. A longer Tpe_c predicted appropriate ICD therapy, death, and the combination of appropriate ICD therapy or death ($P < 0.01$ for each endpoint). On multivariable analysis correcting for other univariable predictors, Tpe_c remained predictive of ICD therapy [hazard ratio (HR) per 10 ms increase: 1.16, $P = 0.02$], all-cause mortality (HR per 10 ms: 1.14, $P = 0.03$), and the composite endpoint of ICD therapy or death (HR per 10 ms: 1.16, $P < 0.01$).

Conclusions In patients with left ventricular systolic dysfunction and an implanted ICD, Tpe_c independently predicts both ventricular tachyarrhythmia and overall mortality.

Keywords Risk stratification • Ventricular tachyarrhythmia • Electrocardiography • Death

Introduction

Sudden cardiac arrest often can be attributed to reentrant ventricular tachyarrhythmias. Since one of the requirements of reentry is local dispersion of myocardial repolarization, it is reasonable to expect that an increase in total ventricular dispersion of repolarization (DVR) may predispose patients to ventricular tachyarrhythmia and cardiac arrest. Various surface electrocardiogram (ECG) markers of DVR, including QT_c, Q-T_{peak} (QTp), and T_{peak}–T_{end} (Tpe), have been proposed as predictors of risk for ventricular arrhythmia.

In particular, Tpe has attracted increased attention in recent years. It has been shown to be a measure of transmural dispersion of repolarization (TDR) in various experimental models and computer simulations.[1–3] In intact mammalian hearts, thorough electroanatomic mapping of monophasic action potentials has shown Tpe to correlate closely with overall ventricular repolarization dispersion (DVR_{total}).[4–7] Tpe also has been shown to correlate with inducibility at electrophysiology study in investigations of small human populations.[8,9] In a retrospective case–control analysis of the Oregon Sudden Unexpected Death Study, prolongation of Tpe was associated with sudden cardiac death.[10] The true clinical

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utility of Tpe for prospective risk stratification for ventricular tachyarrhythmic events and mortality is still in question.

Patients with cardiomyopathy (CM) are at high risk of sudden cardiac arrest due to ventricular tachyarrhythmia. While several large-scale clinical trials have shown implantable cardioverter-defibrillators (ICDs) to be lifesaving in this population, only a minority of such patients with ICDs ultimately receive appropriate ICD therapy.[11–14] Thus, further risk stratification within this high-risk population would be of clinical value.

The purpose of this study was to assess whether surface ECG indices of ventricular repolarization could risk-stratify patients with CM and an implanted ICD for the endpoints of appropriate ICD therapy and mortality.

Methods

The study complied with the Declaration of Helsinki and was approved by the Ochsner Medical Center institutional review committee. The subjects were drawn from the patient population of the Ochsner Health System hospitals in southeastern Louisiana. We queried our electronic medical record for patients with an implanted ICD and left ventricular ejection fraction (LVEF) $\leq$35% as determined by echocardiography, angiography, or radionucleotide scanning. Inclusion in the study also required the availability of a non-paced standard surface 12-lead ECG recorded at the beginning of follow-up. All ECGs were recorded using a General Electric MAC 5000 (GE Healthcare, Milwaukee, WI, USA).

Demographic data including age, sex, and race were obtained by querying the medical record. Clinical data including blood pressure, body mass index (BMI), smoking status, prior sustained ventricular tachyarrhythmia, diabetes, atrial fibrillation, New York Heart Association (NYHA) heart failure class, laboratory data, and medication use were assessed at baseline. Cardiomyopathy was classified as ischaemic in origin based on a history of coronary revascularization (either percutaneous or surgical), documented prior myocardial infarction, or coronary stenosis $\geq$70% on angiogram. If none of these criteria was present, the cardiomyopathy was classified as non-ischaemic.

Electrocardiogram analysis

Automated electrocardiographic analysis of the baseline ECG was performed at a central laboratory (GE Healthcare, Wauwatosa, WI, USA) using the commercially available GE Healthcare Marquette 12SL ECG analysis program, which uses validated algorithms for measurement as previously reported.[15,16] Prior investigations by other authors have utilized widely varying methodologies for measurement of Tpe. No standard method has been established. The majority of prior publications describe manual measurements that vary in terms of ECG leads used, in the means of determining the peak and end of the T-wave, and whether or not some combination of leads is 'averaged' in any way. Briefly, the GE 12SL software uses the vector magnitude of all 12 leads to determine the onset and offset of the QRS complex as well as the offset of the T-wave. In contrast, because the precordial leads allow optimal morphological measurement of the T-wave and because the timing of the T-wave's peak often differs from lead to lead, the GE 12SL analysis package identifies the T-wave's peak (Tp) in leads V_2–V_5 individually, and these values are averaged to obtain the global Tp. This process minimizes the effect of variation in precordial electrode placement on the measurement of Tp. Using this methodology, the relative mean difference between successive measurements of Tpe in the same patient has been shown to be 5.1%.[17] A random sample of the automatic ECG readings was manually checked, and no change to any measurement was required.

Bazett's formula ($n/\sqrt{RR}$) was applied to the QT, Q-Tp, and Tpe intervals to find QT_c, QTp_c, and Tpe_c, respectively.[18] The corrected intervals are expressed in the same units as the original parameters, as recommended by Molnar *et al.*[19] Because there is some uncertainty in the literature regarding whether Tpe is rate-dependent, both Tpe and Tpe_c were evaluated. Left bundle branch block (LBBB) was classified according to Minnesota Code criteria.[20]

Follow-up

Prospective follow-up for appropriate ICD therapy was conducted via periodic device interrogation. Device programming was at the discretion of the treating physician. A physician blinded to other clinical data reviewed all ICD therapy events. Inappropriate ICD therapies, such as those delivered for supraventricular tachyarrhythmia or oversensing, were not scored as events.

Follow-up for mortality was conducted via chart review and query of the Social Security Death Index (SSDI).

Data analysis

Categorical variables are expressed as *n* (%), and continuous variables are expressed as mean $\pm$ SD. In all analyses, two-sided $P \leq 0.05$ was considered significant. The normality of variables' distributions was verified using histograms and Q–Q plots.

All analyses were performed using SPSS Version 16.0 (SPSS Inc., Chicago, IL, USA). Associations between measured variables and each endpoint were assessed using Cox proportional hazard models. Because different modes of follow-up were used for the two endpoints, event rates were first analysed separately for each endpoint. For patients without an event, the date of the last ICD clinic visit was used as the end of follow-up for the endpoint of appropriate ICD therapy, and the date of SSDI search was used as the end of follow-up regarding mortality. The relationships between variables and outcomes are expressed as hazard ratios (HR), with aggregate risk per 5-unit or 10-unit step calculated when appropriate. Graphs depicting event-free follow-up were constructed using the Kaplan–Meier method, stratified by tertiles of the predictor variable as recommended by Altman.[21] The log-rank statistic was used to compare these curves.

To minimize the effect of disparate follow-up duration for the two endpoints, assessment of the combined endpoint of ventricular tachycardia/ventricular fibrillation (VT/VF) or death was limited to 2 years. This combined endpoint was assessed in additional Cox and Kaplan–Meier analyses.

For each endpoint, significant variables were then assessed in stepwise multivariable Cox models, using $P < 0.05$ for entry into the model and $P > 0.1$ for variable removal. Receiver-operator curve (ROC) analysis was used to determine the cut-off value of Tpe with the best clinical predictive value.

Results

Our search identified 327 patients who met the inclusion criteria. Their baseline demographic and clinical data are presented in *Table 1*.

The date of first follow-up ranged from January 2006 to March 2009. During subsequent device clinic follow-up over 17 $\pm$ 12 months [median: 13 months, interquartile range (IQR): 5–25 months], 59 (18%) patients had at least one appropriate ICD

Table 1 Baseline demographic and clinical features of the study population ($n = 327$)

Age (years)	**67 ± 11**
Sex, male	244 (75%)
Currently smoking	37 (11%)
Race, non-black	244 (76%)
Ischemic cardiomyopathy	277 (85%)
History of sustained VT/VF	22 (7%)
History of diabetes mellitus	127 (39%)
History of atrial fibrillation	83 (25%)
NYHA class	
1	37 (14%)
2	107 (39%)
3	124 (46%)
4	4 (2%)
BMI (kg/m^2)	29 ± 6
Systolic BP (mmHg)	121 ± 18
Diastolic BP (mmHg)	70 ± 11
Heart rate (bpm)	71 ± 14
LVEF (%)	23 ± 7
BUN (mg/dl)	26 ± 16
CrCl (ml/min)	69 ± 33
Beta-blocker	302 (92%)
Calcium channel blocker	25 (8%)
ACEi/ARB	256 (78%)
Amiodarone	48 (15%)
Aspirin	248 (76%)
Aldosterone blocker	97 (30%)
Clopidogrel	110 (34%)
Diuretic	229 (70%)
Hydralazine	18 (6%)
Statin	270 (83%)
Nitrate	60 (18%)
Antihyperlipidemic	59 (18%)
Tpe (ms)	100 ± 20
Tpe$_c$ (ms)	108 ± 23
QT$_c$ (ms)	460 ± 38
QTp (ms)	328 ± 43
QTp$_c$ (ms)	353 ± 34
QRS duration (ms)	120 ± 28
LBBB	62 (19%)
Cornell voltage (mV)	17 ± 11
Sokolow–Lyon voltage (mV)	16 ± 11

ACEi/ARB, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CrCl, creatinine clearance; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VT/VF, ventricular tachycardia/ventricular fibrillation.

therapy (50 patients had VT only, 8 had both VT and VF, and 1 had VF only), with the first therapy occurring at an average of 10 ± 9 months (median: 7 months, IQR 4–15 months) into follow-up. The total of 388 VT events were treated as follows: antitachycardia pacing (ATP) in 312 (81%), high-voltage shock in 37 (10%), and both ATP and shock in 39 (10%). All 13 VF events were treated with high-voltage shocks.

There were 67 (21%) deaths, occurring over a mean mortality follow-up of 30 ± 13 months (median: 29 months, IQR 19–44 months). Of these, 15 (22%) previously had received appropriate therapy for ventricular tachyarrhythmia.

Univariable analysis

The results of univariable analysis are summarized in *Table 2*. In univariable Cox models, Tpe, Tpe$_c$, QT$_c$, sex, prior VT/VF, diabetes, heart rate, and Cornell voltage were predictors of appropriate ICD therapy. Age, aetiology of cardiomyopathy, history of atrial fibrillation, LVEF, BMI, systolic or diastolic blood pressure (BP), smoking status, NYHA class, renal function, the use of a variety of medications, QTp, QTp$_c$, QRS duration, LBBB, and Sokolow–Lyon voltage did not predict appropriate ICD therapy (all $P > 0.05$).

Each 10-ms increase in Tpe was associated with a 14% increase in risk for ventricular tachyarrhythmia (HR 1.14 [95% confidence interval: 1.01–1.30], $P = 0.04$), and Tpe$_c$ seemed to be an even more powerful predictor (HR per 10 ms increase: 1.21 [1.07–1.36], $P < 0.01$). As seen in *Figure 1*, patients in the lowest tertile of Tpe$_c$ (<98.5 ms) had significantly less VT/VF compared with those in tertiles 2 and 3 (98.5–116.2 and >116.2 ms, respectively). Tertiles 2 and 3 had similar event rates. The 2-year ventricular tachyarrhythmia event rate was 8% for those in the lowest tertile of Tpe$_c$, and 33 and 35% for those in tertiles 2 and 3, respectively.

In univariable Cox models, Tpe, Tpe$_c$, QT$_c$, diastolic BP, age, blood urea nitrogen (BUN), creatinine clearance, NYHA class, use of diuretics and/or hydralazine, and lack of statin use were predictors of death. Each 10-ms increment in Tpe$_c$ was associated with a 19% increase in risk of death (HR 1.19, $P < 0.01$). *Figure 2* illustrates that patients in Tpe$_c$ tertile 1 had superior survival compared with those in tertile 3, with intermediate survival among patients in tertile 2. The 2-year mortality rates for the three tertiles were 12, 15, and 20%, respectively.

When the combined endpoint of ventricular tachyarrhythmia or death was examined, univariable predictors included Tpe, Tpe$_c$, age, history of ventricular tachyarrhythmia, creatinine clearance, and hydralazine use. Each 10-ms increment in Tpe$_c$ was associated with a 21% increase in risk (HR 1.21, $P < 0.01$). As shown in *Figure 3*, Tpe$_c$ was able to risk-stratify for the combined endpoint, with patients in Tertile 1 showing significantly better arrhythmia-free survival than those in the other two tertiles. Kaplan–Meier estimates of 2-year composite event rates were 21, 43, and 49%, respectively.

Analysis of ROC curves further demonstrated the utility of Tpe$_c$ for risk stratification for each endpoint. For ventricular tachyarrhythmia within 2 years, the area under the curve (AUC) was 0.64 ($P = 0.001$). The cut-off point that maximized combined sensitivity and specificity was 103.5 ms (sensitivity 85%, specificity 48%). For all-cause mortality within 2 years, the AUC was 0.60 ($P = 0.03$), with optimal cut-off point 126.7 ms (sensitivity 37%, specificity 80%). For the combined endpoint, the AUC was 0.64

Table 2 Univariable predictors of ventricular tachycardia/ventricular fibrillation, overall mortality, and the combined endpoint of ventricular tachycardia/ventricular fibrillation or death

	VT/VF		Overall mortality		VT/VF or death	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Age, per 10 y	1.22 (0.96–1.56)	0.11	1.31 (1.04–1.66)	0.02	1.23 (1.02–1.50)	0.03
Sex, male	2.05 (1.00–4.17)	0.05	0.92 (0.53–1.57)	0.75	1.43 (0.87–2.38)	0.17
Currently smoking	0.59 (0.21–1.63)	0.31	1.08 (0.52–2.26)	0.84	0.98 (0.51–1.88)	0.94
Race, non-black	0.74 (0.42–1.28)	0.27	1.09 (0.94–1.28)	0.26	0.79 (0.52–1.21)	0.28
Ischemic cardiomyopathy	1.04 (0.53–2.06)	0.91	2.08 (0.90–4.81)	0.09	1.38 (0.75–2.53)	0.30
History of sustained VT/VF	3.51 (1.81–6.79)	<0.01	0.82 (0.30–2.25)	0.70	2.60 (1.45–4.68)	<0.01
History of diabetes mellitus	0.50 (0.28–0.92)	0.02	1.49 (0.92–2.42)	0.10	0.90 (0.59–1.38)	0.63
History of atrial fibrillation	0.94 (0.53–1.68)	0.84	1.41 (0.84–2.36)	0.20	1.04 (0.66–1.66)	0.85
NYHA Class I	(ref)	0.32	(ref)	0.03	(ref)	0.47
NYHA Class II	3.29 (0.76–14.20)		0.85 (0.35–2.05)		1.21 (0.55–2.67)	
NYHA Class III	3.96 (0.93–16.87)		1.50 (0.66–3.42)		1.63 (0.76–3.50)	
NYHA Class IV	–[a]		4.85 (1.25–18.85)		1.01 (0.13–8.07)	
BMI, per 5 kg/m^2	1.09 (0.89–1.34)	0.41	0.95 (0.77–1.18)	0.66	0.99 (0.83–1.18)	0.89
Systolic BP, per 10 mmHg	0.93 (0.80–1.08)	0.34	0.91 (0.79–1.05)	0.18	0.91 (0.81–1.02)	0.10
Diastolic BP, per 10 mmHg	0.96 (0.76–1.21)	0.75	0.80 (0.64–1.00)	0.05	0.89 (0.74–1.07)	0.23
Heart rate, per 10 bpm	1.20 (1.01–1.41)	0.03	1.13 (0.96–1.33)	0.14	1.15 (1.00–1.32)	0.05
LVEF, per 5% increase	0.87 (0.61–1.25)	0.45	0.86 (0.73–1.01)	0.07	0.88 (0.76–1.01)	0.07
BUN, per 10 mg/dl	1.08 (0.92–1.25)	0.35	1.29 (1.16–1.44)	<0.01	1.19 (1.08–1.32)	<0.01
CrCl, per 10 ml/min	0.96 (0.88–1.05)	0.36	0.82 (0.75–0.91)	<0.01	0.88 (0.81–0.95)	<0.01
Beta-blocker	1.61 (0.50–5.14)	0.42	0.78 (0.36–1.71)	0.53	1.03 (0.48–2.22)	0.95
Calcium channel blocker	1.69 (0.80–3.56)	0.17	0.16 (0.02–1.13)	0.07	1.05 (0.51–2.17)	0.90
ACEi/ARB	1.07 (0.57–2.03)	0.82	0.74 (0.43–1.27)	0.27	0.73 (0.46–1.15)	0.18
Amiodarone	0.70 (0.33–1.48)	0.35	1.38 (0.75–2.52)	0.30	1.04 (0.62–1.77)	0.88
Aspirin	1.48 (0.77–2.85)	0.24	0.88 (0.51–1.52)	0.65	0.99 (0.62–1.58)	0.98
Aldosterone blocker	0.86 (0.48–1.52)	0.60	0.66 (0.37–1.17)	0.15	0.83 (0.52–1.32)	0.43
Clopidogrel	1.01 (0.58–1.76)	0.97	1.50 (0.92–2.45)	0.10	1.25 (0.81–1.91)	0.31
Diuretic	1.65 (0.88–3.12)	0.12	2.10 (1.12–3.92)	0.02	1.72 (1.02–2.88)	0.04
Hydralazine	0.65 (0.16–2.67)	0.55	3.17 (1.57–6.41)	<0.01	1.84 (0.89–3.81)	0.10
Statin	1.05 (0.55–2.02)	0.88	0.54 (0.32–0.92)	0.02	0.92 (0.56–1.53)	0.75
Nitrate	0.62 (0.30–1.32)	0.22	1.35 (0.77–2.36)	0.30	0.96 (0.57–1.63)	0.88
Antihyperlipidemic	0.61 (0.29–1.29)	0.20	0.97 (0.52–1.81)	0.92	0.71 (0.40–1.26)	0.24
Tpe, per 10 ms	1.14 (1.01–1.30)	0.04	1.17 (1.05–1.32)	<0.01	1.17 (1.06–1.30)	<0.01
Tpe_c, per 10 ms	1.21 (1.07–1.36)	<0.01	1.19 (1.07–1.33)	<0.01	1.21 (1.10–1.33)	<0.01
QT_c, per 10 ms	1.07 (1.01–1.14)	0.03	1.06 (1.00–1.13)	0.05	1.06 (1.01–1.12)	0.02
Q-Tp, per 10 ms	0.96 (0.91–1.02)	0.20	0.97 (0.92–1.03)	0.29	0.96 (0.92–1.01)	0.10
Q-Tp_c, per 10 ms	1.01 (0.95–1.09)	0.69	1.00 (0.94–1.07)	0.89	1.00 (0.94–1.06)	0.99
QRS duration, per 10 ms	1.03 (0.94–1.13)	0.49	1.06 (0.97–1.15)	0.20	1.05 (0.98–1.12)	0.18
LBBB	1.38 (0.75–2.56)	0.30	1.32 (0.74–2.35)	0.34	1.49 (0.92–2.40)	0.11
Cornell voltage, per 1 mV	1.02 (1.00–1.05)	0.05	1.01 (0.99–1.03)	0.40	1.01 (1.00–1.03)	0.15
Sokolow–Lyon voltage, per 1 mV	1.00 (0.97–1.02)	0.76	1.01 (0.99–1.03)	0.39	1.01 (0.99–1.03)	0.53

Abbreviations as in *Table 1*.
[a]There was no VT/VF event among NYHA Class 4 patients.

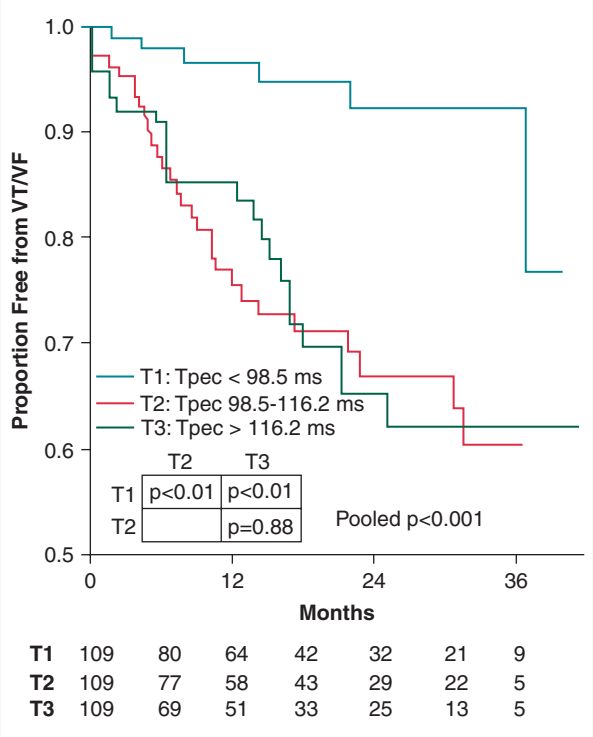

Figure 1 Freedom from ventricular tachycardia/ventricular fibrillation: Kaplan–Meier plot of freedom from appropriate implantable cardioverter-defibrillator therapy, stratified by tertiles (T) of Tpe_c.

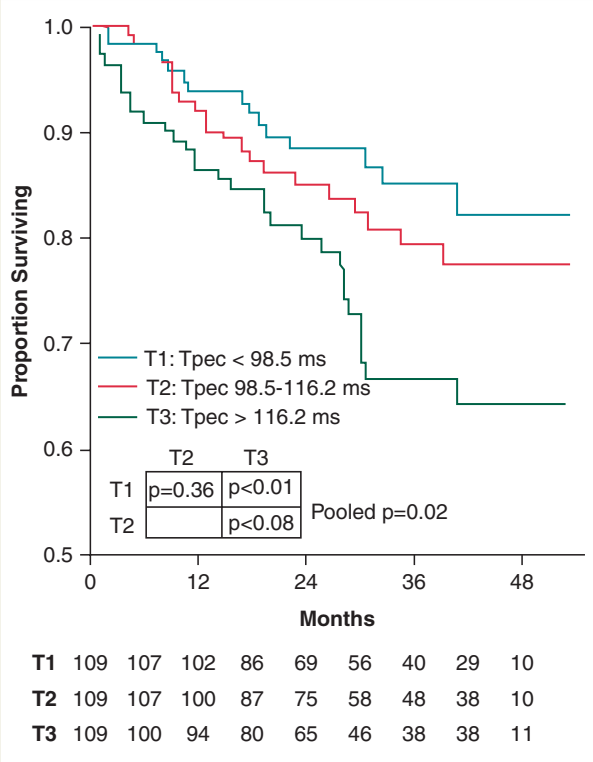

Figure 2 Overall survival: Kaplan–Meier plot of all-cause mortality, stratified by tertiles (T) of Tpe_c.

($P < 0.001$), with optimal cut-off point 103.5 ms (sensitivity 80%, specificity 51%).

Multivariable analysis

The relationships between Tpe_c, other univariable predictors, and the endpoints were further evaluated via stepwise multivariable analysis. After correction, Tpe_c remained significantly predictive of ICD therapy (adjusted HR 1.16 per 10 ms, $P = 0.02$), all-cause mortality (HR 1.14, $P = 0.03$), and the combined endpoint (HR 1.16, $P < 0.01$).

Other significant multivariable predictors of ICD therapy were prior VT/VF (HR 3.62, $P < 0.01$), diabetes (HR 0.44, $P < 0.01$), and heart rate (HR per 10 bpm 1.2, $P = 0.05$).

For overall mortality, the other significant factors on multivariable analysis were diuretic use (HR 2.45, $P = 0.02$), statin use (HR 0.47, $P = 0.01$), BUN (HR per 10 mg/dL increase 1.15, $P = 0.04$), and creatinine clearance (HR per 10 mL/min increase 0.87, $P = 0.02$).

Multivariable analysis of the combined endpoint revealed that in addition to Tpe_c, other predictors included prior VT/VF (HR 2.8, $P < 0.01$), diuretic use (HR 2.23, $P < 0.01$), and creatinine clearance (HR per 10 mL/min 0.88, $P < 0.01$).

Following multivariable correction, no univariable predictor other than these remained predictive. There was no difference in the predictive value of Tpe_c based on history of prior VT/VF (interactions $P = 0.89–0.99$).

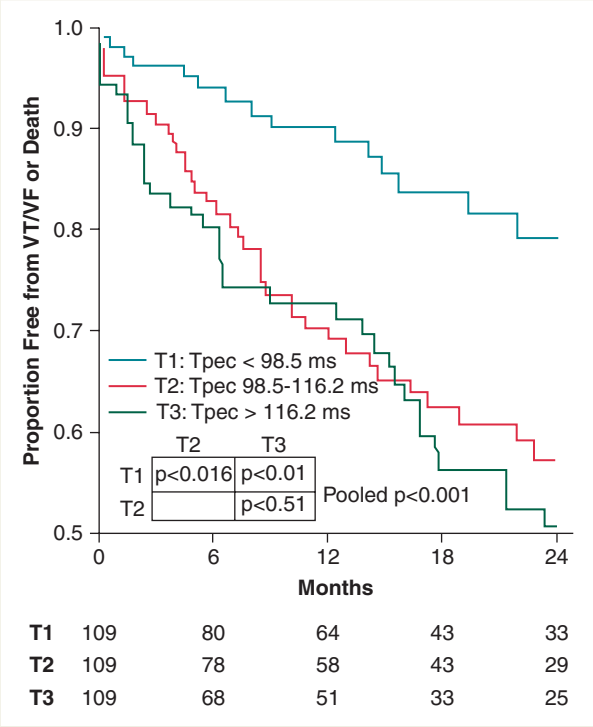

Figure 3 Combined endpoint: Kaplan–Meier plot of arrhythmia-free survival, stratified by tertiles (T) of Tpe_c.

Discussion

There are several important findings of this investigation. In patients with depressed LV systolic function and an ICD, longer Tpe_c strongly predicts both ventricular tachyarrhythmia and death, as well the composite of these two endpoints. In comparison with CM patients in the lowest tertile of Tpe_c, those patients in the highest tertile demonstrate not only a greater than four-fold higher risk of ventricular tachyarrhythmia, but also 67% higher all-cause mortality. Multivariable analysis showed that the additional predictive value of Tpe_c was independent of other covariates. In addition, the finding of no interaction between Tpe_c and prior VT/VF suggests that Tpe_c's predictive value is similar regardless of prior history of sustained tachyarrhythmia. These data suggest that Tpe_c may be valuable for risk stratification and may help to guide decisions about therapy.

Tpe and arrhythmic risk

There has been considerable interest in the association between repolarization patterns, and their electrocardiographic correlates, with arrhythmic risk. For example, studies in the perfused cardiac wedge preparation showed Tpe to correlate closely with TDR.[2] *In vivo* electroanatomic mapping has correlated Tpe with overall dispersion of repolarization (DVR_{total}).[4–7] Subsequent retrospective analyses in specific human populations, including those with acquired long QT syndrome, Brugada syndrome, and hypertrophic cardiomyopathy, showed Tpe to be associated with torsades de pointes, appropriate ICD therapy, and sudden cardiac death, respectively.[22–24] Lubinski *et al.*[9] showed that Tpe correlated with inducibility of VT/VF, but no follow-up was reported. Later, in a relatively small case–control study of a heterogeneous population of patients undergoing electrophysiology study (EPS), Watanabe *et al.*[8] also showed inducibility of VT at EPS to correlate with longer Tpe_c. Their subsequent follow-up suggested that Tpe_c predicted spontaneous occurrence of VT, but that study's 'case' group differed significantly from the 'control' group, follow-up was not uniform, and only 13 events were detected.

The present study is the largest reported investigation into the value of repolarization indices for the prediction of ventricular tachyarrhythmia in a population of patients with cardiomyopathy. In a comparable study, Lellouche *et al.*[25] examined a population of 100 patients who underwent biventricular ICD implantation, and found that post-implantation Tpe (at which time ventricular pacing was present) predicted subsequent appropriate ICD therapy, but that *pre*-implantation Tpe was not predictive. Of note, the cause of the predictive disparity they found between pre- and post-implant Tpe is unclear—possibilities include effects of pacing vs. non-pacing, the influence of heart rate (potentially higher during pacing than without), or the result of cardiac resynchronization. There were significant differences between that of study's population and our own: all patients studied by Lellouche *et al.* had significant heart failure and a wide QRS and/or echocardiographic systolic dyssynchrony, 18% of them had right ventricular pacing prior to upgrade to a resynchronization device, and 33% of them already had suffered a sustained tachyarrhythmic event. In contrast, we measured Tpe_c during spontaneous rhythm (i.e. in the absence of pacing), a CRT device was implanted in only a small minority of our population ($n = 43$), and far fewer (7%) previously had sustained VT or VF. Our study included significantly longer follow-up with nearly three times the number of events, and also assessed the additional endpoint of mortality.

Potential mechanisms linking Tpe to ventricular tachyarrhythmia

While our study design does not permit an analysis of the pathophysiology linking Tpe to ventricular tachyarrhythmic events in our population, some hypotheses may be advanced.

Early studies of experimental preparations concluded that Tpe reflected *transmural* dispersion of repolarization, but others have since argued that the Tpe duration may reflect more accurately the overall heterogeneity of ventricular repolarization across all dimensions of the intact heart (i.e. *total* dispersion of ventricular repolarization, or DVR_{total}).[3–7,26–30] Because differential repolarization is a requirement for electrical reentry (together with an appropriately timed premature activation),[31] an increase in dispersion—in any dimension—could be expected to increase arrhythmic susceptibility. Most prior models and hypotheses examined relatively homogeneous myocardial tissue layers with intact perfusion, concluding that differences in repolarization parameters intrinsic to the various tissues resulted in increased TDR (i.e. the cardiac wedge preparation's epi- and endocardial repolarization preceding repolarization of the M cell layer) or DVR_{total} (with more complex spatiotemporal dispersion of repolarization at play in the intact heart). Whether these mechanisms pertain to Tpe prolongation in patients with left ventricular systolic dysfunction is unclear. In the cardiomyopathy population, for example, regional scarring or patchy fibrosis could lead to increased DVR_{total}. Further modelling and/or invasive study would be required to evaluate this possibility.

Thus, the debate continues regarding the electrophysiologic mechanism(s) underlying inscription of the T-wave. Regardless of the source of increased repolarization dispersion, it still may be expected that increased DVR correlates with risk. It is possible that the scientific community may come to consensus about the clinical usefulness of Tpe as a risk marker, even without a consensus on what exactly Tpe represents electrophysiologically. Whatever the molecular and/or structural mechanisms underlying the inscription of the T-wave, our results support the hypothesis that Tpe prolongation is a useful marker of risk in cardiomyopathy patients with at least moderately depressed LVEF.

Tpe and mortality risk

Prior investigations into the utility of a longer Tpe to predict death have shown varying results. For example, one examination of a general population sample did not find the uncorrected Tpe to be useful for mortality prediction.[32] In patients undergoing percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction; however, a longer pre-PCI (but not post-PCI) Tpe predicted all-cause one-year mortality.[33] In stark contrast, a recent study following male United States cardiovascular patients with average LVEF 56% found that a *shorter* Tpe correlated with a higher risk of death from any cause.[34] In the present investigation,

we found that a longer Tpe_c predicted overall mortality in patients with established cardiomyopathy, even in the presence of ICDs, and even after correction for other predictors of mortality. Thus, Tpe may be a useful marker of mortality risk only for specific populations under certain circumstances.

Given that the ICD is an effective treatment for tachyarrhythmic events, one could hypothesize from our data that in patients with cardiomyopathy, a longer Tpe_c portends not only a higher incidence of ventricular tachyarrhythmia, but also a higher risk of death via other mechanisms—e.g. progressive heart failure. Further prospective study with cause of death or mode of death would be required to examine this hypothesis.

Clinical implications and suggestions for further study

The optimal method for the allocation of ICD therapy is not known at present. Our study's results support the use of Tpe_c as a risk stratification tool. In the higher-risk population of patients with left ventricular dysfunction studied here, a shorter Tpe_c was associated with lower risk for ventricular tachyarrhythmia. In fact, patients in the lowest tertile of Tpe_c had more than fourfold lower risk than those in tertiles 2 or 3.

Despite the extensive work that has been done on risk-stratification for sudden death, the identification of a single predictive test or risk factor remains elusive. Our study's relatively low annual ventricular tachyarrhythmia event rate of 8% among cardiomyopathy patients in tertile 1 of Tpe_c probably is not low enough to *not* implant an ICD in such patients based on their short Tpe_c alone. However, our data suggest that Tpe_c may be useful as part of a risk-stratification schema. It seems likely that optimal risk stratification will require the construction of a composite index combining various indicators of risk, perhaps including not only LVEF and other currently approved methods of risk assessment (e.g. EPS and microvolt T-wave alternans), but also other data such as the electrocardiographic indicators Tpe_c and left ventricular hypertrophy severity. In high-risk populations, such a tool could be used to identify lower-risk patients who may then opt not to undergo ICD implantation. Conversely, it is also possible that further study could find Tpe_c and other indicators to be predictive in populations not currently indicated for ICD implantation (e.g. those with preserved LVEF), perhaps guiding decisions regarding ICD implantation or other therapy.

Limitations

Because our population was limited to patients with at least moderately depressed LVEF and an implanted ICD, this study's conclusions may not be applicable to populations with different characteristics. As sequential ECGs were not available for the bulk of our patients, we could not investigate the effects of potential changes in predictor variables over time. These are directions for further study.

It is recognized that ICD therapy does not necessarily equate to the avoidance of sudden death, and our conclusions should be viewed in this light. For example, some tachyarrhythmic events may have been self-terminating in the absence of an ICD. However, only by withholding therapy could we have assessed whether the arrhythmia would self-terminate. In addition, in our study event detection bias was not present because of uniform, thorough surveillance for ventricular tachyarrhythmia via the presence of an ICD in all subjects. However, because in the United States it is rare for decedents' ICDs to be interrogated, some tachyarrhythmic events may have been missed late in life. Lastly, although all-cause mortality is certainly an important endpoint, in our population, data were not available on cause of death or mode of death.

Conclusion

In patients with left ventricular systolic dysfunction and an ICD, Tpe_c predicts both appropriate ICD therapy for ventricular tachyarrhythmia and overall mortality, even after correction for other independent predictors.

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Conflict of interest: D.P.M. has received speaker's honoraria from Boston Scientific, Medtronic, St Jude Medical, and Zoll. J.Q.X. is an employee of GE Healthcare. S.K. and O.S.N.-T. have received speaker's honoraria from Medtronic and St Jude Medical. F.M.A.-S. has received research support from Biotronik and speaker's honoraria from Sanofi-Aventis, Sorin, St Jude Medical, and Zoll. The other authors report no conflicts.

Author Contributions

Concept and design of the study: D.P.M: Data collection; D.P.M., M.N.S., O.F.S., S.O., and J.Q.X. Data analysis and interpretation: D.P.M. and J.Q.X. Drafting of article: D.P.M. Critical revision of article: All authors.

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